Queen Mary University of London

1.0 Title Page

Full Title

AZD1656 in Transplantation with **D**iabetes t**O** **P**romo**T**e **I**mmune T**O**lera**N**ce

Short Title

The **ADOPTION** Study

Sponsor

Queen Mary University of London

Representative of the Sponsor:

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REC Number 19/EE/0209

Sponsor Reference 012657

2.0 Research Reference Numbers

IRAS Number:	252155
EudraCT Number:	2019-001587-30
ISRCTN Number / Clinical trials.gov Number:	TBC

3.0 Signature Pages

Chief Investigator Declaration

I confirm that the following protocol (Version 1.8, dated 07th July 2021), has been written by me and I, as the Chief Investigator, agree to conduct the trial in compliance with this version of the protocol.

I will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), and all subsequent amendments of the clinical trial regulations; current UK Policy Framework for Health and Social Care Research; the World Medical Association Declaration of Helsinki (1996); GCP guidelines; the Sponsor's SOPs; and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

I also confirm that I will make the findings of the study publicly available through publication and/or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:	Kieran McCafferty
Chief Investigator Site:	Barts Health NHS Trust
Signature:	
Date:	07.07.21
Name:	Dr Kieran McCafferty

Statistician Declaration

The clinical study as detailed within this research protocol (Version 1.8, dated 07th July 2021), involves the use of an investigational medicinal product and will be conducted in accordance with the current UK Policy Framework for Health & Social Care Research; the World Medical Association Declaration of Helsinki (1996); Principles of ICH E6-GCP; ICH E9 - Statistical principles for Clinical Trials; ICH E10 - Choice of Control Groups; and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

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Committees	For membership and contract details please see TSC/DMC document

5.0 Trial Summary

Full title	**A**ZD1656 in Transplantation with **D**iabetes t**O** **P**romo**T**e **I**mmune T**O**lera**N**ce
Short title and/or Acronym	The **ADOPTION** Study
Trial Design Methodology	Single site, placebo controlled, double blind randomised clinical trial.
Phase of the Trial	II
Study Duration	27 months
Study setting	Single NHS site
Investigational Medicinal Product(s)	AZD1656
Medical condition or disease under investigation	Post-renal transplant diabetes and graft rejection
Planned Sample Size	50
(Maximum) Treatment duration	3 months
Follow up duration	9 months
End of Trial definition	The last patient has completed their last follow up point at 1 year post-transplant (data review visit).

6.0 Protocol Contributors

Key Protocol Contributors	Full contact details including phone, email and fax numbers
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8.0 List of Abbreviations / Glossary of Terms

AE	Adverse event
APR	Annual Progress Report
AR	Adverse reaction
AUC	Area under curve
BMI	Body mass index
BP	Blood pressure
CI	Chief investigator
CKD	Chronic kidney disease
C_{max}	Maximum concentration
CTA	Clinical Trial Authorisation
CMV	Cytomegalovirus
CRF	Case report form
DSM	Drug safety monitoring
DSUR	Development Annual Safety Update
ECD	Extended Criteria Donor
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated Glomerular Filtration Rate
EOT	End of trial
FACS	Fluorescent-activated cell sorting
GCP	Good Clinical Practice
HbA1c	Haemoglobin A1c
HDL	High-density lipoprotein
HLA	Human leukocyte antigen
HOMA	Homeostatic model assessment
HOMA IR	Homeostatic model assessment of insulin resistance
HRA	Health Research Authority
IB	Investigator brochure
ID	Identifier
IMP	Investigational medical product
IRAS	Integrated Research Approval System
ISF	Investigator site file
ITT	Intention to treat
JRMO	Joint research management office (Sponsor)
LDL	Low-density lipoprotein
MHRA	Medicines and Healthcare products Regulatory Agency
mTORC2	Mammalian target of rapamycin complex 2
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
ONS	Office for National Statistics

PD	Pharmacodynamics
PI	Primary investigator
PI3K-Akt	Phosphoinositide 3-kinase – Protein kinase B
PIS	Patient information sheet
PK	Pharmacokinetics
QMUL	Queen Mary University of London
R&D	Research and Development
REC	Research Ethics Committee
RLH	Royal London Hospital
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SOP	Standard operating procedure
SUB-I	Sub investigator
SUSAR	Serious unexpected serious adverse reaction
$T_{1/2}$	Half-life
Treg	Thymic regulatory T cells
TSC	Trial steering committee
ULN	Upper limit of normal
UKAS	United Kingdom Accreditation Service

9.0 Introduction

9.1 Background

Renal Transplantation and glucose control

Type 2 diabetes is the most common cause of end-stage renal failure in the UK. Kidney transplantation is widely held to be the optimal form of renal replacement therapy for patients with end-stage renal disease, leading to a longer survival and improved quality of life in patients receiving a renal transplant compared to those that remain on dialysis (Reese et al, 2015).

However transplantation leads to a higher glucose burden in patients. This has been associated with acute rejection, sepsis and worse outcomes, and patients frequently have to increase their anti-diabetic medication in the early post-transplant period.

One reason for this is that immunosuppressive medications (glucocorticoids and calcineurin inhibitors) can lead directly to hyperglycaemia. In addition, as renal function improves, there is greater renal clearance of anti-diabetic agents and endogenous insulin leading to a reduced potency of these medications. These effects are most pronounced within the early post-transplant period, as this is the period when the immunosuppressive burden is the strongest and the changes in renal function most marked.

The role of Glucokinase in glucose control

Glucokinase is an enzyme which has two effects to lower glucose. In the pancreas, beta cells control insulin secretion. In pancreatic beta cells glucokinase converts glucose to glucose-6-phosphate, which is a rate-limiting step in the secretion of insulin; as such, increased glucokinase activity leads to more insulin secretion. Secondly, in the liver, glucokinase increases hepatic uptake of glucose (Scheen, 2018). Defective glucose-induced insulin secretion and increased hepatic glucose output are of the hallmarks of type 2 diabetes. Because of these effects, glucokinase activators have been promising therapeutics for type 2 diabetes for almost two decades.

One agent studied is AZD1656: a potent, selective activator of human glucokinase. Twenty-five clinical studies have been completed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and drug interactions with AZD1656. Approximately 960 subjects have been exposed to AZD1656 in 25 clinical studies covering phase I to phase IIb as part of a global development program by AstraZeneca. Single oral doses of AZD1656 up to 180 mg have been given to healthy volunteers during euglycaemic clamp conditions (Ericsson et al, 2012). Patients with type 2 diabetes have been administered single oral doses up to 450 mg; and also daily doses of 10 to 200 mg have been given to

patients with type 2 diabetes for up to 6 months' duration. AZD1656 has been shown to be a, well-tolerated medication in patients with type 2 diabetes and no safety concerns were raised in studies up to 6 months. Unfortunately, the anti-diabetic effect of AZD1656 has been found to wear off after several months, thus limiting its long-term use for patients with diabetes (Kiyosue et al, 2013; Wilding et al, 2013).

A shorter course of AZD1656 may be of benefit in controlling the glucose levels of patients with diabetes during the time shortly after renal transplantation when the immunosuppressive burden, and hence gluconeogenesis, is greatest. In addition, AZD1656 may have other benefits post-renal transplantation in an unrelated action to its anti-diabetic action, which involve its effects on immune function.

Treg cells in renal transplantation and tissue injury

Thymic regulatory T (Treg) cells are a subpopulation of T cells that modulate the immune system. These cells have immunosuppressive functions and downregulate other effector T cell populations. As such, they are instrumental for the maintenance of tolerance to self-antigens. A crucial step in their immuno-modulatory function is the ability of active Treg cells to migrate in the body and, during inflammation, to home on inflamed tissue (Tang et al, 2004; Kishore et al, 2017).

In transplantation a major unmet need is to develop management strategies to prevent both acute and chronic rejection which are associated with poorer graft survival. Current therapies to minimise rejection rates have their own side effects including direct renal and pancreatic toxicity and the progression of cardiovascular disease. Treg cells are an attractive potential therapy for transplantation to reduce the immunosuppressive burden (Zwang et al, 2017). Evidence for the role of Treg cells' beneficial effects in transplantation is suggested by data which demonstrates that Treg cells directly reduce inflammation and reperfusion injury in kidneys (Kinsey et al, 2009; Hu et al, 2016).

Furthermore Treg cells suppress immune function *in vitro*, and are associated with transplant acceptance in kidney transplant patients (Daniel et al, 2012). High levels of Treg cells positively correlate with renal allograft survival and function (Schaier et al, 2012). In addition, in renal biopsies, Treg infiltration is associated with better graft function (Bestard et al, 2008). Finally, there is evidence of tissue protection in transplantation mouse models following transfer of humanised Treg cells (Yi et al, 2012). Therefore, Treg cell proliferation and activation may hold the keys to unlock the future promise of immune tolerance which is the 'Holy Grail' of transplant immunology: the potential to be able to perform solid organ transplants without the need for long term immunosuppression with all the advantages that this would bring.

Role of glucokinase in Treg biology

Recent data combines the two streams of research involving glucokinase biology, in the fields of immunosuppression and glucose lowering effects. As well as being

involved in glucose homeostasis, glucokinase has been shown to increase Treg migration and trafficking. Treg migration has been shown to be dependent on glycolysis which is mediated via the PI3K-Akt pathway and activation of mTORC2. mTORC2 in turn induces glucokinase expression which appears to be necessary for Treg migration. AZD1656 has been demonstrated to increase glucokinase activity, thus leading to reduced numbers of circulating Treg cells, with the hypothesis that they have been activated and migrated into the inflamed tissues (Kishore et al, 2017). Further evidence for the role of glucokinase comes from data demonstrating that inhibition of glucokinase resulted in less Treg motility, leading to increased rejection in a skin transplant animal model. In addition, humans who have reduced inhibition of glucokinase due to a mutation in a glucokinase regulatory protein have been shown to have increased motility and decreased circulating numbers (Kishore et al, 2017).

