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CLINICAL STUDY PROTOCOL

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

EudraCT No: 2020-002211-21

Protocol No.: SGS.1656.201

Original Protocol	**Version No: 1.0, 03 July 2020**
Amendment 1	**Version No: 1.1 (CZ), 10 December 2020**
Amendment 2	**Version No: 1.2 (ROM), 17 December 2020**
Amendment 3	**Version No: 2.0 (Global), 21 December 2020**

Sponsor: St George Street Capital, 2a/2b Thrales End Business Centre, Thrales End Lane, Harpenden, AL5 3NS, UK

Confidentiality Statement:
This protocol contains information which is the property of St George Street Capital and therefore is provided to you in confidence for review by you, your staff, an applicable ethics committee/institutional review board and regulatory authorities. It is understood that this information will not be disclosed to others without the written approval of St George Street Capital.

This study will be conducted in compliance with Good Clinical Practice (GCP), the principles of the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements

1. PROTOCOL SYNOPSIS

PROTOCOL TITLE	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.
SHORT TITLE	The ARCADIA Trial (**A**lleviation of cardio**R**espiratory complications in patients with **C**OVID-19 **A**nd **DIA**betes)
PROTOCOL No.	SGS.1656.201
COORDINATING INVESTIGATOR	Dr Kieran McCafferty
SPONSOR	St George Street Capital
INVESTIGATIONAL PRODUCT	AZD1656
PHASE OF DEVELOPMENT	II
INDICATION AND RATIONALE	Alleviation of cardiorespiratory complications in diabetic patients with suspected or confirmed COVID-19. AZD1656 is a glucokinase activator which has previously been shown to be well tolerated in patients with type 2 diabetes mellitus (T2DM). Twenty-five clinical trials of up to 6 months' treatment duration have been conducted, exposing approximately 960 subjects to AZD1656 with no safety concerns raised to date. A rapid and dose-dependent glucose-lowering effect (in the range 0.8-2 mmol/L) has been demonstrated after dosing of AZD1656 in both healthy volunteers and in T2DM patients. The antidiabetic effects of AZD1656 did not persist beyond 4 months, thus limiting its long-term use for patients with diabetes (Kiyosue *et al.* (2013), Wilding *et al*. (2013)). However, a shorter course of AZD1656 may be of benefit in controlling the abnormal glucose variability observed

in diabetic patients with COVID-19, which may be an important contributing factor to disease development.

Mortality rates are increased in diabetic patients with COVID-19 (China CDC Weekly (2020)). Such patients are at particular risk of progressing rapidly with acute respiratory distress syndrome and sepsis and are more likely to require Intensive Care Unit (ICU) care than non-diabetic COVID-19 patients (22.2% vs 5.9%) (Wang D *et al*. (2020)). In a retrospective cohort study of 191 hospitalised patients examining risk factors for mortality associated with COVID-19, 31% of non-survivors had diabetes compared with 14% of survivors, p=0.0051 (Zhou *et al.* (2020)).

Patients with diabetes who develop sepsis often develop hyperglycaemia and have to increase their diabetic therapy. Furthermore, compared with good glycaemic control those patients with poor glycaemic control on admission had poor control during their in-patient stay and had poorer outcomes including acute kidney injury, acute heart injury, acute respiratory distress syndrome and all-cause mortality (Zhu *et al.* (2020)).

In addition to its glucose lowering effect, AZD1656 may have additional benefits to COVID-19 patients which involve its effects on immune function (Kishore *et al*. (2017)).

In the immune response to infection, a delicate balance exists between T cell activation to fight infection and excessive inflammation with cytokine release which is known to cause damage to infected host cells. Regulatory T cells (Tregs) are important in maintaining this balance.

Migration of activated Tregs to inflamed tissue is crucial for their immune-modulatory function, a process which is regulated by glucokinase-dependent glycolysis (Kishore *et al*. (2017)). A glucokinase activator, such as AZD1656, could enhance Treg migratory capacity and may prevent the development of cardiorespiratory complications observed in hospitalised patients with COVID-19, leading to lower requirements for oxygen therapy and assisted ventilation, and reduced incidences of pneumonia and acute respiratory distress syndrome (ARDS).

In-vivo studies using Tregs as an interventional treatment through adoptive transfer have shown benefit in an acute lung injury model through mediating the resolution of lung injury (D'Alessio *et al*. (2009)). This research shows that resolution in experimental lung injury is an active process in which Tregs play an essential role. The

ability of Tregs to suppress the innate immune response is an important component of this (Pietropaoli *et al*. (2009)).

In an IL-6-rich inflammatory microenvironment, which is known to be a feature of COVID-19 infection, inflammatory Th17 cells are enhanced while Tregs are suppressed (Chen *et al*. (2020)). A therapeutic agent which can shift the Th17/Treg balance towards Tregs might reduce the amplificatory inflammatory loop and therefore reduce the uncontrolled inflammation which occurs in ARDS. In an observational study, Th17/Treg ratio was positively correlated with disease severity scores and 28-day mortality in a retrospective study of ARDS in 2015 (Yu *et al.* (2015)). In addition, a recent study reported that 90-day survival for patients with ARDS was 83% for patients with Tregs/CD4+ percentage equal to or greater than 10.5%, but only 41% for patients with Tregs/CD4+ percentage less than 10.5% (P = 0.01) (Halter *et al.* (2020)).

STUDY DESIGN

This is a Phase II, randomised, placebo-controlled, double-blind clinical trial to assess the safety and efficacy of AZD1656 on the cardiorespiratory complications of COVID-19 in hospitalised diabetic patients with known or suspected COVID-19. All patients will receive usual care plus either AZD1656 or placebo.

The World Health Organization (WHO) 8-point Ordinal Scale for Clinical Improvement will be used as the standard methodology for measuring patient outcomes (Appendix 1).

Safety Review Committee

A Safety Review Committee (SRC) consisting of clinical and other experts will be established by the Sponsor to review safety findings during the study and to help ensure patient safety.

STUDY OBJECTIVES

Primary Objective:

- 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 (see Appendix 1) compared to placebo.

Secondary Objectives:

- To assess the extent to which AZD1656 supports maintainance of adequate glycaemic control in hospitalised diabetic patients with known or suspected COVID-19.
- To assess the safety and tolerability of AZD1656 in the management of diabetes in hospitalised diabetic patients with

known or suspected COVID-19.

- To determine whether AZD1656 affects duration of hospital stay, requirement for mechanical ventilation or mortality in diabetic patients with known or suspected COVID-19.

Exploratory Objectives:

- To determine the pharmacokinetics (PK) of AZD1656 in diabetic patients with known or suspected COVID-19.
- To explore the effects of AZD1656 on immunophenotyping characteristics during COVID-19 infection in hospitalised diabetic patients.
- To explore the effects of AZD1656 on immunochemistry characteristics during COVID-19 infection in hospitalised diabetic patients.
- To explore whether AZD1656 affects the extent of any cardiac injury related to COVID-19 in hospitalised diabetic patients.
- To explore if ethnicity affects the clinical outcome of hospitalised diabetic patients with known or suspected COVID-19 treated with AZD1656 versus placebo.
- To explore if 25-hydroxyvitamin D levels at baseline affect the clinical outcome of hospitalised diabetic patients with known or suspected COVID-19 treated with AZD1656 versus placebo.

STUDY ENDPOINTS

Primary Endpoint:

- Clinical Improvement measured as the percentage of subjects at Day 14 who are in categories 1-3 according to the WHO 8-point Ordinal Scale for Clinical Improvement, comparing AZD1656 treatment to placebo.

Secondary Endpoints:

- Clinical Improvement measured as the percentage of patients categorised at each severity rating on the WHO 8-point Ordinal Scale at Day 7, Day 14 and Day 21 versus baseline, comparing AZD1656 treatment with placebo.
- Degree of glycaemic control as measured by the need to increase baseline medication requirements or the need to add additional diabetic medications to maintain appropriate blood glucose levels in patients receiving AZD1656 compared with placebo.
- Proportion of Treatment Emergent Adverse Events (TEAEs) leading to study drug discontinuation in patients receiving AZD1656 compared with placebo.
- Proportion of Serious Adverse Events (SAEs) in patients

receiving AZD1656 compared with placebo.

- Time from hospital admission to hospital discharge (in hours) in patients receiving AZD1656 compared with placebo.
- Time from hospital admission to receiving intubation/ mechanical ventilation in patients receiving AZD1656 compared with placebo.
- Mortality Rate in patients receiving AZD1656 compared with placebo.

Exploratory Endpoints:

- Plasma AZD1656 levels during first 7 days of treatment in patients receiving AZD1656 compared with placebo.
- Immunophenotyping panel to be conducted by Flow Cytometry: between group comparison (AZD1656 versus placebo) of levels of T, B and NK cells (including specific Treg and memory T cell populations); monocyte, neutrophil and eosinophil numeration to include activation markers for neutrophils (CD11b) and Monocytes subsets (CD14/CD16 identification including 6-Sulfo LacNAc (SLAN)).
- Immunochemistry panel to be conducted using the MSD U-Plex multiplex assay for assessment of the following biomarkers: G-CSF, GM-CSF, IL-1B, IL-4, IL-6, IL-8, IL-10, IL-12, and MIP-1a.
- Measurement of hsTroponin and NTproBNP to determine extent of cardiac injury in patients receiving AZD1656 compared with placebo.
- Measurement of 25-hydroxyvitamin D levels before treatment to determine whether there is any correlation between Vitamin D level and clinical outcomes.
- Correlation of clinical outcomes with patient ethnicity.

PLANNED SAMPLE SIZE

Approximately 165 patients will be screened to achieve 150 patients randomly assigned to AZD1656 or placebo.

PATIENT POPULATION

Inclusion Criteria

1. Male or Female.
2. Aged 18 and older.
3. Have either type 1 diabetes mellitus (T1DM) or T2DM.
4. Hospitalised with suspected or confirmed novel coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-

CoV-2)) infection at time of enrolment, categorised as stage 3, 4 or 5 on the WHO Ordinal Scale for Clinical Improvement.

5. Blood glucose level at or above 4 mmol/L.
6. Able to take oral (tablet) formulation of medication.
7. Patient is able to provide written informed consent prior to initiation of any study procedures.

