AZD1656 in Organ Transplants for Promoting Immune Tolerance in Diabetes (ADOPTION)

Full Title: AZD1656 in Transplantation with Diabetes for Promotion of Immune Tolerance
Short Title: The ADOPTION Study
Sponsor: Queen Mary University of London

1.1 Primary Objective/s

The primary goal is to determine whether administering AZD1656 to post-transplant patients for a duration of 3 months results in the alteration of Treg migration when compared to a placebo.

1.2 Secondary Objective/s

The secondary objectives include assessing the safety and efficacy of AZD1656 in managing diabetes after transplantation and investigating its impact on the infiltration of Treg cells in renal transplant tissue.

2.0 Eligibility Criteria

To qualify for participation in the trial, individuals must meet all the inclusion criteria listed below and not meet any of the exclusion criteria.

2.1 Inclusion Criteria

a) Individuals of both genders, aged 18 years and older.

b) Recent renal transplant recipients at the Royal London Hospital, within the last 24 hours.

c) Pre-transplant diagnosis of Type 2 diabetes.

d) Willingness to provide written, informed consent before undergoing any study-specific procedures.

e) Women of childbearing potential must provide documentation of a negative pregnancy test during their admission for renal transplant.

*Women of childbearing potential are defined as those who have reached menarche but have not yet entered menopause, unless they are permanently sterile. Permanent sterilization

methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A post-menopausal state is defined as the absence of menstrual cycles for 12 months without any other medical explanation.

2.2 Exclusion Criteria

a) Incapable of providing consent.

b) Known allergy or intolerance to AZD1656.

c) Pregnant or breastfeeding women.

d) Individuals who plan to become pregnant or are unwilling to use highly effective contraception during the 3-month treatment period and for 2 weeks following treatment. This also applies to men with female partners of childbearing potential who refuse to use contraceptives, and their female partners who plan to become pregnant or are unwilling to use highly effective contraception during the 3-month treatment period and for 2 weeks afterward.

e) Clinically significant medical or mental health history, as determined by the investigator, except for conditions related to chronic kidney disease.

f) Current or planned use of strong inhibitors of CYP2C8.

g) Participation in an investigational drug trial within the 3 months preceding the administration of the initial dose of the study drug.

*Highly effective contraception methods are those with a failure rate of less than 1% per year when used correctly and consistently. These methods include:

- Patients receiving renal transplants who are 18 years of age or older will make up the patient population.
- Combined hormonal contraception (containing both estrogen and progestogen) associated with ovulation inhibition, available in oral, transvaginal, or transdermal forms.
- Progestogen-only hormonal contraception associated with ovulation inhibition, available in oral, injectable, or implantable forms.
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.

- A vasectomized partner, provided that the partner is the sole sexual partner of the participant and has received a medical evaluation confirming the success of the vasectomy.

3.0 Subject Enrollment

3.1 Informed Consent:

Before the participant undergoes procedures unique to the trial and outside of standard routine care at the participating site (such as collecting identifiable participant data), informed consent will be obtained either before or within 24 hours after the transplant.

It is impossible to contact patients in the days and weeks leading up to their transplant in the event of deceased donor transplantation since patients are unaware of when they will get a transplant. Patients will already have been granted permission for undertake their kidney transplant as soon as possible, although some individuals might not be able to provide fully informed permission either the day before or the day following.

3.2 Consent considerations:

The participant must have the freedom to leave the study at any moment, without explanation, and without doing so jeopardizing their ability to get future care. They also need to be given a contact number where they can get more details on the trial. In situations where re-consent is necessary, such as when during the trial new Research Safety Information is made accessible, or after a modification that impacts the patient or requires that a participant be given new information. The following are the considerations to be followed.

- Patients receiving renal transplants who are 18 years of age or older will make up the patient population.
- It is the duty of the CI to guarantee that all subjects who are considered vulnerable are safeguarded and take part willingly in an atmosphere free from undue influence or pressure.
- Since cognitive impairment is a common reason not to receive a kidney transplant, patients won't experience any cognitive impairment. When a patient does not speak English, we shall use conventional clinical translation support services or independent advocates, both of which are easily accessible during the operation's consent process.