9.2 Assessment and management of risk

Standard of care

Renal transplantation is not without risk; however, overall the benefit of a functioning renal transplant outweighs the risks of remaining on dialysis.

Patients in this study will have all their pre- and post-transplant care as per usual clinical care, with the exception of the following intervention: treatment with AZD1656 or placebo for 3 months post-renal transplant.

The standard of care follow up is that patients attend clinic twice a week for the first 6 weeks post-transplant, then weekly for another 6 weeks, they remain on weekly or fortnightly clinic visits for a further 12 weeks, after which point depending on the stability of the patients graft function they reduce clinic visits to every 2-4 weeks up to one year.

As with all patients with diabetes who have had a renal transplant, there is the risk of both hypoglycaemia and hyperglycaemia due to changing renal function and new medications which may alter glucose levels. Because of this, we measure patient's glucose levels and diabetic control routinely when they are seen frequently in clinic and enquire as to any episodes of hypo or hyperglycaemia. The transplant clinician may alter patient's anti-diabetic medications to maintain optimal glycaemic control as part of routine care.

Risks associated with AZD1656

The known risks to human subjects.

Justification for the choice of route of administration, dosage, dosage regimen, and treatment period(s)

We are using a dose within the higher range that has shown to be safe and efficacious in clinical studies. We do not have human T reg efficacy data: therefore as this is an exploratory study, this is scientifically a good dose to use. We would therefore not up-titrate from this dose. We are working on the hypothesis that the pharmacodynamic effect of AZD1656 on Treg migration activity is the same as for glucose lowering (we have no evidence to suggest this is not correct), and we proposed using what we know is an effective and safe dose in order to adequately test the hypothesis. We have chosen not to start at and lower dose and subsequently up-titrate the dose: given the proposed mechanism of action of AZD1656, early mobilisation of regulatory T cells with subsequent amelioration of renal ischaemia-reperfusion injury is required in order to benefit the new transplant. We are measuring delayed graft function as one of the secondary clinical endpoints as a surrogate for improved renal outcome within the first 7 days.

From a safety perspective, all of the patients will be diabetic and induction therapy given for renal transplantation is associated with hyperglycaemia; in addition as the patients are inpatients for the first 5-7 days post transplant (and during initiation of study drug) they are closely monitored for hypoglycaemia. The risk of hypoglycaemia after this period is low based on the data from the previous Phase 2 diabetes studies with AZD1656. If recurrent hypoglycaemia occurs despite removal of other anti-diabetic medications, then the study medication will be withdrawn as per withdrawal criteria.

Preclinical & Clinical Data

Investigator's Brochure AZD1656, Edition 9, September 2020

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. In patients with type 2 diabetes and renal impairment, the PK and PD effects after single doses of AZD1656 were comparable to diabetic patients with normal renal function.

Across clinical studies, AZD1656 has been well tolerated and no safety concerns have been raised. 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.

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.

Reproductive restrictions

No data is available on the effects of AZD1656 on pregnancy and lactation in humans. Preclinical studies have shown that AZD1656 is not genotoxic. There was no effect on male fertility in rat. Overall, the effects of AZD1656 on embryofoetal development seen in pre-clinical studies were considered to be secondary to maternal hypoglycaemia. Results from the preclinical repro-toxicity studies support inclusion of women of childbearing potential in clinical studies, provided that pregnancy is prevented using a highly effective form of contraception. In case of pregnancy during the study, treatment should be stopped.

How the risk will be minimised/managed

Hypoglycaemia:
As with most anti-diabetic medications there is a risk of hypoglycaemia. However, following a renal transplant, given the increased glucose production from the steroid medications along with increased insulin metabolism, hyperglycaemia rather than hypoglycaemia is more of an issue. 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.

All patients will be seen frequently in a specialist post-transplant clinic where, as part of their standard of care, they will have their blood glucose measured regularly along with makers of diabetic control including HbA1c. The patient will be given instructions to measure blood glucose if they get symptoms of hyperglycaemia (e.g. thirst, polyuria) or hypoglycaemia (cold sweat, dizziness). If a major hypoglycaemic event occurs, or more than one minor event since last visit, the patient will be told to contact the investigator before the next visit.

As with all patients with diabetes post-transplant, if a patient's blood glucose control is considered by their clinical team to be too high or low, then their regular anti-diabetic medications will be altered to achieve diabetic control targets as per our

standard of clinical care. National guidelines in the management of CKD patients with diabetes suggest controlling the HbA1c to between 6.5% (48mmol/mol) to 8.5% (68mmol/mol). Within this range there are suggestions to aim for tighter control (towards 6.5%) or less tight control (towards 8.5%) on an individualised patient basis (Renal Association 2018).

Reproductive restrictions

Female study participants

Women of child-bearing potential are permitted to participate in this study provided that they agree to avoid pregnancy through the use of a highly effective form of contraception starting from the time of study enrolment until the final safety follow-up visit has been completed (2 weeks after cessation of study medication). AZD1656 has low potential for drug-drug interaction through induction of any of the CYP enzymes so an interaction with hormonal contraception is not anticipated. Methods of highly effective contraception are outlined in section 12.2 (Exclusion criteria). If a female participant should become pregnant, then the study medication will be stopped. She will be asked to consent to the collection of data about her pregnancy, and the birth and health of her baby.

Male study participants

It is important that women of childbearing potential, who are the partners of male patients, do not become pregnant during the study and until the participant has completed the safety follow up visit.

All male study participants should avoid fathering a child by using an effective method of contraception together with their female partner/spouse, starting from the time of study enrolment until the final safety follow-up visit has been completed. In this scenario, we have advised the use of a condom and female partners to use a method of highly effective contraception. If a female partner of a male patient should become pregnant, then she will also be asked to consent to the collection of data about her pregnancy, and the birth and health of her baby.

For male patients whose partner is pregnant, the man should use a condom for the duration of the study and until the final safety follow-up visit has been completed.

Sperm Donation

Male patients should not donate sperm for the duration of their participation in the study and until they have completed the study follow-up visit.

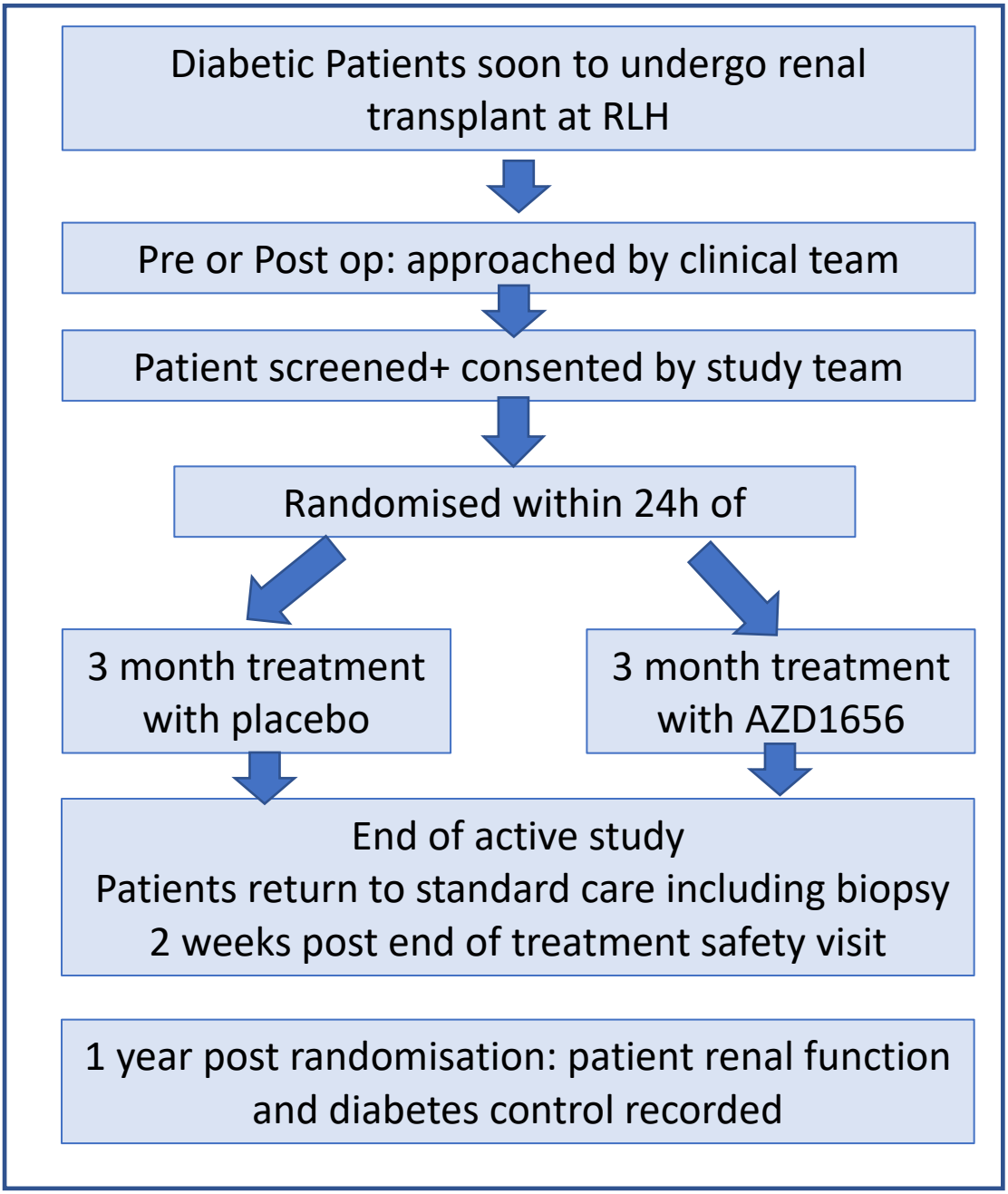
This trial is categorised as: Type C

9.3 Rationale for study design

Our hypothesis is that treatment with AZD1656 may lead to increased Treg localisation to the transplant kidney in the early post-operative course. This may lead to reduced ischaemia reperfusion injury through the immunosuppressive effects of Tregs, measurable by a change in the incidence of delayed grant function. At 3 months we hypothesize that AZD1656 may lead to increased Treg cell localisation in the transplanted kidney, as a marker for improved graft survival. We will measure peripheral Treg population as a marker for Treg trafficking to the kidney as this can be measured serially with minimal risk to the patient. We will include histological parameters from the standard of care 3 month protocol biopsy as a key secondary endpoint. Finally, we hypothesize that AZD1656 may be an effective and safe adjunct for the early management of diabetes post-renal transplant.