Exclusion Criteria

1. In the opinion of the clinical team, progression to intubation or mechanical ventilation is imminent and inevitable, within the next 24 hours, irrespective of the provision of treatments.
2. Patients admitted with primary suspected or proven Mycoplasma pneumoniae, Chlamydia pneumoniae and bacterial pneumonia, who acquired COVID-19 while hospitalised.
3. Treatment with immunomodulators or anti-rejection drugs within the last 3 months.
4. Pregnant or breast feeding.
5. Men, and women of child-bearing potential, unwilling to use highly effective contraception during their participation in the trial and for 2 weeks after study completion.
6. Anticipated transfer to another hospital which is not a study site within 72 hours.
7. Known sensitivity to any of the study medication/placebo excipients (see section 9.3).
8. Prior dosing with AZD1656 on a previous clinical trial.
9. Patients admitted as a result of and receiving immediate treatment for an acute asthmatic attack, acute myocardial infarction, acute cerebrovascular event.
10. Any known non-COVID-19, non-diabetes related, serious condition which, in the opinion of the clinical team, makes the patient unsuitable for the trial.
11. Known history of drug or alcohol abuse within previous 12 months of screening.
12. Known history of HIV, hepatitis C or unresolved hepatitis B or severe liver disease.
13. Current or planned use of gemfibrozil or any other strong inhibitors of CYP2C8.
14. Current or previous participation in another clinical trial where the patient has received a dose of an Investigational Medicinal

	Product (IMP) containing small molecule treatment(s) within 30 days or 5 half-lives (whichever is longer) prior to enrolment into this study, or containing biological treatment(s) within 3 months prior to entry into this study.
AZD1656 FORMULATION/DOSE	50 mg film-coated tablets of AZD1656 or placebo to be dosed at 100 mg BID
ROUTE OF ADMINISTRATION	Oral
DURATION/FREQUENCY OF TREATMENT	Two 50 mg tablets to be taken twice per day with food for up to 21 days
EFFICACY ASSESSMENTS	The study will evaluate efficacy across a range of assessments evaluating clinical improvement, glycaemic control, time from hospital admission to hospital discharge and time from hospital admission to receiving intubation/mechanical ventilation.
SAFETY ASSESSMENTS	This study will compare the incidence of AEs, including SAEs, across the course of the 21-day treatment period and until the final visit. The incidence of abnormal findings in objective assessments (e.g. clinical laboratory values, urinalysis, physical examination findings, vital signs, and ECG) during the course of the study will also be assessed.
STATISTICAL METHODS	The WHO 8-point Ordinal Scale will be used to assess the impact of treatment with AZD1656 in diabetic patients with COVID-19 versus those treated with placebo. The primary endpoint in this trial will be the proportion of patients treated with AZD1656 in WHO categories 1-3 at Day 14 compared to placebo. 60-65% of patients treated with usual care alone are expected to meet this condition within the first 14 days. (Zhou *et al* (2020), Chen *et al* (2020), Guan *et al* (2020), Guan *et al* [2] (2020)). A two group Chi-square (χ^2) test with a 5% two-sided significance level will have 76.74% power to detect the difference between a placebo proportion of 0.6 and an AZD1656 proportion of 0.8 when the sample size is 150 (75/group). In the case that the portion of placebo patients meeting WHO categories 1-3 at Day 14 is higher (0.65), then the power to find a similar 20 percentage point increase would be 81.4%. The primary analysis will test the null hypothesis that the proportion of patients who respond to AZD1656 plus usual care is similar to that of those treated with placebo plus usual care at Day 14. The primary analysis will include all patients treated according to their randomised treatment (Intention To Treat (ITT) analysis set). The

	difference in proportions (AZD1656 compared to placebo) of patients meeting the response criteria (WHO category 1-3 at Day 14) will be analysed using the χ^2 test for the difference of proportions with a 0.05 two-sided significance level. Patients who are assigned to WHO category 1-3 at Day 14 will be considered responders. In the unlikely event that a patient leaves the hospital without being formally discharged and is lost to follow-up, the last post-baseline observation carried forward will be used to impute results for this patient. In the event that a patient is lost to follow-up without having recorded at least one post-baseline value, that patient will be considered a non-responder.
PLANNED DATE OF FIRST PATIENT ENROLLED	September 2020
PLANNED DATE OF LAST PATIENT COMPLETED	March 2021
NUMBER OF STUDY CENTRES	Approximately 35 sites in the UK, Czech Republic and Romania

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse event
ALT	Alanine amino transferase
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate amino transferase
AUC	Area under the plasma drug concentration-time curve
BID	Twice a day
BAME	Black, Asian and minority ethnic
Cmax	Maximum plasma concentration observed
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organisation
CT	Computed Tomography
CTFG	Clinical Trial Facilitation Group
ECG	Electro cardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GKA	glucokinase activator
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product

IRT	Interactive Response Technology
ITT	Intention To Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LDH	Lactate dehydrogenase
MAD	Multiple Ascending Dose
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PI	Principal Investigator
PK	Pharmacokinetic
PPS	Per Protocol Set
RTSM	Randomization and Trial Supply Management
SAE	Serious Adverse Event
SAF	Safety Set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SLAN	6-Sulfo LacNAc
SoA	Schedule of Assessments
SRC	Safety Review Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TEAEs	Treatment Emergent Adverse Events
tmax	Time to maximum plasma concentration
Tregs	Regulatory T cells
TZD	Thiazolidinedione
ULN	Upper Limit of Normal
WHO	World Health Organization

4. INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

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5. BACKGROUND INFORMATION

5.1 COVID-19

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified in December 2019 in Wuhan, the capital of China's Hubei province, and has since spread globally, resulting in an ongoing pandemic. As of 19th June 2020, more than 8.3 million cases have been reported across 187 countries and territories, resulting in more than 450,000 deaths.

Mortality rates are increased in diabetic patients with COVID-19 (China CDC Weekly (2020)). Such patients are at particular risk of progressing rapidly with acute respiratory distress syndrome and sepsis and are more likely to require intensive care unit (ICU) care than non-diabetic COVID-19 patients (22.2% vs 5.9%) (Wang D *et al*. (2020)). In a retrospective cohort study of 191 hospitalised patients examining risk factors for mortality associated with COVID-19, 31% of non-survivors had diabetes compared with 14% of survivors, p=0.0051 (Zhou *et al.* (2020)). In Guan et al (European Respiratory Journal 2020) results for a subset of 130 diabetic patients (in a cohort of 1590) showed that 10% of diabetic patients died, 14.6% required treatment in an ICU setting and 8.5% required mechanical ventilation compared to 3.1%, 6.2% and 3.1% for the total cohort, respectively.

5.2 AZD1656 and Study Rationale

AZD1656 is a glucokinase activator which has previously been shown to be well tolerated in patients with type 2 diabetes mellitus (T2DM).

A rapid and dose-dependent glucose-lowering effect (in the range 0.8-2 mmol/L) has been demonstrated after dosing of AZD1656 in both healthy volunteers and in T2DM patients. The antidiabetic effects of AZD1656 did not persist beyond 4 months, thus limiting its long-term use for patients with diabetes (Kiyosue *et al*. (2013), Wilding *et al*. (2013)). However, a shorter course of AZD1656 may be of benefit in controlling the abnormal glucose variability observed in diabetic patients with COVID-19, which may be an important contributing factor to disease development.

Whilst AZD1656 has largely been tested in patients with type 2 diabetes with no safety concerns reported, there is some Phase I data from type 1 diabetics demonstrating the drug is also safe in this population. In addition, a large Ph II study was run in type 2 diabetic patients who were also insulin dependent and again no safety concerns were noted. The highest repeated doses in prior trials (300 mg per day) were given as an add on to insulin therapy. AZD1656 is anticipated to be beneficial to both type 1 and type 2 diabetic patients, with both diseases making patients more vulnerable to severe COVID-19. Recent reports from the UK showed people with type 1 diabetes are 3.5 times more likely to die and type 2 diabetes were 2 times as likely to die from COVID-19 compared with non-diabetics, hence both groups represent particularly vulnerable cohorts (Valabhji *et al.* (2020)). AZD1656 will reduce blood glucose levels and will thus provide additional glucose control in both diabetic populations, who typically present with hyperglycaemia when admitted with COVID-19. This trial will allow the effects of this additional glycaemic control to be elucidated in both populations. In addition, the hyperinflammatory process causing much of the damage in COVID-19

patients is not thought to be any different between type 1 and type 2 diabetics and so both populations could benefit from the potential immunomodulatory mechanism of action of AZD1656.

Patients with diabetes who develop sepsis often develop hyperglycaemia and have to increase their diabetic therapy. Furthermore, compared with good glycaemic control those patients with poor glycaemic control on admission have poor control during their in-patient stay and have poorer outcomes including acute kidney injury, acute heart injury, acute respiratory diseases syndrome and all-cause mortality (Zhu *et al.* (2020)).

In addition to its glucose lowering effect, AZD1656 may have additional benefits to COVID-19 patients which involve its effects on immune function (Kishore *et al*. (2017)). In the immune response to infection, a delicate balance exists between T cell activation to fight infection and excessive inflammation with cytokine release which is known to cause damage to infected host cells. Regulatory T cells (Tregs) are important in maintaining this balance.

Migration of activated Tregs to inflamed tissue is crucial for their immune-modulatory function, a process which is regulated by glucokinase-dependent glycolysis (Kishore *et al*. (2017)). A glucokinase activator, such as AZD1656, could enhance Treg migratory capacity and may prevent the development of cardiorespiratory complications observed in hospitalised patients with COVID-19, leading to lower requirements for oxygen therapy and assisted ventilation, and reduced incidences of pneumonia and acute respiratory distress syndrome (ARDS).

In-vivo studies using Tregs as an interventional treatment through adoptive transfer have shown benefit in an acute lung injury model through mediating the resolution of lung injury (D'Alessio *et al*. (2009)). This research shows that resolution in experimental lung injury is an active process in which Tregs play an essential role. The ability of Tregs to suppress the innate immune response is an important component of this (Pietropaoli *et al*. (2009)).

In an IL-6-rich inflammatory microenvironment, which is known to be a feature of COVID-19 infection, inflammatory Th17 cells are enhanced while Tregs are suppressed (Chen *et al*. (2020)). A therapeutic agent which can shift the Th17/Treg balance towards Tregs might reduce the amplificatory inflammatory loop and therefore reduce the uncontrolled inflammation which occurs in ARDS. In an observational study, Th17/Treg ratio was positively correlated with disease severity scores and 28-day mortality in a retrospective study of ARDS in 2015 (Yu *et al*. (2015)). In addition, a recent study reported that 90-day survival for patients with ARDS was 83% for patients with Tregs/CD4+ percentage equal to or greater than 10.5%, but only 41% for patients with Tregs/CD4+ percentage less than 10.5% (P = 0.01) (Halter *et al*. (2020)).

Dose
AZD1656 is given twice daily. The dose of 200 mg per day of AZD1656 to be evaluated in this study has been defined based on data from T2DM patients in prior studies.

Patient Population
Hospitalised T1DM and T2DM patients with suspected or confirmed COVID-19, fulfilling the entry criteria set out in sections 7.2 and 7.3.

Pharmacokinetics
Pharmacokinetic (PK) blood samples will be collected in order to characterise the PK properties of AZD1656 in diabetic patients with COVID-19.

Safety
Twenty-five clinical trials of up to 6 months' treatment duration have been completed, exposing approximately 960 subjects to AZD1656 with no safety concerns raised to date.