- Patients whom the clinical staff determines are not capable of participating in the study will not be approached by them. Participants in the study must be at least 18 years old.

3.3 Treatment assignment

a) Randomization method:

Simple randomization with pre-filled envelopes bearing study numbers 1 through 50 printed on them will be the approach used for randomization. An impartial member of the clinical team will conduct quality control checks and document the results, and a doctor who is not involved in the study will prefill the envelopes. Within A treatment code will be included in the package and forwarded to the pharmacist together with the patient's research ID. If a patient is assigned at random but does not get any IMP and placebo subjects will not be added to the trial or substituted. The patient's treatment code and study number will both be recorded in the master file trial.

b) Blinding:

The patient and the research team will be blind to the therapy intervention in this double-blind placebo study. The pharmacy employees who administer the research drug won't be blinded, nor will Employees of the Sponsor Office are in charge of sending the unblinded SUSAR reports to the firm.

4.0 <u>Study Procedure</u>

- AZD1656 is a monoclonal antibody that targets the CD40 receptor on cells involved in the immune response. It is being investigated for its potential to promote immune tolerance in transplantation patients with diabetes.
- The following study visits and parameters could be measured in a clinical trial ofAZD1656 in transplantation patients with diabetes:

4.1 Parameters

- General safety: Vital signs, physical examination, laboratory tests (including bloodcounts, liver and kidney function tests, electrolytes, and blood glucose levels)
- Immune tolerance: Mixed lymphocyte reaction (MLR), T cell proliferation assays,cytokine assays, regulatory T cell (Treg) analysis, chimerism analysis
- Diabetes management: Blood glucose levels, insulin requirements, HbA1c levels
- Transplant function: Kidney function tests, liver function tests, blood pressure, weight
- Patient-reported outcomes: Quality of life surveys, diabetes-specific questionnaire

4.2 Drug to be used dose, method, schedule of administration, dose modification, toxicity include

Patients will receive 50mg tablets of the IMP, to be taken twice daily in sets of two. They willalso receive counseling about their dosage during their visits.

Patients will receive a 3-month supply of either placebo or AZD1656 tablets. These are oral tablets of 50mg each, to be taken twice daily with meals or after meals. If a patient misses a dose,they should take the next one at the regular time. At each visit, adherence to the medication will be emphasized. During study visits, patients are required to return any unused tablets. Non- adherence will be determined if medication taken falls below 80% or exceeds 120% of the prescribed amount.

Dosage adjustments are not permitted. Nevertheless, the study medication can be discontinued ifthe investigator deems it unsafe for the patient to continue. In such cases, the patient will be removed from the study medication for the remainder of the trial but will continue participating in all other study-related activities.

Data collection: Patient data is gathered from the source document during hospital visits. Site staff extract and input this data into the CRF. At the end of the trial, monitoring personnel

extract data from theCRF during their hospital visits. The clinical data management team evaluates this informationand presents it in tabular form. Subsequently, the biostatistics team analyzes the data and presents their findings to the authorities.

4.3StudyVisit

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		

5.0 Risks and Side Effects of AZD1656

5.1 Standard of Care

Renal transplantation comes with a standard of care that includes frequent clinic visits in the initial post-transplantation period. Patients attend clinic twice a week for the first six weeks, followed by weekly visits for another six weeks. Subsequently, the frequency of visits is adjusted based on graft stability, with patients continuing weekly or transitioning to bi-weekly visits for 12 weeks. To address the risk of hypoglycemia and hyperglycemia, glucose levels and diabetic control are routinely monitored. Adjustments to anti-diabetic medications are made as necessary to maintain optimal glycemic control.