We propose an exploratory phase 2 study, examining the efficacy and safety of 3 months' treatment with AZD1656 100mg twice daily in patients with diabetes undergoing renal transplantation in a tertiary renal unit.

10.0 Trial Flowchart



11.0 Trial Objectives and Design

11.1 Primary Objective/s

To determine whether treating post-transplant patients with AZD1656 compared to placebo for 3 months leads to altered Treg migration.

11.2 Secondary Objective/s

To determine the safety and efficacy of AZD1656 to control diabetes post-transplant. To investigate the effect of AZD1656 on Treg cell infiltration in renal transplant tissue.

11.3 Endpoints

11.3.1 Primary Endpoint

The primary endpoint is the change in mean peripheral Treg cell number between baseline and 3 months measured using flow cytometry analysis (FACS) between AZD1656 and placebo.

11.3.2 Secondary Endpoints

1) Histological staining for Treg cells in renal biopsy tissue between baseline and 3 month protocol biopsy
2) Incidence of delayed graft function, defined as the need for dialysis within 1 week post-transplant
3) Diabetic control between baseline and month 3 using change in HbA1c measurement
4) Dose of other anti-diabetic medication between baseline and month 3 (descriptive)
5) Safety endpoints: i.e. number of hypoglycaemic episodes (descriptive)
6) Insulin resistance: HOMA IR measurement at month 3
7) Graft function: (eGFR) at month 3
8) Episodes of acute rejection (defined as biopsy proven acute rejection)
9) Episodes of opportunistic infections: bacterial and viral (descriptive)

11.4 Exploratory or Tertiary Endpoints/outcomes

1) 12-month graft function (eGFR) and diabetic control (HbA1c; medication review) to assess legacy effect (potential follow up publication)
2) Differences in other peripheral T cell populations, measured by FACS analysis
3) Histological staining for Treg cells in any renal biopsy taken for clinical indications between baseline and month 3 protocol biopsy
4) Differences in the functional phenotype of the Treg cells

11.5 Objectives and Endpoints Summary

Objective	How objective measured	Outcome
Examine the effect of AZD1656 on Treg cell migration	Change in peripheral Treg population between randomisation and month 3 measured by mean change in Treg cell number between baseline and 3 months using FACS analysis.	Does AZD1656 lead to enhanced migration as demonstrated by a fall in peripheral Treg population over time compared to placebo?
Examine the effectiveness of AZD1656 on diabetic control	Change in HbA1c between baseline and month 3 visit, HOMA-IR at month 3, descriptive change in anti diabetic medication dose/need for additional anti-diabetic therapy.	Is there a difference between placebo and IMP on diabetic control/insulin resistance?
To investigate the effect of AZD1656 on renal transplant function	Renal function (eGFR CKD EPI) measured at 3 months and 12 months.	Is there a difference between AZD1656 and placebo treated patients' renal function at 3 and 12 months?
To determine the safety of AZD1656 to control diabetes post-transplant.	Patient and graft survival, number and type of AE (hypoglycaemic episodes, infective episodes), number and type of SAE, rejection rates (defined as incidence of biopsy proven acute rejection)	Is there a difference between placebo and AZD1656 treated groups in terms of number of AE, SAE, renal function and rejection rates?
Effect of AZD156 on Treg cell infiltration in renal transplant tissue	Change in Treg staining on renal biopsies collected as standard of care at implantation and 3 months post transplant.	Is there a difference between placebo and AZD1656 treated groups in terms of change in Treg cell infiltration between baseline and 3 month transplant biopsy?

11.6 Trial Design

A single site, prospective, double blind randomised controlled pilot study investigating the safety and efficacy of 3 months' treatment with AZD1656 100mg twice daily or placebo in 50 patients who have undergone a renal transplant at the Royal London Hospital.

11.7 Study Setting

This is a single centre study with no other patient identification centres or sites.

The study will take place in an NHS setting (Barts Health NHS Trust), specifically in the Renal Department at the Royal London Hospital.

Patients will be recruited exclusively from a cohort of patients undergoing renal transplantation at the Royal London Hospital.

12.0 Eligibility Criteria

In order to be eligible for the trial, participants must meet all of the below inclusion criteria and none of the below exclusion criteria.

12.1 Inclusion Criteria

a) Females or males aged 18 years and above
b) Having undergone renal transplantation at the Royal London Hospital within the previous 24 hours
c) A pre-transplant diagnosis of Type 2 diabetes
d) Provision of written, informed consent prior to any study specific procedures
e) In women of childbearing potential* documentation of a negative pregnancy test during admission for renal transplant.

*Women of childbearing potential are defined as women following menarche until becoming post-menopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A post-menopausal state is defined as the absence of menses for 12 months without an alternative medical cause.

12.2 Exclusion Criteria

a) Unable to consent
b) Known allergy/intolerance to AZD1656
c) Pregnant or breastfeeding women
d) Planning on becoming pregnant/unwilling to use highly effective contraception* during the 3 month treatment period and for 2 weeks afterwards
    a. In the case of men with sexual partners who are women of childbearing potential: refusal to wear a condom **and** female partner planning on becoming pregnant/unwilling to use highly effective contraception* during the 3 month treatment period and for 2 weeks afterwards
e) Clinically significant history of abnormal physical and/or mental health as judged by the investigator other than conditions related to chronic kidney disease
f) Current or planned use of strong inhibitors of CYP2C8
g) Participation in an investigational drug trial in the 3 months prior to administration of the initial dose of study drug

*Highly effective contraception methods are defined as those that can achieve a failure rate of <1% per year when used correctly and consistently. These include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation – either oral, transvaginal or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation – either oral, injectable or implantable
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner – provided that the partner is the sole sexual partner of the participant and that the vasectomised partner has received medical assessment of surgical success

13.0 Trial Procedures

13.1 Participant identification

Participants will be identified by their regular clinical team from those patients admitted or soon to be admitted for a renal transplant. Eligibility decision will be made by the Chief Investigator (CI) or Sub Investigator (Sub-I).

13.2 Informed Consent Procedures

Informed consent will be obtained either pre-transplantation or within 24 hours post-transplantation, but prior to the participant undergoing procedures that are specific to the trial, and are outside standard routine care at the participating site (including the collection of identifiable participant data).

In the case of deceased donor transplantation, patients do not know when they will receive a transplant, and it is therefore impossible to approach patients in the days and weeks before their transplant. Patients will have already given consent to undergo their renal transplant at short notice, however some patients may be unable to give fully informed consent in the time immediately before or within 24 hours after transplant for this research study. If the PI or patient feels they are unable to give fully informed consent within the first 24 hours after the operation, then they will not be consented.

Patients who are planned to undergo live-donor transplantation will be given information about the study pre-transplantation during the assessment process, but will not be consented until they proceed with the transplant.

We hold regular pre-transplant open days to which all patients on the transplant waiting list are invited. At these open days we will inform patients of the current study opportunities. We will use the PIS as the text for these discussions and will be free to verbally discuss the study with patients on the day.

13.2.1 Responsibility for obtaining consent

The CI 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 Good Clinical Practice (GCP) and the Declaration of Helsinki. If delegation of consent occurs then details must be provided in the Site Delegation Log.

Consent can only be taken by the CI or a medical practitioner trained in the study and delegated on the study log.

13.2.2 Consent Considerations

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

The participant must remain free to withdraw from the trial at any time without giving reasons and without this compromising his/her further treatment and must be provided with a contact point where he/she may obtain further information about the trial. Where a participant 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 participant, it is the responsibility of the CI to ensure this is done in a timely manner.

13.2.3 Population

The patient population will be patients aged 18 or over undergoing renal transplantation at the Royal London Hospital.

13.2.4 Vulnerable participants' considerations

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

13.2.5 Written/ reading / translation considerations

Patients will not have cognitive impairment as this is a standard contraindication to undergoing renal transplantation. In the case of patients who speak no English, we will use independent advocates or standard clinical translation support services which are readily available during the consent process for the operation itself. Once consented verbally, patients will be provided with a translation of the patient information sheet and consent form.

In addition, we recognise that there are a significant number of patients who speak Bengali in our local population. We will consent these patients with a Bengali-translated PIS and consent form.

13.2.6 Participants lacking capacity

The clinical team will not approach any patient who is felt not to have capacity to take part in the study.

13.2.7 Minors

Patients under 18 are not eligible to participate in the study.

13.2.8 Consenting process

Patients will be approached by a member of the clinical team and asked if they would like to know more about the study. If the patient is interested, the research team will contact the patient to discuss the trial. They will inform the potential participant or his/her legal representative about the nature and objectives of the trial and possible risks associated with their participation.

They will receive the PIS and have as long as they need to read it and have all their queries satisfactorily answered. However if they are unable to come to a decision 24 hours after their transplant the consent process will be abandoned and they will not take part in the trial.

The consent process will be documented in the source documents.

13.2.9 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies

Patient samples will be stored as per standard practice. These samples may only be used in future research following a substantial amendment to the protocol and ethical approval. Patients would be re-consented in such a scenario.

13.3 Screening Procedures

All participants that undergo screening will be logged into a study specific screening log.

Following informed consent being signed, and before randomisation takes place, the following information will be collected:

Inclusion/exclusion criteria
Demographic data
Transplant data (if appropriate)
Concomitant medication
Medical history

13.4 Treatment Allocation

13.4.1 Randomisation Method

The method of randomisation will be a simple randomisation using pre-filled envelopes with study numbers 1 - 50 printed on them. The envelopes will be pre-filled by a doctor who is independent to the study and quality control checks will be performed and documented by an independent member of the clinical team. Inside the envelope there will be a treatment code, which will be sent to pharmacy along with the patient's study number. If a patient is randomised but does not receive any IMP/placebo they will not be included in the study and will not be replaced.