Duration
A treatment duration of 21 days has been selected to explore the effects of AZD1656 on safety and efficacy. Treatment durations of up to 6 months have been evaluated in previous trials, so the duration in this trial is considered safe and is appropriate for this patient population based on the expected duration of hospitalisation for diabetic patients requiring hospital treatment for COVID-19.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) and the applicable regulatory requirements.

5.3 Pre-Clinical Research

A comprehensive International Council for Harmonisation (ICH)-compliant pre-clinical program has been conducted with AZD1656. Summary information is described in this section, with additional information on the non-clinical studies conducted to date contained within the current version of the Investigator's Brochure.

A strong and predictive PK/pharmacodynamic (PD) relationship has been established between AZD1656 levels and the magnitude and duration of glucose lowering in animal models. AZD1656 induced hypoglycaemia (blood glucose <2.5 mM) at higher doses/exposures in normoglycaemic animals but not in diabetic animals.

The safety and tolerability of AZD1656 has been investigated in toxicology studies of up to 6 months duration in rats and dogs. AZD1656 showed a potent glucose lowering effect and the results of these, and preceding toxicology studies, in healthy animals were confounded by severe hypoglycaemia at higher doses. Towards the end of the 6-month rat toxicology study, some animals in the high-dose group (20 mg/kg/day) were found dead with muscular wastage in their hind legs. Dose related increased incidence and severity of neuropathy (Wallerian type nerve degeneration) and myopathy (skeletal muscle fibre degeneration) were seen in rats at the mid and high-dose levels, but not in the low-dose group (5 mg/kg/day). These changes seen in the mid and high-dose groups were considered to be associated with hypoglycaemia.

5.4 Clinical Experience

As of December 2019, 25 clinical trials of up to 6 months' treatment duration have been completed in humans with no safety concerns raised to date. All the clinical studies were conducted in accordance with GCP regulations.

The clinical pharmacology (Phase I) programme consisted of 21 studies in 459 subjects, 397 of whom were dosed with AZD1656. The majority of subjects were diagnosed with T2DM, 67 were healthy male volunteers and 12 were patients with type 1 diabetes mellitus (T1DM).

Based on previous experience with glucokinase activator (GKA) compounds and toxicology results, the glucose lowering effect of a GKA could be pronounced in non-diabetic subjects and therefore AZD1656 was evaluated on a euglycaemic clamp background in some Phase I studies in healthy volunteers.

The Phase IIa and Phase IIb worldwide clinical program included 5 studies (including Part B of the 28-day multiple ascending dose study D1020C00002) ranging from 4 weeks to 6 months duration and in which 566 patients were randomised to AZD1656 and whereof 117 provided data on 6 months treatment with AZD1656.

One additional clinical trial of AZD1656 (in diabetic patients who have undergone renal transplant) was initiated in 2019 and was ongoing at the time of writing (the ADOPTION trial, EudraCT Number 2019-001587-30).

In summary, approximately 1280 subjects have been randomised in the clinical programme, and of these 962 were exposed to AZD1656. Approximately 30% of the diabetic patients were females, all of whom were non-fertile.

Overview of Safety & Efficacy

Safety and tolerability data have been reported from 20 Phase I, 3 Phase IIa and 2 Phase IIb studies. An overview of the design and key results of completed clinical studies are presented in Appendix A (Table 12) of the AZD1656 Investigator's Brochure. A full risk benefit assessment is presented in Section 16.

AZD1656 has been well tolerated in clinical studies. Single oral doses of AZD1656 up to 180 mg have been given to healthy volunteers during euglycaemic clamp conditions. Patients with T2DM have been administered single oral doses up to 450 mg. Daily doses of 10 to 200 mg AZD1656 have been given to patients with T2DM for up to 6 months duration. No deaths have been reported.

As with most diabetic medications there is a risk of hypoglycaemia. For AZD1656, in Phase I to IIa, few hypoglycaemic events have been reported and only rarely with a plasma glucose level below 3 mmol/L (54 mg/dL). In Phase IIb, the proportion of patients reporting hypoglycaemic events was overall small. Fewer patients in the AZD1656 treatment groups reported hypoglycaemic events compared to the glipizide group. Low glucose levels were either asymptomatic (detected in scheduled measurement) or associated with mild symptoms, and in all cases manageable by the patients. All events with low plasma glucose have responded rapidly to carbohydrate intake.

Although the Phase I and Phase IIa studies were not primarily designed to evaluate efficacy, AZD1656 showed a rapid glucose-lowering effect for a dose range from 7 to 10 mg once daily to the highest tested daily dose of 450 mg. The glucose-lowering effect of AZD1656 was observed when

AZD1656 was given alone and in combination with other antidiabetic drugs (metformin, insulin, Thiazolidinedione (TZD) or glipizide).

In Phase IIb, statistically significant and clinically relevant improvements in glucose control were observed after 4 months in the global, but not the Japanese dose-finding study, with individually titrated doses of 10-200 mg of AZD1656 as compared to placebo. However, Japanese Phase IIb data up to 4 months and global extension study results up to 6 months indicate that glucose control deteriorated over time with AZD1656.

6. STUDY OBJECTIVES AND PURPOSE

6.1 Primary Objective

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 (see Appendix 1) compared to placebo.

6.2 Secondary Objectives

Secondary objectives of this study are:

- To assess the extent to which AZD1656 supports maintenance of adequate glycaemic control in hospitalised diabetic patients with known or suspected COVID-19.
- To assess the safety and tolerability of AZD1656 in the management of diabetes in hospitalised diabetic patients with known or suspected COVID-19.
- To determine whether AZD1656 affects duration of hospital stay, requirement for mechanical ventilation or mortality in diabetic patients with known or suspected COVID-19.

6.3 Exploratory Objectives

Exploratory objectives of this study are:

- To determine the pharmacokinetics (PK) of AZD1656 in diabetic patients with known or suspected COVID-19.
- To explore the effects of AZD1656 on immunophenotyping characteristics during COVID-19 infection in hospitalised diabetic patients.
- To explore the effects of AZD1656 on immunochemistry characteristics during COVID-19 infection in hospitalised diabetic patients.
- To explore whether AZD1656 affects the extent of any cardiac injury related to COVID-19 in hospitalised diabetic patients.

- To explore if ethnicity affects the clinical outcome of hospitalised diabetic patients with known or suspected COVID-19 treated with AZD1656 versus placebo.

- To explore if 25-hydroxyvitamin D levels at baseline affect the clinical outcome of hospitalised diabetic patients with known or suspected COVID-19 treated with AZD1656 versus placebo.

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1 Patient Numbers

This is a double-blind, randomised, study of AZD1656 versus placebo across a 21-day treatment period. Up to 150 adult patients will be eligible to participate in the study. Subjects that withdraw from the study after receiving treatment will not be replaced.

7.2 Inclusion Criteria

1. Male or Female.
2. Aged 18 and older.
3. Have either T1DM or T2DM.
4. Hospitalised with suspected or confirmed novel coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)) infection at time of enrolment, categorised as stage 3, 4 or 5 on the WHO Ordinal Scale for Clinical Improvement.
5. Blood glucose level at or above 4 mmol/L.
6. Able to take oral (tablet) formulation of medication.
7. Patient is able to provide written informed consent prior to initiation of any study procedures.

7.3 Exclusion Criteria

1. In the opinion of the clinical team, progression to intubation or mechanical ventilation is imminent and inevitable, within the next 24 hours, irrespective of the provision of treatments.
2. Patients admitted with primary suspected or proven Mycoplasma pneumoniae, Chlamydia pneumoniae and bacterial pneumonia, who acquired COVID-19 while hospitalized.
3. Treatment with immunomodulators or anti-rejection drugs within the last 3 months.
4. Pregnant or breast feeding.
5. Men, and women of child-bearing potential, unwilling to use highly effective contraception during their participation in the trial and for 2 weeks after study completion.*
6. Anticipated transfer to another hospital which is not a study site within 72 hours.
7. Known sensitivity to any of the study medication/placebo excipients (see section 9.3).
8. Prior dosing with AZD1656 on a previous clinical trial.
9. Patients admitted as a result of and receiving immediate treatment for an acute asthmatic attack, acute myocardial infarction, acute cerebrovascular event.
10. Any known non-COVID-19, non-diabetes related, serious condition which, in the opinion of the clinical team, makes the patient unsuitable for the trial.
11. Known history of drug or alcohol abuse within previous 12 months of screening.

12. Known history of HIV, hepatitis C or unresolved hepatitis B or severe liver disease.
13. Current or planned use of gemfibrozil or any other strong inhibitors of CYP2C8.
14. Current or previous participation in another clinical trial where the patient has received a dose of an Investigational Medicinal Product (IMP) containing small molecule treatment(s) within 30 days or 5 half-lives (whichever is longer) prior to enrolment into this study, or containing biological treatment(s) within 3 months prior to entry into this study.

*Highly effective contraception is considered to be using one of the following birth control methods:

- combined (estrogen and progestogen containing) hormonal contraception[1]
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - injectable
  - implantable[2]
- intrauterine device (IUD) [2]
- intrauterine hormone-releasing system (IUS) [2]
- bilateral tubal occlusion [2]
- vasectomised partner [2,3]
- sexual abstinence[4]

[1]Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception

[2]Contraception methods that in the context of the Clinical Trial Facilitation Group's (CTFG) 'Recommendations related to contraception and pregnancy testing in clinical trials' guidance are considered to have low user dependency.

[3]Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4]In the context of the CTFG guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

7.4 Participant Identification

Potential participants will be identified by the clinical team from those patients admitted to hospital with suspected or confirmed COVID-19.

7.5 Informed Consent

For each study patient, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the Principal Investigator (PI) or one of his associates will explain orally and in writing the nature, duration, purpose of the study, and the action of the study drug in such a manner that the patient is aware of the potential risks, inconveniences, or adverse effects that may occur. The patients will be provided ample time to review the information and ask questions. They will be informed that their medical records may be reviewed by appropriately qualified monitors of the Sponsor or Sponsor Representative, and by auditors or regulatory authorities to ensure the accuracy of the details recorded as part of the study. They will be informed that they may withdraw from the study at any time without prejudice to further treatment. They will receive all information that is required by local regulations and ICH GCP guidelines. The consent process must be fully documented in the patient's source medical records. A copy of the signed consent form must be provided to the patient and the original must be retained at site.

7.6 Responsibility for the Informed Consent Process

The PI retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of GCP and the Declaration of Helsinki. If delegation of consent occurs, then details must be provided in the Site Delegation Log.

7.7 Consent Considerations

The right of a patient to refuse participation without giving reasons will be respected.

Where a patient is required to re-consent, for example if during the trial new Research Safety Information becomes available, or following an amendment that affects the patient, or new information needs to be provided to a patient, it is the responsibility of the PI to ensure this is done in a timely manner.

7.8 Vulnerable Participants' Considerations

The PI takes responsibility for ensuring that all subjects are protected and participate voluntarily in an environment free from coercion or undue influence.