5.2 Risks Associated with AZD1656

The known risks associated with AZD1656 are carefully considered. The choice of route of administration, dosage, dosage regimen, and treatment period is based on scientific reasoning. The selected dosage is within a safe and efficacious range observed in clinical studies, which justifies its use. The study's hypothesis revolves around AZD1656's effect on Treg migration activity, which is assumed to be similar to its impact on glucose levels. This hypothesis guides the choice of an effective and safe dosage without the need for titration. The risk of hypoglycemia after the initial post-transplant period is low. However, recurrent hypoglycemia may lead to the withdrawal of the study medication. Delayed graft function is a key clinical endpoint that will be measured as a surrogate for improved renal outcomes within the first week post-transplant.

5.3 Preclinical and Clinical Data

The safety, tolerability, pharmacokinetics, pharmacodynamics, and drug interactions of AZD1656 are assessed based on data from the Investigator's Brochure (Edition 9, September 2020). Approximately 960 subjects have been exposed to AZD1656 for up to six months across 25 clinical studies. In patients with type 2 diabetes and renal impairment, AZD1656's effects are comparable to those in diabetic patients with normal renal function. No safety concerns or signals have been identified, including no significant treatment-related changes in safety laboratory variables. The metabolism of AZD1656 mainly involves CYP2C8, and its interaction with inhibitors of this enzyme is noted. Although no significant drug-drug interactions have been reported in phase I/II clinical trials, unknown interactions may exist.

5.4 Reproductive Restrictions

The effects of AZD1656 on pregnancy and lactation in humans are not well-documented. Preclinical studies suggest that observed embryo-fetal development effects are related to maternal hypoglycemia. Thus, women of childbearing potential may participate in clinical studies if they use highly effective contraception to prevent pregnancy. The same restrictions are placed on male study participants, who should ensure their female partners use highly effective contraception methods. Male patients are advised not to donate sperm during their participation in the study.

5.5 Risk Minimization and Management

Hypoglycemia is a potential risk addressed in the study. While glucose production increases in renal transplant recipients due to steroid medications and insulin metabolism, hypoglycemia is rare. The study ensures regular monitoring of blood glucose and provides instructions for self-monitoring based on symptoms. Anti-diabetic medication adjustments are made to maintain optimal glycemic control. National guidelines are followed to manage patients' HbA1c levels.

5.6 Rationale for Study Design

The study design is grounded in the hypothesis that AZD1656 treatment leads to increased Treg localization in the transplanted kidney, reducing ischemia-reperfusion injury and improving graft survival. This study aims to assess AZD1656's effectiveness and safety as an adjunct for early diabetes management post-renal transplant. It's structured as an exploratory phase 2 study with a 3-month treatment regimen of AZD1656 (100mg twice daily) for diabetic patients undergoing renal transplantation in a tertiary renal unit.

6.0 Potential Benefits

AZD 1656 is a glucokinase activator, which implies it stimulates the glucokinase enzyme. Glucokinase is an enzyme that aids the body in the digestion of glucose (sugar). Although AZD 1656 is still under development, it has demonstrated potential benefits for diabetics.

Here are some of the potential diabetes benefits of AZD 1656:

- Blood sugar control is improved: AZD 1656 has been demonstrated to improve blood sugar control in diabetics. This is due to the fact that it aids the body's glucose processing

- Improved blood sugar control can assist to minimize the chance of developing diabetic complications such as heart disease, stroke, kidney disease, and blindness.
- Weight loss: AZD 1656 has also been demonstrated to help diabetics lose weight. This is most likely because it helps the body burn calories more efficiently.
- Improved quality of life: AZD 1656 has the potential to improve the quality of life of diabetics by alleviating symptoms such as fatigue, thirst, and frequent urination.
- It should be noted that AZD 1656 is still under development, and further study is required to validate its safety and efficacy in diabetics. However, first results are encouraging, and AZD 1656 has the potential to become a new and successful medication for diabetics.

AZD 1656 is being studied for its potential to enhance the outcomes of persons with COVID-19 who have diabetes, in addition to the potential benefits indicated above. This is because AZD 1656 has been demonstrated to have immunomodulatory properties, which means it can aid in immune system regulation.