Both the patient's study number and the treatment code will be documented in the trial master file.

13.4.2 Randomisation Procedure

A spreadsheet of treatment codes (linked to either IMP or placebo) will be created using an online generator using a block randomisation sequence (Sealed Envelope Ltd. 2016. Create a blocked randomisation list. [Online] Available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists [Accessed 31 Jul 2017].)
This spread sheet will be stored in the pharmacy dispensary.

Each treatment code (for example A1, A2,…A50) will be written on a card and sealed in an envelope.

At randomisation, one of these envelopes will be chosen at random to associate the patient's study ID (e.g. patient 01 or 13) to the treatment code, which will be recorded in the CRF. This linked study code and patient identification will be sent to pharmacy for dispensing. The pharmacist will use their spread sheet, which links the treatment code with the allocation of IMP or placebo.

Finally, each study participant will have their Study ID linked to their treatment allocation written on a card, which will be sealed in an envelope with their study ID on the front of the envelope (this will be created by an independent doctor). This means that breaking the study allocation will only compromise that individual patient's allocation.

The people who will have access to the envelope section are the CI and Sub-I only. The people who will have access to the treatment code (without the treatment allocation) are the study team. The people who will have access to the treatment code matched to the treatment allocation are the pharmacy team and sponsor office only. Should there be the need to break the treatment allocation, the CI or Sub

investigator will open the locked container which is stored on the renal unit to allow out of hours access, and pick out the relevant patient's ID number and open only this envelope.

13.5 Blinding

This is a double blind placebo study: both the patient and the study team will be blinded to the treatment intervention.
Pharmacy staff who dispense the study medication will not be blinded, nor will Sponsor Office staff responsible for reporting unblinded SUSAR reports to the MHRA.

13.6 Unblinding

The code breaks for the trial will be held in the research office of the renal department and are the responsibility of the CI Kieran McCafferty.

If a patient has a significant adverse reaction or a SUSAR then they should stop the study medication and be managed by their clinical team as if the patient was on the active drug. Further advice should be sought from the CI as necessary.

In the event a code is required to be broken a request for unblinding will be made by the Investigator or treating health care professional.

If the person requiring the unblinding is not the CI or their team then the healthcare professional will notify the Investigator team that an unblinding is required for a trial subject which will then occur.

In emergency situations, the responsibility to break the unblinding treatment code resides solely with the CI and will not be delayed in any way. The CI may delegate this duty to the sub-I or senior renal research nurse if there would otherwise be unreasonable delay in unblinding.

On receipt of the treatment allocation details the CI or treating health care professional will continue to deal with the participant's medical emergency as appropriate.

The CI must document the breaking of the code and the reasons for doing so on the CRF/data collection tool, in the site file and medical notes. The CI will ensure it is also documented in the final study report and/or statistical report at the end of the study.

The written information will be disseminated to the Trial Steering Committee.

13.7 Trial Schedule

13.7.1 Schedule of Assessment (in Diagrammatic Format)

Schedule of visits	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Data review
Day/Month	Before or within 24h post transplant	Randomisation up to 24h post transplant	week 1 post randomisation (+/- 3 days)	week 2 post randomisation (+/- 3 days)	week 4 post randomisation (+/- 3 days)	week 8 post randomisation (+/- 1 week)	week 12 post randomisation (+/- 1 week)	2 weeks after stopping study medication (+/- 1 week)	1 yr post transplant +/- 2 weeks
Informed Consent	X								
Inclusion/ exclusion criteria	X	X							
Negative pregnancy test	X	X	X	X	X	X	X	X	
Demographics	X								
Transplant data		X							
Medical history	X								X*
Randomisation		X							
Study drug dispense		X							
Drug accountability			X	X	X	X	X		
Physical examination		X	X	X	X	X	X	X	
Weight		X	X	X	X	X	X	X	X*
Vital signs		X	X	X	X	X	X	X	X*
Concomitant medication	X	X	X	X	X	X	X	X	X*
Laboratory bloods**		X	X	X	X	X	X	X	X*
Blood for Treg quantification		X	X				X	X	
AE assessment		X	X	X	X	X	X	X	X*
End-point assessment							X		

*At this review, the patient's medical records will be reviewed and their clinical data extracted to include:

Graft function as measured by eGFR and serum creatinine
Episodes of rejection
Episodes of infection
Diabetic control measured by HbA1c
Vital signs
Weight
Current medication and anti-diabetic medication regimen

**Laboratory bloods: including fasting c-peptide, cholesterol and serum glucose; serum urea and electrolytes (including creatinine), albumin, alkaline phosphatase (ALP), bilirubin, alanine aminotransferase (ALT), bone profile and C-reactive protein; haemoglobin and HbA1c; and serum save +/- blood for peripheral Tregs as per protocol. The serum save will be taken and processed in keeping with normal protocols but will be used for functional assays to measure the activity of the Tregs at different time points.

13.7.2 Trial assessments

Screening visit
Informed consent
Inclusion/exclusion criteria
Documentation of a negative pregnancy test from pre-transplant care
In women of childbearing potential: defined as women following menarche until becoming post-menopausal, unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as the absence of menses for 12 months without an alternative medical cause.
Medical history
Demographic data
Concomitant medication

Visit 1 - to occur within 24 hours post-transplant
Inclusion/exclusion criteria
Transplant data
Documentation of a negative pregnancy test
Concomitant medication
Targeted physical examination
Adverse event reporting
Laboratory bloods: including fasting c-peptide, cholesterol and serum glucose; serum urea and electrolytes (including creatinine), albumin, alkaline phosphatase (ALP), bilirubin, alanine aminotransferase (ALT), bone profile and C-reactive protein; haemoglobin and HbA1c; and serum save. Results from bloods that have been taken as part of routine care may also be included on the case record forms.
20ml of blood will also be taken for peripheral Treg quantification.
Vital signs recording
Weight
Randomisation
Study drug dispense

In addition, the renal biopsy specimen collected as per clinical care at time of biopsy will be stained for Treg cell markers.

Visit 2 (1 week post randomisation +/- 3 days))
Check drug adherence
Concomitant medication
Documentation of a negative pregnancy test
Targeted physical examination
Weight
Vital signs recording

Fasting blood tests: including fasting c-peptide, cholesterol and serum glucose; serum urea and electrolytes (including creatinine), albumin, alkaline phosphatase (ALP), bilirubin, alanine aminotransferase (ALT), bone profile and C-reactive protein; haemoglobin and HbA1c and serum save. Results from bloods that have been taken as part of routine care may also be included on the case record forms.
20ml of blood will also be taken for peripheral Treg quantification.
Adverse event reporting

Visit 3 (2 weeks post randomisation +/- 3 days)
Activities as per visit 2 with exception of blood collection for Treg quantification

Visit 4 (4 weeks post randomisation +/- 3 days)
Activities as per visit 3

Visit 5 (8 weeks post randomisation +/- 1 week)
Activities as per visit 3

Visit 6 (12 week post randomisation +/- 1 week)
Activities as per visit 2 (i.e. additional blood taken for Treg quantification).
In addition, patient will stop study medication and then revert back to usual care.
Drug accountability (formal)
Endpoint assessment

As part of their usual care, and like all patients who undergo a renal transplant, patients have a transplant biopsy at 3 months. This histology specimen will be examined for Treg cell infiltration in addition to standard of care review.

Visit 7 (2 weeks after stopping study medication +/- 1 week)
Patients will have their vital signs and weight recorded, a targeted physical examination, an AE assessment, their laboratory bloods done (as above), blood taken for Treg quantification, and their concomitant medication checked. Female patients will have a pregnancy test.

13.7.3 Follow-up Procedures

After the last patient has completed visit 7, there will be an interim deadlock, at which point we will analyse the primary endpoint data.

At 1 year post-transplant the patient's medical records will be reviewed for the following data which will be extracted:
Graft function as measured by eGFR and serum creatinine
Episodes of rejection
Episodes of infection
Diabetic control measured by HbA1c

Current anti-diabetic medication regimen

We will then perform a secondary data analysis.

13.8 Withdrawal criteria

Study medication will be stopped in the following situations:

1. Hypoglycaemia despite removal of other glucose-lowering drugs: e.g. repeated events of minor hypoglycaemia defined as:
   − An episode with symptoms and confirmed low glucose (<3.9 mmol/L).
   − An episode with low glucose (<3.9 mmol/L).
   − An episode with symptoms suggestive of hypoglycaemia when glucose was not measured.
   If a patient has episodes of hypoglycaemia, their anti-diabetic medications will be altered as per standard of clinical care.

2. One event of major hypoglycaemia regardless of any other diabetes drugs, as defined by the American Diabetes Association (ADA):
   - 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

3. Impaired hepatic function (AST/ALT >x3 ULN,) due to the hepatic metabolism of AZD1656

4. The patient's target HbA1c is less than 6.5% and their other anti-diabetic medications have been withdrawn.

If any of these situations occur, the subject will be withdrawn from the study medication, but will continue in the study with other study related activities.

If the patient's clinical care team feel that the patient requires treatment with gemfibrozil, then the patient will be withdrawn from the study medication, but continue other study related activities. This is not expected to happen in practice as gemfibrozil interacts with other immunosuppression medication the patient takes as part of their standard transplant regime, so gemfibrozil is avoided in transplantation medicine.

Patients may be withdrawn from the study if the investigator feels that individual adverse events or new information gained mean that it is not safe to continue the study, or if it is felt to be in the participant's best interest to stop the study.

Should a participant wish to withdraw from the study treatment, the patient will stop the study medication. Patients would be encouraged to continue with the study visits for safety, however should they not want to take part in any further study visits, they will continue to be followed up by their clinical care team as standard. It should be noted that routine clinical visits are very frequent for patients in their first year post-transplant so it is unlikely that any patients will get lost to follow-up, or be put at risk should they withdraw from the study.

Participants will continue to receive follow up procedures unless they specifically opt out.