7.9 Patient Withdrawal Criteria

Patients may withdraw from the study at any time without stating a reason and without prejudice to further treatment. The Investigator may withdraw a patient from the study and discontinue study treatment and assessments at any time. If a patient is withdrawn at any time after entering the study the Investigator will make every effort to see the patient and complete the final visit assessments.

Early withdrawal of any patient who has given informed consent to participate will be recorded including the reason for withdrawal. The primary reason for a patient withdrawing prematurely will be selected from the following standard categories:

- **Failed to meet enrolment criteria after providing informed consent**
- **Withdrawal of Consent**: The patient desired to withdraw from further participation in the study. The patient is not obliged to provide any reason for withdrawal of consent, but where a reason is given this will be recorded on the electronic Case Report Form (eCRF).
- **Lost to Follow-Up**: The patient leaves hospital without being formally discharged and study personnel were unable to contact the patient.

The trial may be terminated by the Sponsor at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the trial, practical reasons (including slow enrolment), or for regulatory, medical, scientific or ethical reasons. Should this be necessary, patients must be seen as soon as possible and treated as a prematurely discontinued patient. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The Independent Ethics Committees (IECs) must be informed of the early termination of the trial.

8. STUDY DESIGN

8.1 Primary Endpoint

Clinical Improvement measured as the percentage of subjects at Day 14 who are in categories 1-3 according to the World Health Organization (WHO) 8-point Ordinal Scale for Clinical Improvement, comparing AZD1656 treatment to placebo.

8.2 Secondary Endpoints

- Clinical Improvement measured as the percentage of patients categorised at each severity rating on the WHO 8-point Ordinal Scale at Day 7, Day 14 and Day 21 versus baseline, comparing AZD1656 treatment with placebo.
- Degree of glycaemic control as measured by the need to increase baseline medication requirements or the need to add additional diabetic medications to maintain appropriate blood glucose levels in patients receiving AZD1656 compared with placebo.
- Proportion of Treatment Emergent Adverse Events (TEAEs) leading to study drug discontinuation in patients receiving AZD1656 compared with placebo.
- Proportion of Serious Adverse Events (SAEs) in patients receiving AZD1656 compared with placebo.
- Time from hospital admission to hospital discharge (in hours) in patients receiving AZD1656 compared with placebo.
- Time from hospital admission to receiving intubation/mechanical ventilation in patients receiving AZD1656 compared with placebo.
- Mortality Rate in patients receiving AZD1656 compared with placebo.

8.3 Exploratory Endpoints

- Plasma AZD1656 levels during first 7 days of treatment in patients receiving AZD1656 compared with placebo.
- Immunophenotyping panel to be conducted by Flow Cytometry: between group comparison (AZD1656 versus placebo) of levels of T, B and NK cells (including specific Treg and memory T cell populations); monocyte, neutrophil and eosinophil numeration to include activation markers for neutrophils (CD11b) and Monocytes subsets (CD14/CD16 identification including 6-Sulfo LacNAc(SLAN)).

- Immunochemistry panel to be conducted using the MSD U-Plex multiplex assay for assessment of the following biomarkers: G-CSF, GM-CSF, IL-1B, IL-4, IL-6, IL-8, IL-10, IL-12, and MIP-1a.

- Measurement of hsTroponin and NTproBNP to determine extent of cardiac injury in patients receiving AZD1656 compared with placebo.

- Measurement of 25-hydroxyvitamin D levels before treatment to determine whether there is any correlation between Vitamin D level and clinical outcomes.

- Correlation of clinical outcomes with patient ethnicity.

8.4 Study Design

This is a Phase II, randomised, placebo-controlled, double blind clinical trial to assess the safety and efficacy of AZD1656 on the alleviation of cardiorespiratory complications in diabetic patients hospitalised with suspected or confirmed COVID-19. All patients will receive usual care plus either AZD1656 or placebo.

In consideration of the appropriate timing for assessment of the primary endpoint, Docherty *et al.* (2020) evaluated features and outcomes for 20,133 patients admitted to hospital in the UK and reported that the median duration of COVID-19-related symptoms prior to hospitalisation was 4 days. Forty-one percent of patients were discharged, 26% died and the remainder were still receiving care at the timepoint cut off for the study, which was 14 days post admission. Docherty *et al* (2020) further reported that 80% of patients in the cohort w o died did so within 14 days. Guan *et al* (2020) further reported in a Chinese cohort of 1099 patients (7.5% diabetic) that the median duration of symptoms prior to admission was 4 days and that the median length of hospital stay was 12 days (interquartile range 10-14 days). Based on these data, a 14 day timepoint to assess the primary endpoint appears appropriate since by this time the majority of patients will have either improved to be discharged or will have progressed to ICU admission, mechanical ventilation or death. Analyses of outcomes at other timepoints e.g. Day 7 and Day 21 will also be undertaken as secondary endpoints.

It is expected that 165 patients will be screened to randomise 150 patients.

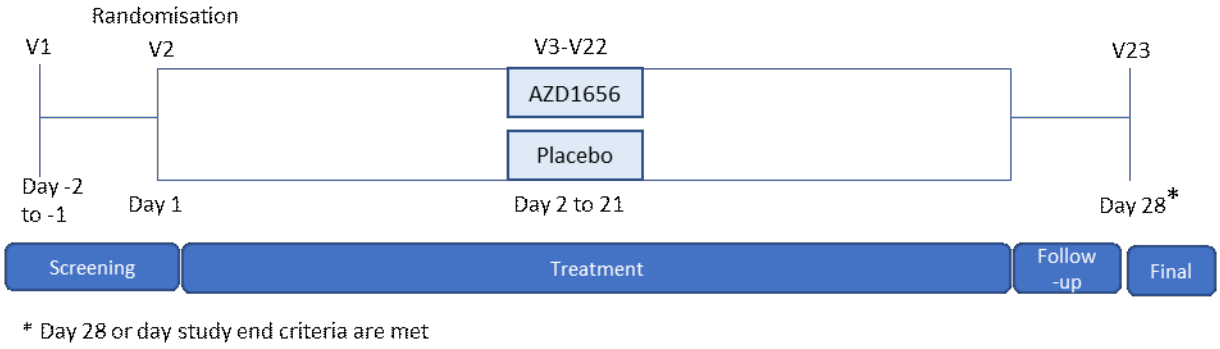
The study will have 3 phases (see Figure 1, Study Design)**:**

- Screening/ Randomisation (Day -2 to 1, V1 to V2)
    - Patients will undergo a Screening Visit (V1) and Randomisation Visit (V2) to evaluate their eligibility to participate in the study and to commence study treatment (Day 1).
- Double-Blind Treatment (Day 1 to Day 21, V2-V22)
    - Patients will receive study treatment for up to a maximum of 21 days, or until date of discharge from hospital, or date of mechanical ventilation or date of death, whichever comes first.

- Safety Follow-up Visit (7 days after completion of study treatment)
    - Patients will have a final visit 7 days after completion of study treatment to capture any new safety information or changes to concomitant medication. This will be at Day 28 for those completing the full treatment period of 21 days or 7 days after treatment discontinuation.
    - Following this visit the patients are discharged from the study.

Procedures should be undertaken as listed in the schedule (see section 10) until study end criteria are met with a final assessment on that date (Visit 23).

Figure 1, Study Design



* Day 28 or day study end criteria are met

8.5 Safety Review Committee

A Safety Review Committee (SRC) consisting of clinical and other experts will be established by the Sponsor to review safety findings during the study and to help ensure subject safety. The SRC will form a Charter prior to their first data review; that Charter will include a description of the Committee, the Members and their responsibilities, the data to be reviewed, the timing of the reviews, and considerations for any statistical items (e.g. data displays) that may be required for the data reviews. Data included for SRC review will be subject to monitoring and/or Medical Monitor review to confirm data quality.

The SRC will meet at intervals during the trial to review safety and tolerability data for the total study population (including frequency, severity and seriousness of adverse events; concomitant medication data; WHO Ordinal Scale data). The SRC review of the study treatment assignments will be blinded. The Sponsor will also remain blinded to the treatment assignments. The SRC will make a recommendation to either proceed with the protocol with no modification or may suggest changes to the protocol. Based on the results of their data reviews, the SRC will submit its recommendations in written form to the Sponsor who is responsible for responding to the recommendations of the SRC and to take appropriate action.

9. STUDY MEDICATION AND ADMINISTRATION

9.1 Study Medication Manufacture and Supply

IMP: AZD1656 film-coated tablets for oral administration and matching placebo.

The tablets were manufactured by Patheon.

Patheon UK Limited.
151 Brook Drive
Milton Park
Abingdon
OX14 4SD
United Kingdom

The tablets will be packed and labelled by Fisher Clinical Services.

Fisher Clinical Services UK Limited
Langhurstwood Road
Horsham
RH12 4QD
United Kingdom

The packed and labelled tablets will be shipped securely from Fisher to the clinical trials pharmacy unit at each investigational site. All medicinal products left over after study completion will be returned to Fisher for destruction.

Note that a separate Pharmacy Manual will be produced to set out the requirements for the IMP management aspects of the trial.

9.2 Dispensing of IMP

Dispensing guidelines will be provided in the Pharmacy Manual, which will be in place within each pharmacy. Each member of pharmacy staff involved in the study must be listed on the study specific trial delegation log. When IMP is dispensed the pharmacy dispensing log will be signed and a patient accountability log completed to ensure appropriate IMP tracking and accountability.

9.3 Selection of Doses in the Study

AZD1656 50 mg tablets will be supplied in plastic bottles. Patients randomised to active treatment will receive 100 mg twice a day (BID) with food, resulting in a total daily dose of 200 mg.

The selected dose of 200 mg/day has been shown to be well tolerated and effective at reducing glucose levels in diabetic patients in prior clinical studies. The selected dose is at the upper end of the range that has been previously studied but will be given for a shorter duration than previously studied. In prior trials, the highest repeated doses were 300 mg daily for 8 days and 200 mg daily for

up to 6 months. Single oral doses of AZD1656 have also been studied up to 450 mg. The 200 mg/day dose is also considered appropriate to test the hypothesis of an immune-modulatory mode of action, since the enzymatic mechanism of action (via activation of glucokinase) is the same for both the glucose lowering effect and the Treg migratory effect of the drug. As such the pharmacodynamic effect of AZD1656 on Treg migration activity is expected to be the same as that required for glucose lowering (there is no evidence in humans to suggest otherwise).

The film-coated tablet formulation contains AZD1656, cellulose microcrystalline, magnesium stearate, mannitol, sodium laurilsulphate, sodium starch glycolate, hydroxypropyl methylcellulose, macrogols and titanium dioxide.

Matching placebo tablets contain cellulose microcrystalline, sodium stearyl fumarate, hydroxypropyl methylcellulose, macrogols and titanium dioxide.

9.4 Allocation to Treatment

This is a double-blind placebo-controlled study: both the patient and the study team will be blinded to the treatment intervention.

The treatment the patient is randomised to is determined by a randomisation scheme which will automatically be assigned by the Interactive Response Technology (IRT) (Medidata RAVE Randomization and Trial Supply Management (RTSM)).