Overall, AZD 1656 appears to be a potential novel medication candidate for the treatment of diabetes and related diseases. More research is required, but the preliminary findings are promising.

7.0 Monitoring and quality assurance

In a clinical trial, for AZD1656 in transplants with diabetes, quality control and monitoring are essential to guaranteeing participant safety and the accuracy of the data gathered. This is a thorough rundown of the clinical trial's quality assurance and monitoring procedures:

Follow the research protocol to the letter. Make sure that the site staff and investigators do the same. This covers dosage schedules, patient selection standards, and methods for gathering data.

guidelines, including those set forth by the International Conference on Harmonization (ICH).

7.1 Data Collection and Management:

Source Data Verification (SDV): Check the case report forms' (CRFs') data for completeness and accuracy by comparing it to the original documents.
Data Monitoring: To find any inconsistencies or abnormalities in the gathered data, put in place a thorough plan for data monitoring.
Data Entry: Verify that competent staff members are doing accurate data entry.

a) **Participant Safety:**

Adverse Event Reporting: Make sure that unfavourable incidents are duly noted, reported, and handled in accordance with protocol and legal mandates.
Safety Oversight: Keep a close eye on participant safety and take appropriate action when needed.

b) **Site Visits:**

Regular Site Visits: Evaluate the site's compliance with the protocol, SOPs, and legal requirements by conducting routine on-site visits.
Site Training: Ascertain that staff members at the site have received the necessary instruction in the protocol and good clinical practice (GCP) guidelines.

c) **Data and Safety Monitoring Board (DSMB):**

Create an impartial DSMB to oversee the regular evaluation of unblinded data in order to gauge study effectiveness and participant safety.
The DSMB's evaluations may lead them to suggest changes, extending, or ending the study.

d) **Randomization and Blinding:**

Make sure blinding is maintained to avoid bias and that randomization is carried out appropriately.

e) **Plans for Quality Control and Assurance (QA/QC):**

Create a thorough QA/QC plan tailored to this particular experiment. Procedures for identifying and fixing errors, handling deviations, and other quality-related issues should be included in this plan. Periodic QA/QC audits ought to be carried out to evaluate the general calibre of the

f) **Document Management:**

Keep an extensive and orderly file of all trial-related papers, such as consent forms, protocol changes, and communications with regulatory bodies.

Communication and Reporting: Ensure that the sponsor, investigators, ethics committees, and regulatory bodies are all in constant communication with one another.

As required, send routine safety and progress reports to the appropriate regulatory bodies.

7.2 Statistics and Data Analysis

Verify that the data analysis is done correctly and that the statistical analysis strategy is followed. To reduce bias, use a data analysis centre or a blinded, impartial statistician.

Ethical considerations: Make sure that the trial complies with ethical guidelines in every way and that the welfare and rights of the participants are safeguarded.

Adherence to Monitoring Plan: Keep an eye on how the trial-specific monitoring plan is being implemented. It should specify the precise duties, deadlines, and accountabilities for every facet of monitoring.

Establish procedures and systems that keep track of data and documentation changes made during the trial in order to create audit trails.

Documentation and Reporting of Deviations: Make sure that any modifications to the protocol are noted and recorded, along with any justifications and any possible effects they may have on the integrity of the study.

Protecting participant data confidentiality and security requires the implementation of appropriate safeguards.

Site Initiation and Close-out Visits: Make sure that sites are ready for the trial and that all protocols are followed when the trial comes to a conclusion by conducting comprehensive site initiation and close-out visits.

Updating a safety database and making sure that adverse event reports are accurate and submitted on time are two important aspects of safety database management.

To properly supervise and manage these trial-related tasks, it is imperative to work with a certified clinical research organization (CRO) or a specialized clinical trial monitoring team. Furthermore, by offering oversight, an impartial Data Safety Monitoring Board (DSMB) can improve the study's safety and trustworthiness. Continuous observation and quality control are necessary

during the length of the clinical experiment to guarantee both the participants' safety and its success.