Routine clinical data collection will continue for patients who have withdrawn from the study unless they specifically opt out of using routine clinical data collection. Should a patient withdraw from the study this will be documented on the CRF using a study termination form, which includes recording reasons for withdrawal and consent for any follow-up information being collected. This would include a scenario in which a female participant had a positive pregnancy test. We would consent her for monitoring her during her pregnancy.

13.9 Early withdrawal

If a patient is withdrawn from the study early they will continue with their standard care at the unit.

It will be documented in the CRF and medical notes if the patient is happy to continue on with study visits (without the study medication), or continue to have their clinical data collected, or no further data collected.

13.10 End of trial (EOT)

It is the CI's responsibility to submit the EOT notification to REC and MHRA once obtaining sponsor approval. The EOT notification must be received by REC and MHRA within 90 days of the end of the trial.

If the study is ended prematurely, the Chief Investigator will notify the Sponsor, REC & MHRA including the reasons for the premature termination (within 15 days).

End of Trial definition: is after the last patient has completed their last follow up point at 1 year post-transplant (data review visit).

14.0 Laboratories and samples

14.1 Local Laboratories

Standard biochemistry samples will be sent to the Royal London Hospital Laboratory. All the tests that will be performed are part of the standard diagnostic set of tests commonly used to test for diabetes.

Research blood samples will be taken at the same time, labelled with the patient's study number and date of sampling. They will be taken to the Immunology laboratories at the Royal London Hospital in order to isolate and store the patient's peripheral blood cells. Flow cytometry analysis of peripheral T cell populations will take place in the Immunology laboratories. Stored peripheral blood cells may also be taken to the William Harvey Research Institute by members of the study team, for functional analysis of peripheral Treg populations and analysis of inflammatory signalling markers. The serum save will be taken and processed in keeping with normal protocols in the Royal London Hospital Laboratory but will be taken to either the Royal London Immunology laboratories or the William Harvey Research Institute to be used in functional assays to measure the activity of the Tregs at different time points.

In addition, renal biopsy tissue collected as part of standard of care at the time of transplant and at month 3 will be examined for Treg cell infiltration. If any renal biopsies are carried out for a clinical indication in the interim period, then these will also be examined for Treg cell infiltration.

14.2 Sample Collection/Labelling/Logging

Samples will be collected by the research nurse or trained phlebotomist as per standard of care.

Samples will be labelled with patient identification and sent to the local labs as per routine care and the results logged on the pathology system and transcribed to the CRF.

The only samples that will be sent to the local lab, which are not part of routine care, are for serum C-peptide.

Volume of samples to be collected:
The total volume of blood which will be taken on top of routine care is:
1 table-spoon (approximately 20ml) of blood per clinic visit (4x 6ml samples of blood) in lithium heparin tubes provided locally.

In addition, 20ml of blood will be taken at visit 1, 2, 6 and 7 for Treg quantification via FACS. This sample will be taken to the Royal London Immunology laboratories by members of the study team for processing.

Any biopsy material will be processed and stored as part of routine clinical care.

14.3 Sample Receipt/Chain of Custody/Accountability

Samples will be sent to the lab by the research nurse, where they will be processed as per the lab's standard SOPs under their UKAS accreditation. The research team will have responsibility for the custody of the samples until they are handed over the lab technicians at the sample collection point. Research blood samples will remain within the custody of the research team.

14.4 Sample Analysis Procedures

All standard (biochemistry, haematology) samples will be taken to the local lab by the research nurse/team after being taken. All samples will be processed in accordance with local procedures.

In addition, research blood samples will be taken at the same time, labelled with the patient's study number. The isolation and FACS analysis of peripheral blood cells will be performed by members of the study team as per the Immunology lab's standard SOPs.

Peripheral blood cell samples and stored serum may also be taken to the William Harvey Research Institute by members of the study team, for functional analysis of peripheral T cell populations and analysis of inflammatory signalling markers. After sample processing is completed the samples will be destroyed and not stored further.

14.5 Sample and Data Recording/Reporting

Data will be recorded on the CRF/eCRF.

The CRF will be completed by the CI, SUB-I or research nurse. The CI will counter-sign completed CRFs and these will be stored securely in the study file in the research office.

14.6 End of study

No biological material will be kept in the department. All biological samples will have been sent to the lab and disposed of as per their routine SOP. No biological samples

will be retained at William Harvey Research Institute: they will be destroyed after sample processing.

15.0 Trial Medication

15.1 Name and description of investigational medicinal product(s)

AZD1656 is a potent and selective glucokinase activator that is administered orally as a tablet formulation. The matching placebo tablets have the same appearance as the tablets containing AZD1656.

15.2 Legal status of the drug

Not licenced

15.3 Summary of Product Characteristics (SmPC) or IB

See IB Edition 9, Sept 15th 2020

15.4 Drug storage and supply

The IMP/placebo will be shipped securely to the clinical trials pharmacy unit from the pharmacy manufacturing unit, where it will be stored until needed. The research nurse will collect the IMP/placebo from the clinical trials pharmacy and give this to the study patients. All medicinal products left over after study completion will be destroyed.

15.5 Supplier

The IMP and placebo will be packed and labelled by Fisher Clinical Services and sent to the clinical trials pharmacy at the Royal London Hospital.

Fisher Clinical Services U.K. Limited
Langhurstwood Road
Horsham
RH12 4QD
United Kingdom

The supply is being made specifically for use in the trial, and will not be used for any other purpose then as stated in the trial.

15.6 Manufacturer

The tablets were manufactured by Patheon.

Patheon UK Limited

151 Brook Drive
Milton Park
Abingdon
OX14 4SD
United Kingdom

15.7 IMP Storage

The drug should not be stored above 25°C or stored anywhere other than in the original package. The containers should be kept tightly closed.

The shelf life of the drug will be updated based on read-outs from an on ongoing stability study. The initial shelf life will be at least 12 months.

There are no special arrangements needed for the storage of the medication (it can be stored at room temperature).

15.8 Details of accountability

The study medication will be dispensed from pharmacy and given to the patient by a member of the research team on the delegation log. An accountability log will be used to record the details of each batch of study medication dispensed to a patient, including subject identification code, drug batch number, date of dispensing and quantity dispenses, date returned and quantity returned, and date destroyed. Accountability logs will be maintained by the clinical trial pharmacist.

15.9 Medication destruction/return and recall

At month 3 any unused study medication will be returned, counted and then destroyed as per local policy.

15.10 Prescription of IMP / Placebo/ NIMP

The ADOPTION prescription form will be used to prescribe IMP or placebo.

15.11 Preparation and labelling of IMP and Placebo

The active treatment is AZD1656 50mg tablets. The placebo tablet contains no active ingredient and is a visual match to the active.

The IMP and placebo will be packed and labelled by Fisher Clinical Services and sent to the clinical trials pharmacy at the Royal London Hospital.

Fisher Clinical Services U.K. Limited
Langhurstwood Road
Horsham
RH12 4QD
United Kingdom

15.12 Preparation and Administration of IMP

The IMP will be dispensed as 50mg tablets with two to be taken twice a day. Patients will be counselled on their dose during visit 1.

15.13 Dosage schedules

The patient will be dispensed either placebo or AZD1656 tablets for a 3 month supply.

These are two 50mg oral tablets to be taken twice a day with or after meals.

Missed doses will be permitted: if a patient misses a dose they should take their next dose at the usual time. Drug adherence will be encouraged at each visit. Drug accountability will be assessed at each study visit where patients will bring back their unused supply with non-adherence defined as less than 80% or more than 120% of medications taken.

15.14 Dispensing of IMP

There will be a dispensing guideline in place within pharmacy. Each member of staff who dispenses the IMP will sign the local/pharmacy dispensing log to document appropriate IMP tracking. All members of the trial team should ensure that they have had study specific training and their involvement should be demonstrated by the study specific trial delegation log.

15.15 Dosage modifications

No dosage modifications will be allowed.

However the study medication may be stopped if the investigator feels it is not safe for the patient to continue treatment with the study medication. At this point the patient will be withdrawn from the treatment with study medication for the rest of the trial but will continue in all other study related activities.

15.16 Known drug reactions and interaction with other therapies

Gemfibrozil is a potent inhibitor of the isoenzyme CYP2C8. When AZD1656 was administered as a single dose together with gemfibrozil, a 2.7-fold increase in AUC of AZD1656 was observed compared to single dose administration of AZD1656 alone. The $t_{1/2}$ of AZD1656 increased, suggesting that AZD1656 will accumulate by approximately 50% following repeated twice daily dosing of AZD1656 to steady state during concomitant gemfibrozil administration. However, the levels of the active metabolite, AZD5658, were reduced during co-administration with gemfibrozil. No statistically significant increase was observed for C_{max} when dosed together with gemfibrozil (D1020C00030).

15.17 Prior and Concomitant medication

Given the theoretical increase in AUC (but not C_{max}) with gemfibrozil. Any patient who is currently taking this agent will be excluded from the study.

Prior and Concomitant medication lists will be recorded in the case record forms

15.18 Assessment of compliance

Compliance will be assessed at study visits, when the research team will count the number of tablets returned and consider less than 80% or more than 120% adherence to be non-compliant.

15.19 Arrangements for post-trial access to IMP and care

This agent will not be available for long-term use as published studies have shown that its biological effect wears off after 3-4 months.

16 Equipment and Devices

No equipment or devices will be used outside of standard care.

17 Pharmacovigilance

17.1 General Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by, or related to, that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility: i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death. • Is life-threatening. • Requires inpatient hospitalisation or prolongation of existing hospitalisation. • Results in persistent or significant disability/incapacity. • Consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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 were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information (RSI): • In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product. • In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

17.2 Site Investigators' Assessment

The Chief Investigator is responsible for the care of the participant, or in his/her absence a delegated medical practitioner and is responsible for assessment of any event for:

- Seriousness
  Assessing whether the event is serious according to the definitions given in section 17.1.