Subjects will be randomised in a 1:1 manner to either AZD1656 or placebo for a maximum dosing period of 21 days.

9.5 Study Treatment and Administration

AZD1656 or placebo will be administered twice per day, at approximately the same time each day with or just after meals, by oral route. Due to the short tmax of AZD1656, the patient must not take their medication without food. Patients will receive treatment for up to 21 consecutive days as in-patients.

Missed doses will be permitted: if a patient misses a dose they should take their next dose at the usual time. Any missed doses must be recorded in the patient's notes.

9.6 Duration of Patient Participation

The maximum duration of patient participation in this study is 30 days, to comprise up to 2 days for Screening, 21 days of treatment and 7 days of follow-up (if patient is not discharged before Day 28).

Once a decision has been made to discharge a patient from hospital, study medication should be stopped and their usual diabetes medication continued with any necessary adjustments as per usual care. If a patient is transferred to another hospital during the study, study medication should be

stopped and their usual diabetes medication continued with any necessary adjustments as per usual care.

9.7 Study Treatment Discontinuation Criteria

Patients will receive study treatment for up to a maximum of 21 days, or until date of discharge from hospital, or date of mechanical ventilation or date of death, whichever comes first. The primary reason for a patient discontinuing treatment prematurely will be selected from the following standard categories:

- **Adverse Event (Adverse Reaction)**: Clinical events occurred or laboratory results are reported that in the medical judgment of the Investigator are grounds for discontinuation in the best interests of the patient.

- **Intubation/Mechanical Ventilation**: any patients who require intubation/mechanical ventilation will be discontinued at the point the intervention is required, since the patient will be unable to take study medication orally.

- **Protocol Violation**: The patient failed to adhere to the protocol requirements, at the Investigator's discretion e.g. the patient requires to start taking a medication from the prohibited medications list (section 9.10.1).

- **Pregnancy**: The subject has either a positive urine or serum pregnancy test during the study.

- **Hypoglycaemia**: that occurs despite removal of other glucose-lowering drugs: e.g. repeated events of minor hypoglycaemia defined as:

  − repeated episodes with symptoms and confirmed low glucose (<3.9 mmol/L)

  − repeated asymptomatic episodes with low glucose (<3.9 mmol/L)

  - repeated episodes with symptoms suggestive of hypoglycaemia when glucose was not measured.

  If a patient has any episodes of hypoglycaemia, their diabetic medications will be altered as per standard of clinical care.

- **One event of major hypoglycaemia regardless of any other diabetes drugs, as defined by the American Diabetes Association (ADA) as**: Requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose level

- **Introduction of gemfibrozil or other strong inhibitors of CYP2C8 (prohibited medication).**

- **Other:** The patient was terminated for a reason other than those listed above, such as termination of study by Sponsor.

9.8 Treatment Accountability and Compliance Checks

The Investigator has overall responsibility for accountability for study treatment that is received at site and dispensed to study patients. In accordance with regulatory requirements, the Investigator or designated site staff must document the amount of IMP dispensed and/or administered to study subjects, the amount unused by study subjects, and the amount received from and returned to the Sponsor (or representative) when applicable. Product accountability records must be maintained throughout the course of the study and IMP must be stored in a locked, secure storage facility with access limited only to those individuals authorised to dispense the IMP. Clinical supplies not to be used for any other purpose than that stated in the protocol.

Used study medication bottles to be retained at site for study treatment accountability until final reconciliation can be conducted.

9.9 Treatment Blinding Code

All participants will be centrally assigned to randomised treatment using an IRT system. Before the study is initiated, the log in information & directions for the IRT will be provided to the site. Study treatment will be dispensed at the study visits as summarised in the Schedule of Assessments (section 10). Returned medication will not be re-dispensed to the participants.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Medical Monitor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the Medical Monitor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

If the blinding is prematurely broken, it is the responsibility of the Investigator to promptly document and explain any unblinding to the Medical Monitor.

9.10 Permitted Concomitant Medications

Any medication or vaccine (***including over-the-counter or prescription medicines, vitamins, and/or herbal supplements***) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

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

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

All treatments, including oxygen, which the patients are receiving as part of their usual care during their hospital admission will be recorded as concomitant medications. Note that the use of dexamethasone will not be contraindicated as part of usual care (if clinically indicated).

9.10.1 Prohibited Concomitant Medication

Given the theoretical increase in AUC (but not Cmax) with gemfibrozil, any patient who is currently taking this agent or other strong inhibitors of CYP2C8 will be excluded from the study.

10. STUDY SCHEDULE

Study procedures and their timing are summarised in the Schedule of Assessments (SoA). Protocol waivers or exemptions are not permitted.

Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g. SARs-CoV-2 PCR test, Chest X-ray, CT Scan, etc.) and obtained before signing of the ICF may be utilised for screening or randomisation purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (i.e. within 2 days of randomisation).

Schedule of Assessments

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Visit Name	Screening	Randomisation	**Patient is on study treatment for up to 21 days, or date of discharge from hospital, or date of mechanical ventilation or date of death, whichever comes first. Procedures should be undertaken as listed in the schedule until study end criteria are met with a final assessment on that date (Visit 23)**																				Safety Follow-up[5]
Day	Day -2 or -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21 or day study end criteria are met[3]	Day 28 or 7 days after study end criteria are met
Obtain written informed consent	+																						
Demographic data	+																						
Medical history[1]	+																						
Inclusion/exclusion criteria	+																						
Urine pregnancy test (females)	+																					+	
Physical Examination	+																						
Vital signs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
12-Lead ECG[2]	+																						
Clinical Chemistry[2]	+	+							+							+						+	
Haematology[2]	+	+							+							+						+	
Urinalysis[2]	+																						
hsTroponin (hs-CTNT) sample[2]	+																					+	
NT-proBNP sample[2]	+																					+	
SARs-CoV-2 PCR test[2, 6]	+																						
HbA1c sample[7]		+																					
25-hydroxyvitamin D		+																					
Randomisation		+																					
Patient WHO clinical status record	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Immunophenotyping blood sample[7]		+							+			+										+	
Immunochemistry blood sample[7]		+							+			+										+	
PK sample[7]			+		+				+														
Clotting Factor Sample [7, 8]		+							+														
Study Drug/placebo Administration		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Adverse Events review		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Visit Name	Screening	Randomisation	**Patient is on study treatment for up to 21 days, or date of discharge from hospital, or date of mechanical ventilation or date of death, whichever comes first. Procedures should be undertaken as listed in the schedule until study end criteria are met with a final assessment on that date (Visit 23)**																				Safety Follow-up[5]
Day	Day -2 or -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21 or day study end criteria are met[3]	Day 28 or 7 days after study end criteria are met
Concomitant /treatment record[4]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Diabetic medication review	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	

[1] If clinically indicated, include record of X-ray/ CT scan if conducted at screening or at any point during the study.
[2] Frequency of testing to be clinically determined outside of specified timings in the schedule of events. If these tests are undertaken at more frequent intervals, only results that are out of range AND considered clinically significant are to be recorded in the eCRF.
[3] Visit timepoint will occur at death, discharge from hospital or up to 21 days after randomisation (whichever is sooner).
[4] To include usual care treatments including details of any respiratory support provision.
[5] To be conducted as in-patient if patient still hospitalised or via telephone call for those discharged.
[6] Patient can be randomised and start study treatment before SARs-CoV-2 PCR test result is available. Please see section 10.4.3.
[7] Samples can be collected +/- 1 day of the scheduled day above.
[8] Clotting factor sample will be collected if patient provides additional consent and if the site is able to store the sample at -70°C.

10.1 Efficacy Assessments

All assessments will be performed by the Investigator or appropriately delegated and trained personnel. Planned timepoints for all efficacy assessments are provided in the SoA.

10.1.1 WHO 8-Point Ordinal Scale

The WHO 8-point Ordinal Scale (Appendix 1) will be used to assess the impact of treatment with AZD1656 of diabetic patients with COVID-19 versus those treated with placebo. The primary endpoint in this trial will be the proportion of patients treated with AZD1656 in WHO categories 1-3 at Day 14 compared to placebo. The highest score measured each day will be recorded for all patients from Visit 1 to the Final Visit inclusive.

10.1.2 Glycaemic Control

The effectiveness of AZD1656 in reducing blood sugar over short durations of treatment has already been demonstrated. Given the short maximum treatment period of 21 days, the usual method of monitoring the level of diabetic control via HbA1c over time is not appropriate. However, a daily record of diabetic medication and doses throughout the study will be recorded in the eCRF. Blood sugars will also be measured, as determined by usual standard of care for a hospitalised diabetic patient with infection. By comparing the AZD1656 and control groups it will be possible to determine whether the requirement to increase diabetic medication to obtain control of glucose levels is reduced in the AZD1656 treated group compared to placebo.

10.1.3 Time from Hospital Admission to Hospital Discharge

Hospital admission and hospital discharge times will be recorded in the eCRF for all applicable patients to assess time from hospital admission to hospital discharge.

10.1.4 Time from Hospital Admission to Receiving Intubation/ Mechanical Ventilation

Hospital admission time and the time a patient receives intubation/mechanical ventilation will be recorded in the eCRF for all applicable patients.

10.2 Safety Assessments

10.2.1 Medical History

Patients' clinically relevant medical history will be collected and recorded in the eCRF. The results of any clinically indicated test procedures, e.g. X-ray, CT scan, ultrasound, performed as part of usual care should be recorded at screening or at any point during the study.

10.2.2 Adverse Events

Adverse events will be assessed and recorded in the eCRF for each patient during the trial. See section 11 for further details.

10.2.3 Physical Examination

A full physical examination will be conducted at the Screening visit (V1). Height and weight may be taken verbally from the patient if it is not possible for the patient to stand. This will be completed by the Investigator or a delegated physician.

A full physical examination is composed of a review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose and throat
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Musculoskeletal
- Neurological

10.2.4 Vital Signs

Vital signs will be measured as per the SoA with patients after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, oxygen saturation using pulse oximeter and respiratory rate.

10.2.5 Electrocardiograms

12-lead ECGs will be performed as outlined in the SoA according to local hospital standard practice. If ECGs are undertaken at more frequent intervals, only results that are out of range AND considered clinically significant are to be recorded in the eCRF.

10.2.6 Clinical Safety Laboratory Assessments

All clinical safety laboratory assays will be performed according to the study site laboratory's normal procedures. Reference ranges will be supplied by the study site laboratory and will be used to assess the laboratory data for clinical significance and out of range changes.

Clinical Chemistry

A clinical sample will be collected as outlined in the SoA. Clinical chemistry blood samples can be drawn with the subject in either a fasting or non-fasting state according to local practice. However, if a sample needs to be repeated, the subsequent sample should be drawn from the subject in the same fasting/non-fasting state.

The clinical chemistry analysis will include, sodium, potassium, urea, creatinine, calcium, phosphate, total protein, bilirubin, alkaline phosphatase, LDH, ALT, AST, GGT and glucose.

Frequency of testing and those analytes tested are to be clinically determined outside of specified timings in the SoA. If these tests are undertaken at more frequent intervals or other parameters tested (e.g. blood gas monitoring), only results that are out of range AND considered clinically significant are to be recorded in the eCRF.

25-hydroxyvitamin D

Vitamin D is known to be important for immune function including increasing the number of Tregs (for example see meta-analysis by Fisher *et al*. (2019)), so vitamin D deficiency may reduce the efficacy of AZD1656. Measuring vitamin D status will allow any such correlation to be assessed, which would inform future protocols. It will also allow research into other effects that vitamin D deficiency has on immune parameters during COVID-19 as immunophenotyping and immunochemistry tests will be run as part of ARCADIA. Vitamin D deficiency is associated with worse COVID outcomes and Vitamin D deficiency is higher in Black, Asian and minority ethnic (BAME) patients in the UK. Hence measuring vitamin D status may additionally aid understanding of some of the disparities that have been observed with higher mortality rates from COVID-19 amongst BAME patients.

Vitamin D levels will be measured at the Randomisation visit (Day 1) to determine whether there is any correlation between Vitamin D level and clinical outcomes.

Haematology

A full blood count with differential should be collected as outlined in the SoA. This should include red blood cell count, platelets, white blood cell count (differential: eosinophils, basophils, neutrophils, lymphocytes, monocytes) haemoglobin and haematocrit. Frequency of testing to be clinically determined outside of specified timings in the SoA. If these tests are undertaken at more frequent intervals, only results that are out of range AND considered clinically significant are to be recorded in the eCRF..

HbA1c

An HbA1c sample should be obtained at Day 1 (V2) to determine the level of glycaemic control on entry to the study.

Urinalysis

Urinalysis will be performed by dipstick and documented in source documents as outlined in the SoA. Abnormal results should be investigated further, as clinically needed. Frequency of testing to be clinically determined outside of specified timings in the SoA. If these tests are undertaken at more frequent intervals, only results that are out of range AND considered clinically significant are to be recorded in the eCRF.

Pregnancy Test

For female patients of child-bearing potential a urine pregnancy test should be obtained at the Screening Visit (V1) and Final Visit (V22).

10.2.7 Chest X-Ray or Chest CT Scan

If clinically indicated, a Chest X-Ray or Chest CT scan will be performed according to local hospital standard practice and details recorded in the eCRF.

10.3 Pharmacokinetic Assessments

Whole blood samples will be collected for measurement of plasma concentrations of AZD1656 as specified in the SoA. Instructions for the collection and handling of samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample and the time of last study drug administration will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

10.4 Other Assessments

10.4.1 hsTroponin (hs-CTNT)

A blood sample for analysis of hsTroponin (hs-CTNT) will be collected at Screening (V1) and the Final Visit to determine the extent of cardiac injury in patients receiving AZD1656 versus placebo. Frequency of testing to be clinically determined outside of specified timings in the SoA. If these tests are undertaken at more frequent intervals, only results that are out of range AND considered clinically significant are to be recorded in the eCRF.

10.4.2 NT-proBNP

A blood sample for analysis of NT-proBNP will be collected at Screening (V1) and the Final Visit to determine the extent of cardiac injury in patients receiving AZD1656 versus placebo. Frequency of testing to be clinically determined outside of specified timings in the SoA. If these tests are undertaken at more frequent intervals, r only results that are out of range AND considered clinically significant are to be recorded in the eCRF.

10.4.3 SARs-CoV-2 PCR test

Nasopharyngeal swabs will be taken for SARs-CoV-2 PCR testing at the Screening Visit (V1) to confirm SARs-CoV-2 infection unless a test has been conducted within the previous 48 hours whose results are available. If the SARs-CoV-2 PCR test is negative, but the Investigator believes that the patient's clinical picture strongly supports SARs-CoV-2 infection, the patient will continue on study. If a SARs-CoV-2 PCR test was negative and the patient entered the study based on a clinical diagnosis but the clinical condition of the patient changes to such an extent that the Investigator no longer considers the symptoms to be COVID-19 related, the patient should be withdrawn from the

study. The frequency of testing is to be clinically determined and the results of any additional SARs-CoV-2 PCR tests are to be recorded in the eCRF.

10.4.4 Immunophenotyping

A blood sample for Immunophenotyping analysis will be taken at Day 1 (V2), Day 8, Day 11 and Day 21 (or day study end criteria are met). An Immunophenotyping panel to be conducted by Flow Cytometry to perform a group comparison (AZD1656 versus placebo) of levels of T, B and NK cells (including specific Treg and memory T cell populations); monocyte, neutrophil and eosinophil numeration to include activation markers for neutrophils (CD11b) and Monocytes subsets (CD14/CD16 identification including SLAN).

10.4.5 Immunochemistry

A blood sample for Immunochemistry analysis will be taken at Day 1 (V2) , Day 8, Day 11 and Day 21 (or day study end criteria are met). Samples will be prepared according to the study laboratory manual for central laboratory assessment of the following biomarkers: G-CSF, GM-CSF, IL-1B, IL-4, IL-6, IL-8, IL-10, IL-12, and MIP-1a. The MSD U-Plex multiplex assay will be used for this assessment.

10.4.6 Demographics

Patients' demographics details will be collected in the eCRF including ethnicity.

10.4.7 Clotting Factor Analysis

In order in investigate the impact of clotting factors on patient outcome (such as von Willebrand's factor antigen), a small blood sample will be taken on Day 1 (V2) and on Day 8 and frozen at -70°C on site for future analysis (only sites with the ability to store samples in a -70°C freezer should collect this sample). Patients will be given the option to 'opt-in' to this additional assessment during the consent process.

11. ADVERSE EVENTS

Adverse events may be volunteered spontaneously by the patient, or discovered as a result of general, non-leading questioning. All adverse events should be recorded in the Case Report Form.

11.1.1 Adverse Events that Do Not Require Reporting

Emergence or worsening of symptoms or test parameters clearly associated with the clinical course of the underlying COVID-19 infection do not need to be recorded as adverse events. General deterioration or improvement in clinical status will be recorded as part of the primary outcome measure of the study using the WHO Ordinal Scale. Examples that would not be considered adverse events include, but are not limited to, neutropenia, high alkaline phosphatase levels, abnormal appearance in Chest X-ray, increased requirements for oxygen, introduction of continuous positive airway pressure (CPAP), or worsening shortness of breath.

Pre-existing conditions will be captured in the Medical History, and only clinically significant exacerbation or worsening of symptoms (other than those clearly associated with the clinical course of the underlying COVID-19 infection) will be reported as an AE/SAE.

Planned hospital admissions and/or surgery for pre-existing conditions will not be considered AEs/SAEs.

Death due to progression of disease (COVID-19) will not be reported as an SAE as it will be recorded as an outcome.

11.1.2 Definitions

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. See section 11.1.1 for adverse events that do NOT need to be recorded.

Adverse Drug Reaction (ADR)

All events considered to be untoward and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Serious Adverse Event (SAE)

The Investigator is responsible for reporting all SAEs to the Sponsor, or its designated representative, immediately (within 24 hours of awareness). Any immediate reports should be followed promptly by detailed, written reports. An SAE is an adverse event that at any dose:

- Results in death
- Is life-threatening (i.e. the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation (see explanation below)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is considered to be an important medical event

Based upon medical and scientific judgment, important medical events that may not be immediately life-threatening, or result in death or hospitalisation, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above may be considered a serious adverse event.

Hospitalisations are defined as initial or prolonged admissions that include an overnight stay. Since all patients participating in this trial are hospitalised throughout the trial, only those events resulting in prolongation of hospitalisation not associated with the underlying COVID infection may be considered as SAEs.

Pregnancy

Pregnancy itself is not considered an AE. However, any pregnancy complication, spontaneous or elective abortion (for medical reasons), still birth, neonatal death, or congenital anomaly will be recorded as an AE or SAE.

Any pregnancy that occurs during the course of the study or the follow-up period to a female study participant or to the female partner of a male subject, will be documented and reported by the Investigator within 24 hours of awareness. The pregnancy should be followed up until term (by Investigators) and if any Adverse Event occurs in conjunction with the pregnancy, this will be documented, assessed for seriousness, severity and causal relationship, and reported accordingly. The anticipated date of birth or termination of the pregnancy should be provided at the time of the initial report.

Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

The term 'severity' is used to describe the intensity of a specific event. This has to be distinguished from the term 'serious'.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse event that is suspected to be related to the administered medicinal product and the nature or severity of which is not consistent with applicable product information.

A serious adverse reaction, the nature or severity of which is not consistent with applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

11.1.3 Assessment of Severity and Causality

Severity

The severity (intensity) of each adverse event will be classified as:

- **Mild** Awareness of sign or symptom, but easily tolerated
- **Moderate** Sign or symptom causes discomfort, but does not interfere with normal activities
- **Severe** Sign or symptom of sufficient intensity to interfere with normal activities

Causality

The likely relationship of each adverse event to the medicinal product will be assessed according to the definitions below:

Unrelated

- Time to drug intake that makes a relationship improbable
- Disease or other drugs provide more plausible explanations
- There are no facts or arguments to suggest a causal relationship

Related

- Plausible time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to study drug withdrawal/ rechallenge clinically reasonable (if data available)
- There are facts or arguments to suggest a causal relationship

11.1.4 Outcome Categorisation

All AEs should have an outcome recorded, which should be updated if it changes during the reporting period. The possible outcomes should be:

- Fatal
- Recovered/Resolved
- Recovering/Resolving
- Recovered/Resolved with sequalae
- Not recovered/not resolved

For fatal outcomes, every effort should be made to ensure source documentation (e.g. autopsy report, death certificate) to confirm the cause of death. In case this is not possible, the Investigator will apply medical judgement to identify and report the most likely cause of death. Only one event should be reported as having a fatal outcome, reporting the event which is considered to be the immediate cause of death.

11.1.5 Adverse Event Reporting

St George Street Capital is required to expedite reports to worldwide regulatory authorities of Serious Adverse Events, Serious Adverse Drug Reactions or Suspected Unexpected Serious Adverse Reactions (SUSARs) in line with the relevant legislation, including the European Commission Clinical Studies Directive (2001/20/EC).

All AEs (serious and non-serious) and any reports of pregnancy (either in a female participant or the female partner or a male participant) must be recorded by the Investigator from the time when patient signs the Informed Consent until 7 days after treatment discontinuation.

All AEs will be recorded on the eCRF and assessed by the Investigator for seriousness (Section 11), severity (Section 11.1.3), and causality (Section 11.1.3).

Refer to Section 11.1.1 for adverse events that do not require reporting.