- Causality
  Assessing the causality of all serious adverse events/reactions in relation to the trial treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

- Expectedness
  Assessing the expectedness of all SAEs according to the definition given. If the SAE is unexpected, then it is a SUSAR.

- Severity
  Assessing the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on patient/event outcome criteria.

    - **Mild**: Some discomfort noted but without disruption of daily life
    - **Moderate**: Discomfort enough to affect/reduce normal activity
    - **Severe**: Complete inability to perform daily activities and lead a normal life

17.3 Reference Safety Information

Reference Safety Information is the information used for assessing whether an adverse reaction is expected. See IB Edition 9, September 15th 2020 for further details.

Undesirable effects

Across clinical studies, AZD1656 has been well tolerated and no safety concerns have been raised. 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.

From the phase IIb published studies the following side effects occur more frequently than placebo.

See below for tables 3 and 4 taken from AZD1656 IB version 9 2020.

Table 3 **Adverse Events reported during treatment by at least 2 subjects on either AZD1656 or placebo in the Phase IIa 28-day studies; number of subjects and presented by preferred term**

	Total		AZD1656 as monotherapy in D1020C00002 part B		AZD1656 given on top of metformin in D1020C00019		AZD1656 given on top of insulin in D1020C00020	
Preferred Term	**AZD1656 12.6-90 mg bd N=49**	**Placebo N=18**	**AZD1656 15-45 mg bd N=15**	**Placebo N=5**	**AZD1656 5-50 mg bd N=19**	**Placebo N=8**	**AZD1656 12.6-90 mg bd N=15**	**Placebo N=5**
Total number of subjects with AE	**40**	**13**	**11**	**3**	**16**	**7**	**13**	**3**
Headache	15	5	1	2	4	2	10	1
Blood glucose decreased	11	1			9	1	2	
Pain in extremity	7		3				4	
Diarrhoea	5	2	1		1		3	2
Upper respiratory tract infection	5	1	5					1
Urinary tract infection	4	1	1				3	1
Abdominal pain upper	2		1				1	
Application site reaction	2						2	
Catheter site pain	2						2	
Constipation	2				1		1	
Dizziness	2	3	1	1	1	2		
Ecchymosis	2		1				1	
Erythema	2		1		1			
Nausea	2	2	1			1	1	1
Rhinorrhoea	2				1		1	

All AE reported by at least 2 subjects

Table 4 **Study D1020C00009, add-on to metformin: Number (%) of subjects who had at least 1 AE in any category for Placebo, Glipizide, Open label AZD1656 and total AZD1656 cohort 1 (safety analysis set 0-6 month all patients (regardless of rescue))**

AE category	Number (%) of patients[a]							
	Placebo (n=87)		Glipizide (n=93)		AZD1627 Open label dose[b] (n=71)		Total AZD1656 Cohort 1[c] (n=272)	
Any AE	**32**	**(36.8)**	**38**	**(40.9)**	**22**	**(31.0)**	**114**	**(41.9)**
Any AE with outcome = death	0		0		0		0	
Any SAE (including events with outcome = death)	2	(2.3)	3	(3.2)	1	(1.4)	5	(1.8)
Any AE leading to discontinuation of treatment (DAE)	1	(1.1)	2	(3.2)	1	(1.4)	13	(4.8)
Any other significant AE (OAE)[d]	0		0		0		0	
Mild AE	24	(27.6)	3	(3.2)	1	(1.4)	5	(1.8)
Moderate AE	12	(13.8)	2	(3.2)	1	(1.4)	13	(4.8)
Severe AE	2	(2.3)	0		0		0	

Special warnings and precautions for use

Nil

17.4 Notification and Reporting Adverse Events or Reactions

If the AE is not defined as SERIOUS, the AE is recorded in the CRF and the participant is followed up by the research team. The AE is documented in the participant's medical notes (where appropriate) and the CRF.

If, as part of the routine care of patients post-renal transplant, the clinical care team withhold the study medication, they must inform the CI/research team. Members of the transplant team will be educated on the protocol and study requirements.

In addition to ensure that all AEs are gathered by the research team during the 3-month treatment period in a timely manner, the research team will review the source documents (clinic letters and or clinical entries on electronic patient record) on a regular basis (maximum every month).

17.5 Notification of AEs of special interest

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

17.6 Adverse events that do not require reporting

It is standard protocol to stop CMV prophylaxis within the first-year post transplant. It is also standard practice to wean some patients off prednisolone medication in the first year.

Therefore we do not consider these changes an adverse event and they will not be formally reported.

17.7 Notification and Reporting of Serious Adverse Events & SUSARs

All Serious Adverse Events (SAEs) will be recorded in the participants' notes, the CRF, the sponsor SAE form, and reported to the sponsor (Joint Research Management Office) within 24 hours of the CI or co-investigators becoming aware of the event. Nominated co-investigators (as listed in the delegation log) will sign the SAE forms in the absence of the CI.

Reporting of SUSARs

Suspected Unexpected Serious Adverse Reactions (SUSARs) that occur during the trial will be reported to the sponsor (joint management research office) within 24 hours of the CI or co-investigator becoming aware of the event. The sponsor will then report this to the MHRA.

Reporting of SAE/SUSAR to Astra Zeneca (see appendix 1: Safety Reporting Responsibilities)

Report unblinded Suspected Unexpected Serious Adverse Reactions (SUSARs) to AstraZeneca (via Kinapse) as individual case reports as they occur.

17.8 Sponsor Medical Assessment

The CI retains overall responsibility for oversight of IMP safety profile and medical assessment of SAEs and SUSARs. The CI must review all SAEs within 48 hours of receipt. This review should encompass seriousness, relatedness and expectedness. Day 0 for all SUSARs is when the SAE/SUSAR is received by the CI and/or coordinating team and/or sponsor whichever is first.

It is expected that the CI will achieve oversight of IMP safety profile through trial committees as per section 28.0.

17.9 Urgent Safety Measures

The CI 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 should be taken immediately. In this instance, approval from the

Competent Authority prior to implementing these safety measures is not required. However, it is the responsibility of the CI to attempt, where possible, to discuss the proposed measures with the Sponsor and Medical Advisor at the MHRA (via telephone) prior to implementing them if possible.

The CI has an obligation to inform both the MHRA and Research Ethics Committee **in writing within 3 days**, in the form of a substantial amendment. The sponsor (JRMO) must be sent a copy of the correspondence with regards to this matter as soon as it is sent.

17.10 Procedures for reporting blinded SUSARs

The CI as sponsor medical assessor will assess the event blinded, and will assess for active IMP and Placebo. For SUSARS the CI will remain blinded, however the sponsor will be unblinded for reporting to the MHRA.

17.11 Pregnancy

If a patient becomes pregnant whilst enrolled in the study, the study medication will be withdrawn but the patient will continue on in the study. No data is available on the effects of AZD1656 on pregnancy and lactation in humans. Results from the repro-toxicity studies in animals (fertility and embryo-foetal development) support inclusion of women of childbearing potential in clinical studies, provided that pregnancy is prevented using a reliable form of contraception. The results from the animal studies suggest that any adverse effect observed was as a result of maternal hypoglycaemia.

If a patient on the study medication becomes pregnant the CI has the responsibility to ensure that the pregnancy form is completed and sent to the sponsor within the agreed timelines. The initial report should be sent within 24 hours and follow up information submitted as and when it becomes available up to agreed follow up time after birth.

If a female patient on the study medication, or the female partner of a patient on the study medication, becomes pregnant, she will be asked to sign an additional consent form to allow data collection and monitoring during her pregnancy.

18.0 Annual reporting

Development Annual Safety Update (DSUR)

The DSUR will be written by the CI (using the Sponsor's template) and submitted to the sponsor for review prior to submission to the MHRA. The DSUR is due for submission within 60 days of the end of the reporting period. The reporting period is annually from the date on the "notice of acceptance letter" from the MHRA. As delegated Sponsor Medical Assessor the CI will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the trial. REC will be sent a copy of the DSUR. Any findings in the DSUR that are inconsistent with the Investigator Brochure should be communicated to AZ during DSUR production but at the latest in parallel to the DSUR being sent to the RA/Ethics committee.

Annual Progress Report (APR)

The APR will be written by the CI (using HRA template) and submitted to the sponsor for review prior to submission to the REC. The APR is due within 30 days of the anniversary date of the "favourable opinion" letter from the REC.

19.0 Statistical and Data Analysis

19.1 Sample size calculation

n=25 in each arm. This is a pilot/exploratory study: the numbers were chosen as this was felt to be feasible given the resources of the site, and will enable generation of data for a larger scale trial should the results of this pilot be encouraging.

19.2 Planned recruitment rate

Based on analysis from the renal unit at the Royal London Hospital (where the study will be based), around 140 transplants are performed per year, of which 30% have type 2 diabetes. We expect up to 20% of patients to decline to take part. Therefore, it is expected that the recruitment will be complete within 16-20 months.

19.3 Statistical analysis plan (SAP)

Please refer to SAP for full details

Primary Endpoint

The primary endpoint is the change in mean peripheral Treg cell number between baseline and 3 months measured using FACS analysis between AZD1656 and placebo.

This will be analysed at the first data analysis.

Secondary Endpoints:

1) Histological staining for Treg cells in renal biopsy tissue between baseline and 3 month protocol biopsy
2) Incidence of delayed graft function, defined as the need for dialysis within 1 week post-transplant
3) Diabetic control between baseline and month 3 using change in HbA1c measurement
4) Dose of other anti-diabetic medication between baseline and month 3 (descriptive)
5) Safety endpoints i.e. number of hypoglycaemic episodes (descriptive)
6) Insulin resistance: HOMA IR measurement at month 3
7) Graft function: (eGFR) at month 3
8) Episodes of acute rejection (defined as biopsy proven acute rejection)
9) Episodes of opportunistic infections: bacterial and viral (descriptive)

All of these endpoints will be analysed at the first data analysis; endpoints 8 and 9 will also be re-examined at the second data analysis.

Exploratory or Tertiary Endpoints/outcomes

1) 12-month graft function (eGFR) and diabetic control (HbA1c; medication review) to assess legacy effect (potential follow up publication)
2) Differences in other peripheral T cell populations, measured by FACS analysis
3) Histological staining for Treg cells in any renal biopsy taken for clinical indications between baseline and month 3 protocol biopsy
4) Differences in the functional phenotype of the Treg cells

Endpoints 2 and 3-4 will be analysed at the first data analysis; endpoint 1 will be analysed at the second data analysis.

Baseline Demographics and Biochemical parameters

Demographics and Clinical Characteristics

- Age at recruitment (derived from date of birth; continuous)
- Sex (categorical)
- Self-reported ethnicity (using ONS categories; categorical)
- Weight (continuous)
- Systolic BP (continuous)
- Diastolic BP (continuous)

Medical History

- Cause of end stage renal failure (categorical)
- Dialysis modality (categorical)
- Dialysis vintage (continuous)
- Diabetes duration (continuous)
- Retinopathy (yes/no, categorical)
- Neuropathy (yes/no, categorical)
- Coronary artery disease (yes/no, categorical)
- Peripheral artery disease (yes/no, categorical)
- Cerebrovascular disease (yes/no, categorical)
- Hypertension (yes/no, categorical)
- Heart failure (yes/no, categorical)

Pregnancy test

- **Pregnancy test negative (either serum or urine) (yes/no, categorical)**

Transplant details

- Cold ischaemia time in hours (continuous)
- Warm ischaemic rime minutes (continuous)
- Donor age (continuous)
- ECD (yes/no, categorical)
- CMV mismatch (yes/no, categorical)
- HLA mismatch (categorical)

Medication

Each medication will be recorded as name/dose/start date (categorical)

Biochemical Parameters

- Fasting c-peptide (continuous)
- Fasting cholesterol (continuous)
- Haemoglobin (continuous)
- Serum sodium (continuous)
- Serum potassium (continuous)
- Serum urea (continuous)
- Serum creatinine (continuous)
- eGFR (CKD-EPI formula, continuous)
- Serum albumin (continuous)
- Serum alkaline phosphatase (continuous)
- Serum bilirubin (continuous)
- Serum alanine aminotransferase (continuous)
- Serum calcium (continuous)
- Serum phosphate (continuous)
- C-reactive protein (continuous)
- Glucose (continuous)
- Haemoglobin A1C (DCCT aligned; continuous)
- Peripheral Treg Cell number (interval)
- HOMA IR (continuous)

19.4 Summary of baseline data and flow of patients

The IMP versus placebo groups will be compared using standard statistical methods.

19.5 Primary outcome analysis

The endpoint data will be analysed on an ITT basis, with no subgroup analysis using unpaired parametric and non-parametric analysis as necessary, comparing the

change in mean Treg cell number between baseline and month 3 between the 2 groups.

Continuous variables will be tested for normality using D'Agostino-Pearson normality test. Mean (standard deviation), median (interquartile ranges) will be displayed along with max-min point estimate and confidence intervals. Statistical analysis will be by student t-test (unpaired) or Mann-Whitney U test.

Categorical data will be analysed by Chi Square test.

Statistical significance considered if P-value <0.05.

19.6 Secondary outcome analysis

Each of the secondary endpoints will be analysed with the null hypothesis that the IMP and placebo are similar for the primary endpoint.

19.7 Interim analysis and criteria for the premature termination of the trial

There will be an interim datalock after the last patient has completed visit 7, at which point we will analyse the primary endpoint data and the relevant secondary and tertiary endpoints. There will be a secondary analysis after the final data collection review one year after transplant.

19.8 Subject population

The study population will be those patients undergoing a renal transplant at the RLH renal unit who satisfy the inclusion criteria and do not meet any of the exclusion criteria.

19.9 Procedure(s) to account for missing or spurious data

As this group of patients attend standard of care clinic visits very frequently post transplantation, it is not expected that they will be lost to follow up. The research team will make every effort to rectify any missing or spurious data.

20.0 Data Handling & Record Keeping

20.1 Confidentiality

The Chief Investigator has the responsibility to ensure that participant anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study participants will be kept confidential and managed in accordance with the Data Protection Act; NHS Caldicott Guardian; the UK Policy Framework of Health and Social Care Research; and Ethics Committee Approval. All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act 2018, and archived in line with the Medicines for Human Use (Clinical Trials) and all subsequent amendments as defined in the JRMO SOP 20 Archiving.

The Chief Investigator and the study team will adhere to these regulations to ensure that the participants' identities are protected at every stage of their participation in the study. To ensure this is done accordingly, at time of consent each participant will be allocated a unique screening number by either the CI or a member of the study team before undergoing any screening procedures.

All investigators and trial site staff will comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

20.2 Data Custodian Details

The Chief Investigator Kieran McCafferty, Royal London Hospital, E1 1BB is the 'Custodian' of the research data.

20.3 Pseudononymisation

Data will be in the form of linked anonymised data. Unique study numbers will be used, which are linked to a treatment code. This will be contained in the ISF on the enrolment log.

20.4 Transferring/Transporting Data

All patient-identifiable information will be stored in a locked environment, or on password protected NHS computers on an electronic database.

No data will be transferred out of this environment.

20.5 Data collection tools and source document identification

The source document will be paper medical records and the electronic patient record CRS Millenium. Data from the source document will be added to a paper CRF.

20.6 Source Data

The source documents will comprise the site medical notes and health records (paper and electronic), including Barts Health laboratory and pharmacy records.

20.7 Case Report Form

Data will be transcribed from source documents to paper Case Report Forms. Paper CRFs will be kept in the investigator file and they will be reviewed as part of source data verification during site monitoring. Patients will be identified only by initials, trial number and day (dd) of birth.

20.8 Data handling and record keeping

Data will be recorded from study visits in the source data and transcribed to the CRF. All documents (CRF, signed consent forms etc.) will be kept according to the sponsor's requirements. All research staff will be trained on the use of the database and CRF.

20.9 Access to Data, Source Data and Documents

Direct access will be granted to authorised representatives from the Sponsor or delegate, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

21.0 Archiving

During the course of research and for the archiving period, all records are the responsibility of the Chief Investigator and must be kept in secure conditions. When the research trial is complete, it is a requirement of the Trust Policy that the records are kept for a further 25 years.

Destruction of essential documents will require authorisation from the Sponsor.

Archiving will be authorised by the sponsor following submission of the end of study report.

22.0 Monitoring, Audit and Inspection

22.1 Monitoring

A Trial Monitoring Plan will be developed and signed by the Sponsor and Chief investigator based on the sponsor's trial risk assessment, this will include on site monitoring. Monitoring procedures are detailed in the Trial Monitoring Plan.

A sponsor monitor will monitor the trial on a regular basis.

22.2 Auditing

The sponsor retains the right to audit the trial. In addition, any part of the trial may be inspected by the regulatory bodies and funders where applicable.

22.3 Notification of Serious Breaches to GCP and/or the protocol

The CI is responsible for reporting any serious breaches to the sponsor (JRMO) **within 24 hours of becoming aware of the breach.**

The sponsor will work with the CI to investigate any potential breach. The sponsor will notify the MHRA, and the CI will notify the REC, within 7 working days of becoming aware of the serious breach.

22.4 Compliance

The CI will ensure that the trial is conducted in compliance with the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), and any subsequent amendments of the clinical trial regulations, current UK Policy Framework for Health and Social Care Research, GCP guidelines, the World Medical Association Declaration of Helsinki (1996), the Sponsor's SOPs, and other regulatory requirements as amended.

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA.

22.5 Non-Compliance

Planned deviations or waivers to the protocol and specifically the eligibility criteria are not allowed.

Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

All deviations will be documented in the patient records, deviation log and CRF.

The CI and the co-ordinating team should assess the non-compliances and agree on a timeframe in which they need to be dealt with. This assessment should include the need to escalate to the sponsor. Any event with the potential to affect participant safety or data integrity should be reported to the sponsor within 24 hours of the co-ordinating team becoming aware.

Where applicable, corrective and preventative actions should be taken. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the Sponsor will agree an appropriate action, which could include an on-site audit.

22.6 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA, favourable opinion has been obtained from an NHS REC, and HRA Approval has been granted.

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol participants into the trial, the site will confirm to the CI that it has capacity and capability to run the trial, and the CI will activate the site.

The Chief Investigator will obtain approval from the appropriate review bodies before implementing any amendments to the trial.

This study does not involve ionising radiation.

23.0 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The Chief Investigator has no financial or other competing interests.

All members of committee will sign a competing interests form.

24.0 Ethical and Regulatory Considerations

Before the start of the trial, approval will be sought from the Research Ethics Committee (REC) and MHRA for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters.

The authority to make a decision whether an amendment constitutes a minor or substantial amendment lies with the sponsor.

Substantial amendments that require review by the Sponsor and REC and MHRA (where relevant) will not be implemented until the REC and or MHRA grants a favourable opinion for the study and until capacity and capability has been confirmed by the site.

All correspondence with the Sponsor, REC and MHRA will be retained in the Trial Master File at the lead site and Investigator Site File at each site.

The Chief Investigator will notify the REC, MHRA and Sponsor of the end of the study.

25.0 Peer review

The clinical trial protocol has been reviewed by an independent consultant nephrologist, by IMP supplier AstraZeneca and internally by consultants within the nephrology department at Barts Health NHS Trust.

26.0 Public and Participant Involvement

Haemodialysis patients (who may be potential future recruits) and patients who currently have a renal transplant were involved in reviewing the patient documents to ensure ease of reading and clarity. We have engaged with our patient group to invite them to nominate one or more patients to sit on the Trial Study group.

27.0 Indemnity

Queen Mary University of London's research insurance will apply to the design and management of the trial. The NHS indemnity scheme will apply to site-level research activities taking place at Barts Health NHS Trust.

27.1 Amendments

Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the sponsor may make a non-substantial amendment at any time during a trial. If the sponsor wishes to make a substantial amendment to the CTA or the documents that supported the original application for the CTA, the sponsor must submit a valid notice of amendment to the licencing authority (MHRA) and to the HRA and REC for consideration. The MHRA, REC and HRA will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the MHRA, REC and HRA.