Any Serious Adverse Event will be reported by the Investigator immediately (within 24h) by mail or fax to:

Email: safetyreporting@syneoshealth.com
Fax: +1 877 464 7787

For each Serious Adverse Event the following information should be collected and reported via SAE form (no hospital or patients' related original documents to be shared):

- Detailed patient data including medical history and concomitant medications
- Detailed information about study treatment including timing and the dosing regimen
- Exact documentation of the event including time of onset, signs and symptoms, relevant investigations, treatments applied, event outcome
- Action taken with study treatment and the effects of the dechallenge and rechallenge

- Details of the clinical course and the outcome of the event
- Any data contributing for the causal relationship assessment of the SAE

Each Adverse Event should be followed up until final outcome. Events that are not resolved by the end of the study or patient's death will be recorded as ongoing.

Assessment of event seriousness, severity and causality will be performed and reported by the Investigator with the initial notification. The assessment should be based on the available information even if insufficient and can be updated when new information is available.

Once the event is received by the Sponsor or Sponsor representative, the Sponsor or Sponsor representative's physician will assess causality and expectedness based on the available information and the applicable reference safety information. The causality assessment given by the Investigator will not be downgraded by the Sponsor. If the Sponsor disagrees with the Investigator's causality assessment, the opinion of both the Investigator and the Sponsor will be provided with the report.

Abnormal findings from laboratory tests, ECG records, imaging investigations and patients' vital signs will be assessed by the Investigator and if considered clinically significant and satisfying the definition for an Adverse Event, will be reported accordingly. If abnormal investigational findings are associated with clinical symptoms, then the diagnosis should be reported as an AE rather than reporting the abnormal finding.

The Investigator will apply medical judgement and whenever possible will report a diagnosis as an event term, rather than individual signs and symptoms. However, if at the time of reporting the presented signs and symptoms cannot be medically characterised as a single diagnosis or medical concept, these can be recorded as Adverse Events. When the diagnosis is subsequently established, all previously reported AEs based on signs and symptoms will be nullified and replaced by a single AE report with onset date corresponding to the starting date of the first symptom.

Occurrences that are secondary to other events (clinical sequelae) will not be reported separately but identified by their primary cause. As an exception, a severe or serious secondary event, or a medically significant secondary occurrence that is separated in time from the initiating event, will be reported as an independent Adverse Event.

Any occurrence of overdose will be reported as an AE. Any signs or symptoms resulting from an overdose will also be recorded as AEs and assessed by the Investigator for seriousness, severity, and causality.

Death is considered an outcome and is to be avoided as an event term. The Investigator will identify the event or condition that caused the patient's death and will report accordingly as an event with fatal outcome. Only one AE will be reported as having fatal outcome. In case the death is attributed to progression of the baseline disease, the AE term should be reported as Disease Progression.

All Investigators will receive a safety letter notifying them of relevant SUSAR reports. In accordance with the European Commission Directive 2001/20/EC, St George Street Capital or their

appropriately qualified designee will notify the relevant Ethics Committees in concerned Member states of applicable SUSARs as individual notifications or through a periodic line listing.

St George Street Capital or their appropriately qualified designee will submit to the regulatory authorities all safety updates and periodic reports, as required by applicable regulatory requirements.

11.1.6 Notification of AEs of Special Interest

There are no Adverse Events of Special Interest for this trial.

11.1.7 Urgent Safety Measures

The PI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety. The measures can be taken immediately, however, it is the responsibility of the PI to attempt, where possible, to discuss the proposed measures with the Sponsor and Medical Advisor at the MHRA (via telephone) prior to implementation. If not possible to discuss prior to implementation, the Sponsor must be informed as soon as possible (same day) of the measures being taken in order that the Sponsor can inform both the MHRA and Independent Ethics Committee in writing within 3 days of the urgent safety measure being taken.

12. STATISTICAL CONSIDERATIONS

Details of all planned analyses will be specified in a separate statistical analysis plan (SAP) which will be finalised prior to hard-lock of the study database. The SAP will contain details of all the analyses including specifications for all tables, listings and figures. The SAP will include the definition of major and minor protocol deviations and the link of major protocol deviations to the analysis sets. All statistical programming will be performed using SAS software version 9.4 or higher.

12.1 Estimated Sample Size

Approximately 165 patients will be screened to achieve 150 randomly assigned patients to AZD1656 or placebo for an estimated total of 75 evaluable patients per group. Approximately 35 trials sites in the UK, Czech Republic and Romania will recruit the 150 randomised patients.

A two group χ^2 test with a 5% two-sided significance level will have 76.74% power to detect the difference between a placebo proportion of 0.6 and an AZD1656 proportion of 0.8 when the sample size is 150 (75/group). In the case that the portion of placebo patients meeting WHO categories 1-3 or live discharge at Day 14 is higher (0.65), then the power to find a similar 20 percentage point increase would be 81.4%.

12.2 Study Populations

Full Analysis Set (FAS)
The FAS or intention-to-treat population includes all randomised patients who receive at least one dose of assigned treatment. Following the intent-to-treat principle, patients will be analysed as randomised. This will be the primary analysis set for primary and key secondary endpoints.

Per-Protocol Set (PPS)
The PPS includes all patients of the FAS without major protocol deviations. Patients will be excluded from the PPS for the following reasons:

- Any major deviation from exclusion / inclusion criteria.
- Other major protocol deviations as identified at the blinded data review meeting.

Patients to be excluded from the PPS will be identified and reviewed at the blinded data review meeting held before unblinding of the study.

The PPS will be used for sensitivity analyses for primary and key secondary analyses.

Safety Set (SAF)
The SAF, also known as “treated population”, includes all patients who received at least one dose of IMP and had at least one post-baseline safety assessment (where the statement that a patient had no AE on the AE eCRF constitutes a safety assessment). The assignment of patients to the treatment groups will be as actually treated.

The SAF is the primary analysis set for all safety analyses.

Pharmacokinetic Analysis Set
The PK analysis set includes all patients who received a single dose of AZD1656 and have at least one post-dose PK measurement.

The PK analysis set is the primary analysis set for pharmacokinetic analyses.

12.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be analysed descriptively. Full details of the planned statistical analyses will be described in the trial SAP.

12.4 Statistical Methods for Efficacy Parameters

Primary, key secondary and exploratory efficacy parameters will be displayed descriptively, and appropriate tests are conducted on the treatment impact. Full details of the planned statistical analyses will be described in the trial SAP.

12.5 Statistical Methods for Safety Parameters

Safety parameters will be analysed descriptively. Full details of the planned statistical analyses will be described in the trial SAP

12.6 Handling Missing, Unused or Spurious Data

As enrolled patients will be hospitalised for the duration of the trial, it is not expected that any will be lost to follow up. However, should this occur, the Investigator will make every effort to rectify any missing or spurious data. If a patient leaves the hospital without being formally discharged and is lost to follow-up, the last post-baseline observation carried forward will be used to impute results for this patient. In the event that a patient is lost to follow-up without having recorded at least one post-baseline value, that patient will be considered a non-responder.

For specific sensitivity and robustness analyses for the primary and key secondary efficacy variables, missing data are imputed. Full details of the planned routines will be described in the trial statistical analysis plan.

Missing start and end date/times of adverse events will be imputed conservatively. Full details of the planned routines will be described in the trial SAP.

Two blinded interim analyses will be conducted for the Safety Review Committee. Full details of the planned statistical analyses will be described in the trial SAP.

13. END OF THE STUDY

The end of the study is defined as the last subject's last study assessment, which for this protocol is the final visit which will occur at death or 7 days after discontinuation of study treatment.

14. ETHICS COMMITTEE REVIEW

14.1 Independent Ethics Committee (IEC) and Relevant Authorities

The final study protocol and the patient information and consent form will be approved by an appropriately constituted IEC. Approval will be received in writing before initiation of the study.

Clinical Study Authorisation will be obtained prior to initiation of the study from the relevant Regulatory Authority.

14.2 Ethical Conduct of the Study

The study will be performed in accordance with the local regulations, the principals of GCP as described by the ICH, and the ethical principles that have their origins in the Declaration of Helsinki.

The Investigator agrees to the terms and conditions relating to this study as defined in the protocol, eCRF and any other protocol-related documents ad agrees to conduct the trial in accordance with the protocol. The Investigator fully understands that any changes without previous agreement with the Sponsor would constitute a violation of the protocol, including any ancillary studies or procedures performed on study subjects/patients (other than those procedures necessary for the wellbeing of the subjects/patients).

Any breach of the protocol which is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial will be reported by the Sponsor as a Serious Breach.

14.3 Protocol Amendments

Any amendments to the protocol will require IEC and Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

15. STUDY AND DATA MANAGEMENT

15.1 Monitoring

The Investigator and institution will permit study-related monitoring, providing direct access to source data/documents (on-site and/or remotely), in compliance with local regulations and guidelines.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH/GCP, and all applicable regulatory requirements.

The Investigator and Co-investigators agree to cooperate with the monitor(s) to ensure that any issues detected in the course of monitoring visits are resolved.

Monitoring will include both remote and on-site visits when this is permitted in line with national and local guidelines during the COVID-19 pandemic. An initiation visit will be performed at each site before the first subject is included. Initiation visits may be conducted remotely. Monitoring visits and contacts will occur at regular intervals thereafter. A close-out visit will be performed after the database lock and resolution of all pending queries and follow-up of ongoing AEs/SAEs. Full details of the study monitoring procedures to be employed in this trial will be detailed in the Monitoring Plan.

15.2 Quality Assurance

The Sponsor may conduct audits of clinical research activities in accordance with its internal Quality System to evaluate compliance with the protocol and the principles of ICH GCP. Health Authorities may also wish to conduct an inspection (during the study or after its completion). Should an inspection be requested by Health Authorities, the Investigator must inform the Sponsor immediately that such request has been made. The Investigator will permit such audits by St George Street Capital or Health Authorities and facilitate them by providing access to the relevant source documents.

15.3 Data Recording

15.3.1 Data to be Considered as Source Data

The Investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete ('ALCOAC principles'). Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary (e.g., *via* an audit trail).

For this study, source data can include, but is not limited to: medical records, study specific source sheets (as applicable), laboratory reports, laboratory sample collection forms, ECG traces and clinician correspondence. Source data can be recorded electronically or on paper. Electronic records must be in a validated system that allows ALCOAC principles to apply. Source documents are filed at the site.

15.4 Case Report Form

An electronic Case Report Form (eCRF) using the Medidata Rave Electronic Data Capture (EDC) system will be used to capture subject data. Access to enter data in the eCRF will be limited to delegated and trained Investigator site staff only.

Data in the eCRF will be verified by monitors according to a risk-appropriate monitoring strategy. Subject confidentiality will be maintained at all times during the monitoring process.

15.5 Confidentiality

The Investigator must assure that the patient's anonymity will be maintained. On all study documentation, with the exception of the consent form and patient ID logs, patients will only be identified by their unique identification code and will not be referred to by name. Documents identifying the patients (e.g., signed informed consent forms) must not be sent to St George Street or its representatives and must be kept by the Investigator in strict confidence.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The Sponsor may transfer some data collected during the study to a different company or regulatory authority within/outside Europe for the purpose of processing, review, analysis or storage. Whenever the patient's personal data is transferred, it will be kept confidential and secure, and will be used only for the purpose for which it was collected.

15.6 Retention of Study Data

Following closure of the study, the Investigator must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/ regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The Investigator must assure that all reproductions are legible and are a true and accurate copy of the originals, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable back-up of

these reproductions and that an acceptable quality control process exists for making these reproductions.
St George Street Capital will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or St George Street Capital or delegated CRO's SOPs; otherwise, the retention period will default to 25 years.

The Investigator must notify St George Street Capital of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the Investigator leaves the site. The Investigator may not dispose of any records without prior approval from St George Street Capital.

15.7 Communication and Publication of Results

This study will be registered in the EudraCT database and study results will be posted in accordance with the applicable laws and regulations. A clinical study report will be developed at completion of data analysis according to ICH E3 guidelines submitted to EudraCT in accordance with the required timelines according to The European Clinical Trials Directive 2001/20/EC.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

The Investigator has the right to publish study results from his/her specific site. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. However, any publication that includes St George Street Capital confidential information cannot be submitted for publication without St George Street Capital's prior written approval.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

15.8 Indemnification

In the event of study-related damage or injuries, the public liability insurance of the Sponsor provides compensation for claims that arise in accordance with the regulatory requirements of the country involved, except for claims that arise from wilful misconduct or gross negligence. A copy of the insurance certificates will be held in the Trial Master File and in the Investigator Site File.

15.9 Study and Site Closure

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study treatment development

16. STRUCTURED RISK BENEFIT ANALYSIS

This section provides a structured benefit risk assessment for AZD1656, categorised and summarised in an overall assessment of potential risks for study participants. For AZD1656 effects discussed in the sections below, references were made to the Investigator's Brochure.

16.1 Rationale for Dose and Treatment Period

The total daily dose and treatment period in this study (100 mg BID for a maximum of 21 days) is within the higher dose range and lower treatment duration shown to be safe and effective at lowering blood glucose in prior clinical studies. Patients with type 2 diabetes have been administered single oral doses up to 450 mg; and daily doses of up to 200 mg have been given to patients with type 2 diabetes for up to 6 months' duration as an add-on to metformin.

The selected dose was tested in previous clinical studies and hence this dose is considered scientifically and medically appropriate to investigate the immunomodulatory mode of action of AZD1656. There is no evidence to suggest that the pharmacodynamic effect of AZD1656 on the immune system (and specifically on Treg migration) will be different to that for glucose lowering and so a dose with a good safety profile that is known to effectively lower glucose has been selected to test the hypothesis.

We have chosen not to start at a lower dose and subsequently up-titrate the dose given the proposed immunomodulatory mechanism of action of AZD1656 whereby early mobilisation of regulatory T cells is required to prevent or ameliorate the cytokine storm that can occur in COVID-19 patients.

16.2 Previous Exposure in Humans

Twenty-five clinical studies have been completed to evaluate the safety, tolerability, PK, PD and drug interactions with AZD1656. Approximately 960 subjects have been exposed to AZD1656 for up to 6 months' duration, including in an out-patient setting. In the completed clinical studies to date, AZD1656 has been well tolerated with some low risk of hypoglycaemia. The risk for hypoglycaemia was higher on AZD1656 as compared to placebo, but lower than for Sulfonylurea (glipizide). No other safety issues have been identified for AZD1656 from the completed Phase I to IIb programme. No safety signals have been identified regarding vital signs, ECG, weight, BMI and physical findings. There have been no treatment related changes in safety laboratory variables including muscle biomarkers and liver function tests in Phase I to IIa. From the few cases with increased liver enzymes in Phase IIb, a minor increase from AZD1656 treatments could not be excluded. There was clinical improvement in fasting blood sugar and HbA1C levels in the first few months of treatment with AZD1656.

16.3 Pharmacokinetic Considerations

Extensive PK analysis has been conducted to date, so in this trial only steady state PK will be assessed.

16.4 Drug-Drug Interaction

AZD1656 is mainly metabolised via CYP2C8, therefore potent inhibitors of CYP2C8 (e.g. gemfibrozil) may increase exposure to this drug (AUC). Other than inhibitors of CYP2C8, no significant drug-drug interactions have been reported in phase I/II clinical trials; however there may be drug-drug interactions that are as yet unknown.

16.5 Predictability of Effect in Patients with COVID-19

Across prior phase I and II clinical studies, AZD1656 has been well tolerated and no safety concerns have been raised to date. Except for reduced blood glucose, the pattern of reported adverse events (AEs) during treatment with AZD1656 is not clearly different to placebo. The most common AEs reported on AZD1656 treatment in Phase IIb were infections, gastrointestinal events and CNS related events.

The risk for hypoglycaemia is low based on the data from the previous diabetes studies with AZD1656. Few hypoglycaemic events have been reported and only rarely with a plasma glucose level below 3 mmol/L (54 mg/dL). Low glucose levels were either asymptomatic (detected in scheduled measurement) or associated with mild symptoms, and in all cases manageable by the patients. All events with low plasma glucose have responded rapidly to carbohydrate intake.

In this study all those on study treatment will be in-patients, receiving hospital care. If a patient's blood glucose control is considered by their clinical team to be too high or low, then their regular diabetic medications will be altered to achieve diabetic control targets as per usual care. If recurrent hypoglycaemia occurs despite removal of other diabetic medications, then the study medication will be withdrawn as per the study withdrawal criteria.

No safety signals have been identified in prior studies regarding vital signs, ECG, weight, BMI and physical findings. There have been no treatment related changes in safety laboratory variables including muscle biomarkers and liver function tests in Phase I to IIa. From the few cases with increased liver enzymes in Phase IIb, a minor increase from AZD1656 treatments could not be excluded. Any patient with any non-COVID-19, non-diabetes related, serious condition will be excluded from participation in the trial.

16.6 Benefit Risk Assessment

Diabetes mellitus is estimated to affect almost 7% of all adults worldwide. Despite the range of treatment choices (including lifestyle interventions), many patients with T2DM fail to achieve adequate glycaemic control, even when multiple drugs are taken. AZD1656, being a selective glucokinase activator, has the potential to provide an effective glycaemic control in monotherapy as well as in combination with other anti-diabetic drug classes.

In addition to its glucose lowering effect, AZD1656 may have additional benefits to COVID-19 patients which involve its effects on immune function and may prevent the development of cardiorespiratory complications observed in hospitalised patients with COVID-19, leading to lower

requirements for oxygen therapy and assisted ventilation, and reduced incidences of pneumonia and acute respiratory distress syndrome (ARDS). To date no safety risks have been identified in prior clinical studies with the exception of a low risk of hypoglycaemia.

During the conduct of this trial every effort will be made to minimise potential risk(s) to patients participating in this study. Adequate minimisation measures have been put in place to ensure that participating patients will not be exposed to an unacceptable risk throughout the study.

The risk of hypoglycaemia or hyperglycaemia will be mitigated by usual care for hospitalised diabetic patients including frequent blood glucose measurements and clinical monitoring including physical examination, laboratory tests, as well as clinical correlation to treatment and AE collection.

The current risk analysis supports the initiation of a clinical trial in diabetic patients with COVID-19 to investigate the safety, efficacy, immunological and pharmacokinetic effects of this novel IMP in order to further develop AZD1656 as a potential treatment option for this vulnerable patient group.

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18. SIGNATURES AND AGREEMENT WITH THE PROTOCOL

Sponsor Approval

I have reviewed and approved the protocol and confirm that the protocol follows GCP.

Signature: DocuSigned by:
Signer Name: James Chorlton
Signing Reason: I approve this document
Signing Time: 22-Dec-2020 | 05:38 PST
60494DB03C1B4EE59D85F6C447FCE9D7 Date: 22-Dec-2020 | 05:38 PST

James Chorlton
Head of Clinical Development, St George Street Capital

Signature: DocuSigned by:
Signer Name: Kathryn Owen
Signing Reason: I approve this document
Signing Time: 21-Dec-2020 | 23:46 PST
A30801CD8AF8418FB8B014A3474DFC4F Date: 21-Dec-2020 | 23:46 PST

Dr Kathryn Owen
Consultant Physician, St George Street Capital

Coordinating Investigator Approval

I agree to conduct the study according to the terms and conditions of this protocol, current Good Clinical Practice and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Signature: DocuSigned by:
Signer Name: Kieran McCafferty
Signing Reason: I approve this document
Signing Time: 22-Dec-2020 | 00:20 PST
2AC383CB64F34607B3F9C9462B3A9D40

Date: 22-Dec-2020 | 00:20 PST

Dr Kieran McCafferty
Consultant Nephrologist, Bart's Health NHS Trust

Principal Investigator Approval

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

EudraCT No: 2020-002211-21

Protocol No.: SGS.1656.201

I agree to conduct the study according to the terms and conditions of this protocol, current Good Clinical Practice and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Signature: _____ Date:

Name of Principal Investigator

Title

APPENDICES

Appendix 1: WHO Ordinal Scale for Clinical Improvement (COVID-19 trials, February 18th 2020)

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalised (Mild disease)	Hospitalised, no oxygen therapy required	3
	Hospitalised, oxygen therapy by mask or nasal prongs	4
Hospitalised (Severe disease)	Non-invasive ventilation or high flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation and additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Certificate Of Completion

Envelope Id: F7396F83176D421F9514521B26F93E50
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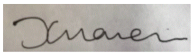
Electronic Record and Signature Disclosure: Accepted: 20 February 2020 | 09:41 ID: 941e6bf6-980f-4806-9d46-2fb7206675a1		
Kathryn Owen kate.owen@aptusclinical.com Kate Owen Security Level: Email, Account Authentication (Required)	 Signature Adoption: Uploaded Signature Image Signature ID: A30801CD-8AF8-418F-B8B0-14A3474DFC4F Using IP Address: 213.104.201.34 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 22 December 2020 | 06:56 Viewed: 22 December 2020 | 07:45 Signed: 22 December 2020 | 07:46
Electronic Record and Signature Disclosure: Accepted: 04 December 2020 | 15:39 ID: e8aad44b-0a1f-4c61-b90d-2c649a8211d1		

Signer Events	Signature	Timestamp
Kieran McCafferty kieran.mccafferty4@nhs.net Dr Security Level: Email, Account Authentication (Required)	 Signature Adoption: Uploaded Signature Image Signature ID: 2AC383CB-64F3-4607-B3F9-C9462B3A9D40 Using IP Address: 86.161.183.54 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 22 December 2020 | 06:56 Viewed: 22 December 2020 | 08:18 Signed: 22 December 2020 | 08:20
Electronic Record and Signature Disclosure: Accepted: 03 July 2020 | 13:50 ID: 9d728fbc-16df-4a7b-9590-bb5e627d9dd6		

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Completed	Security Checked	22 December 2020 | 13:38

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