If applicable, other specialist review bodies (e.g. Clinical Boards) need to be notified about substantial amendments in case the amendment affects their opinion of the study.

Amendments will also be notified to NHS R&D departments of participating sites to assess whether the amendment affects the NHS capability and capacity for that site.

The CI, along with the steering committee, will be responsible for making the decision to amend the protocol. Amendments will be submitted by the CI to the MHRA, HRA and REC and will inform the Trial registries and local R&D departments. Any changes to study documents will be subject to version control and amendment history.

27.2 Access to the final trial dataset

The steering committee will have access to the final dataset along with the CI.

28.0 Trial Committees

The trial steering committee/ drug safety monitoring committee will be made up of:

- Independent Chair
- Trials statistician
- Director of the Diabetic Kidney Centre
- Consultant Transplant Surgery
- Consultant in Transplant surgery/renal medicine/diabetic medicine
- Chief Investigator

For the current names of the members please see TSC/DSM document.

There will be regular documented management meetings and a trial steering committee with independent representation.

This group will meet every 6 months to ensure all practical details of the trial are progressing and working well, and that everyone within the trial understands them. This group will review safety/operational concerns and will have the authority to terminate / prematurely discontinue the trial. They will not have access to unblinded data unless a specific unblinding request is made for an individual patient.

29.0 Publication and Dissemination Policy

29.1 Publication

The study will be registered on clinical trials.gov.

Publications will occur at the end of the study.
The sponsor retains the right to review all publications prior to submission or publication.
Responsibility for ensuring accuracy of any publication from this study is delegated to the Chief Investigator.
All publications should acknowledge the Sponsor.

The full study report will be accessible via EudraCT.

Should the results of the study suggest benefit, an application will be made to consider a further larger powered study.

Publications will be in accordance with the external sponsored research clinical agreement with AZ: the sponsor/PI will provide Astra Zeneca with copies of any materials relating to the Study, the Study Data or the Developed Technologies that it either intends to publish or make any presentations relating to, at least thirty (30) days in advance of publication, submission or presentation.

At the request of the Company, the Sponsor/PI will not include in or remove from any proposed publication any confidential information; and withhold publication, submission for publication or presentation for a period of ninety days from the date on which the Company receives the material to allow the Company to take such measures as the Company considers necessary to preserve its proprietary rights and/or protect its confidential information.

29.2 Dissemination policy

Data arising from the trial is owned by the sponsor. In all publications arising from this study, the Diabetic Kidney Disease Centre will be acknowledged in the final manuscript.

Participants will be notified of the outcome of the trial in writing. Their non-blinded treatment allocation will be made available to patients on request following publication.
The trial protocol and the full study report will be made publicly available via EudraCT.

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This protocol is based on JRMO CTIMP Protocol Template June 2015 version 4.0.

APPENDIX 1: Safety Reporting Responsibilities

Sponsor: QMUL

Trial: ADOPTION

AstraZeneca Reference number:

Sponsors and AstraZeneca will exchange safety information in accordance with the requirements set out in the summary table at the end of this document.

The following information is required.

Before the trial starts:

Sponsor will provide AstraZeneca with:

- A copy of the format of the SAE report form including the AZ Reference number.
- An example of the format by which SAEs (including SUSARS) will be reported from sponsor to AZ. This should include the format of any individual reports (t*his may be the same form used for reporting SAEs above)* and/or the format of quarterly listings if appropriate.
- The format by which site and patient ID will be presented in safety reports so that they can be entered in a consistent way on the AZ safety database.

AstraZeneca will provide the sponsor with:

- The current IB
  An adverse event should only be considered expected for an AstraZeneca Investigational Medicinal Product (IMP) if it is included in Section 5.4 of the IB. These will be available to access through ES^{2}ROS – Externally Sponsored Scientific Research Operations System
- The contact information for our safety reporting: astrazeneca@kinapse.com. All information that needs to be shared with AstraZeneca should be sent to Kinapse at the email address provided according to the guidelines set out in subsequent sections of this document.

During the Trial

Sponsor will:

- Report unblinded Suspected Unexpected Serious Adverse Reactions (SUSARs) to AstraZeneca (via Kinapse) as individual case reports as they occur
- Report blinded listings of Serious Adverse Events (SAEs) and Suspected Serious Adverse Reactions (SSAR's) to AstraZeneca on a quarterly basis.

- Inform AstraZeneca within 24 hours of knowledge of the event of any emerging safety data or actions that the Sponsor is considering as a result of a safety signal with the IMP. This includes but is not limited to:
    - Urgent safety measures to be implemented in the study
    - Safety amendments to protocol/patient information & informed consent
    - Open reports from Independent Data Monitoring Committees (IDMCs) excluding confidential reports to IDMC and minutes of IDMC meetings
    - Interactions with Regulatory Authorities (RA's)/ Ethics Committees (EC's)
    - Inform AZ on an ongoing basis of any new safety trends or signals observed during routine safety surveillance activities

- Include the following essential information in SUSAR, SSAR and SAE reports provided to AstraZeneca (initial and follow-up) :
    - AstraZeneca Reference number
    - Sponsor trial number
    - Centre number
    - Patient trial number
    - Year of birth or age
    - Sex
    - IMP(s) dose, start & stop date
    - SAE onset & stop date
    - Event term as reported by the investigator (and/or the CTCAE V4 term and grade)
    - Investigator's assessment of seriousness (ICH definitions)
    - Investigator's assessment of causality
    - SAE Outcome

During the Trial

AstraZeneca will:

- Immediately inform the sponsor of any emerging safety data or actions that AstraZeneca is considering as a result of a safety signal with the IMP. This includes but is not limited to:
    - New safety information which may alter the benefit risk assessment
    - Urgent safety measures to be implemented

- Request follow-up information on an SAE that is of interest and is related to the IMP(s).
- Provide the Sponsor with IB updates on an annual basis or as new safety information emerges.

- Consult with the sponsor in the unlikely circumstance that code break information is required for an individual patient, should AstraZeneca need to expedite an SAE that has not been reported to RAs by the sponsor.
- Provide SAE Line Listings of the IMP if required

At the end of the Trial
Sponsor will:

- Provide safety listings (details are included in the summary table below)

Summary of Minimum Requirements for Exchange of Safety Data

Sponsors will submit safety information in compliance with clinical trial regulations and the Standard Operating Procedures of their organisation including to:

- Regulatory authorities
- Ethics committees
- Site investigators

In addition, **Sponsors will submit the following safety information to AstraZeneca:**

Category of Adverse Event/ Report	Report Type	When to send report to AZ	Method of Submission	Additional Information
SUSARs	**Individual unblinded case reports** (Initial and follow-up reports)	Within one (1) business day of the reports being sent to the Regulatory Authority	Email to: astrazeneca@kinapse.com	**Sponsor responsible for:** • Expedited reporting of all SUSARs to the RA of participating countries in line with local requirements. • Compliance with local regulations of participating countries for reporting of SUSARs to investigational sites and EC's. **AstraZeneca responsible for:** • Reporting SUSARs to RA's where AstraZeneca sponsored studies are being conducted with the IMP as appropriate. • Reporting SUSARs to investigators participating in any AstraZeneca sponsored studies with the IMP as required by RA's.

SAEs/ SSARs	**Summary Line Listings**	On a quarterly basis from the date of the first patient consent		• SAEs and SSARs should be provided as blinded line listings. • Where possible the listing should include only events that are new or updated since the last report.
Category of Adverse Event/ Report	**Report Type**	**When to send report to AZ**	**Method of Submission**	**Additional Information**
Annual DSUR – (EU only)	**Periodic safety reports** (produced for external purposes e.g. EC or RA of participating countries)	Only required if the DSUR is inconsistent with the IB.	Contact your AZ operational representative	• Ideally any findings in the DSUR that are inconsistent with the IB should be communicated to AZ during DSUR production but at the latest in parallel to the DSUR being sent to the RA/Ethics committee. If this situation arises contact your AZ operational representative. • The production of any DSUR with no new safety concerns should be confirmed in writing to your AZ operational representative.
End of Study SAEs, SSARs & SUSARs (for entry onto AZ Patient Safety database)	**A cumulative final listing** of all unblinded SAEs, SSAR's & SUSARs	At 'clean file' *(when all study queries have been answered and the database is locked)* at the following time points: 1. At primary analysis 2. After last patient has completed study treatment	Email to: astrazeneca@kinapse.com and to AZ operational representative	• For blinded studies AZ require an unblinded listing of SAEs and SSARs to enable unblinding of these events on the AZ safety database. • For convenience and completeness SUSARs should also be included and easily identifiable.

AstraZeneca will submit the following safety information to trial Sponsors:

Category of Adverse Event/ Report	Report Type	Frequency/ Timeframe	Method of Submission	Additional Information
SUSARs	**Final CIOMS report of case (password protected)**	Within 15 days of initial receipt	Email to Sponsor contact.	• These may be provided whilst clinical studies (AZ-sponsored or externally-sponsored) are on-going or until the IMP becomes marketed. • AstraZeneca will provide these over the time period stated in the bullet point above to investigators, EC's and relevant RAs involved in AstraZeneca sponsored studies. • Sponsor will distribute these to investigators and ECs in line with local requirements.

Contact Details

AstraZeneca:

Emerging safety data or actions:	Email to: astrazeneca@kinapse.com
General enquiries to AZ:	AZ Operational or Scientific Representative

The AstraZeneca Reference number and IMP name(s) should be included in email headers and emails should be sent in an encrypted file e.g. WinZip

Sponsor responsibility:

Periodic line listings notification:	Name of Trial Coordinator of Study: Sindu Sivarajan Address: Renal Research Department Whitechapel E1 1BB
SAE follow-up queries:	Name: Kieran McCafferty Email: kieran.mccafferty4@nhs.net Telephone: 07980620627
Unblinded Request:	Name: Dr Conor Byrne Email: conor.byrne1@nhs.net Telephone: 02073777000

Only organisational emails may be used