

# CLINICAL STUDY REPORT

## Renoprotective effects of Ursodeoxycholic acid (Uredia)

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Trial long title

The renoprotective effects of Ursodeoxycholic acid in patients with type 1 diabetes and albuminuria

Sponsor Protocol Code:	UREDIA (2015-003609-41)
EudraCT Number:	2015-003609-41
ClinicalTrials.gov Identifier:	N/A
ISRCTN number:	N/A
REC Number:	15/LO/1951
Investigational Drugs (IMPs):	Ursodeoxycholic acid
Indication:	Type 1 diabetes kidney
Development Phase:	4
Study Begin (FPFV):	31 March 2017
Study End (LPLV):	06 July 2023 (2023/07/06)
Report Version & Issue Date:	1 3rd Sept 2024
Co-sponsor Name and Address:	King's College London and Guy's and St Thomas' NHS Foundation Trust
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Chief Investigator:	Dr Janaka Karalliedde

# SIGNATURE PAGE

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By signing below I approve the contents of this Clinical Study Report, and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. The clinical trial reported herein was conducted in accordance with the principles contained in the Declaration of Helsinki, Good Clinical Practice (GCP) and all applicable laws and regulations.

This was a non-commercial academic trial, the results of this study are not intended to be used or a licensing application.

**Chief Investigator:**

**Printed name**

**Signature**

**Date**

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## **1. Ethics**

### **Independent Ethics Committee or Institutional Review Board**

The study protocol and amendments were reviewed and approved by a National Research Ethics Service (Bloomsbury REC London).

### **Ethical conduct of the study**

The trial was conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (1996) as amended, the principles of Good Clinical Practice (GCP) and in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, the Research Governance Framework for Health and Social Care, the Data Protection Act 1998 and other regulatory requirements as appropriate. The trial protocol and substantial amendments were reviewed by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA)

### **Subject information and consent**

All participants were recruited after they were referred to the study team by their clinical care teams to discuss the study. Patient information sheet was given, and participants were asked to contact the research team after they had read the information if they wished to discuss the study in more detail and attend screening visit after obtaining informed consent. All participants gave informed consent prior to any study procedures and screening visit. All of the above were performed in line with GCP guidance.

## **2. Data Monitoring**

Not applicable and no DMC.

## **3. Sponsors, Investigators and Trial Sites**

King's College London and Guy's and St Thomas' NHS Foundation Trust

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## 5. Study Synopsis

Title of clinical trial	The renoprotective effects of Ursodeoxycholic acid in patients with type 1 diabetes and albuminuria
Protocol Short Title/Acronym	Renoprotective effects of Ursodeoxycholic acid
Study Phase	IV
Sponsor name	King's College London and Guy's and St Thomas' NHS Foundation Trust
Chief Investigator	Dr Janaka Karalliedde
Eudract number	2015-003609-41
REC number	15/LO/1951
IRAS project ID:	<b>147826</b>
Medical condition or disease under investigation	Type 1 diabetes
Purpose of clinical trial	The purpose of this research is to study is the potential renoprotective role of Ursodeoxycholic acid in patients with T1DM and albuminuria
Primary objective	To evaluate if Ursodeoxycholic acid reduces albuminuria in patients with type 1 diabetes mellitus (T1DM) with residual albuminuria despite established standard care.
Secondary objective (s)	To evaluate if Ursodeoxycholic acid improves vascular, metabolic and renal measures / function excretion
Trial Design	This is a single centre double blind placebo controlled cross over trial to evaluate if Ursodeoxycholic acid added to established standard care reduces albuminuria
Endpoints	Primary: Change in albumin excretion rate (AER) after 24 weeks treatment with Ursodeoxycholic acid as compared to 24 weeks on placebo. Secondary: vascular, metabolic and renal measures / function changes

	including Change in serum electrolytes (sodium, potassium), and renal function/estimated GFR Change in brachial blood pressure. Change in central aortic blood pressure and Change in HbA1c, lipid profile.
Planned number of subjects	30
Summary of eligibility criteria	T1DM patients aged 20 to 75 years, with residual albuminuria (defined as an urine albumin to creatinine ratio >3 mg/mmol) or proteinuria in the preceding 6 months on a maximum tolerated and stable dose of RAAS blockade (ACE-inhibitor or angiotensin receptor blocker-ARB). Estimated GFR (by MDRD equation) ≥30 ml/min. Written informed consent to participate in the study prior to any study procedures Ability to communicate and comply with all study procedures Exclusion criteria are history of intolerance to Ursodeoxycholic acid, active gastrointestinal disease (such as gall stones, inflammatory bowel disease primary sclerosing cholangitis), non-diabetic renal disease, absence of diabetic retinopathy, pregnancy, insufficient understanding of the trial, lactating females
IMP, dosage and route of administration	Ursodeoxycholic acid 500mg bid PO
Active comparator product(s)	Placebo
Maximum duration of treatment of a subject	48 weeks
Version and date of protocol amendments	Version 1.0 06 October 2015 Version 2.0 19 January 2016 Version 3.0 24th May 2016 Version 4.0 16th January 2018 Version 4.1 26 March 2018 Version 4.2 18th June 2019 Version 4.3 02nd April 2020

## 6. Glossary of terms

type 1 diabetes mellitus (T1DM)  
diabetic nephropathy (DN)  
end stage renal disease (ESRD)



cardiovascular disease (CVD)  
endoplasmic reticular (ER)  
unfolded protein response (UPR)  
urine albumin excretion rate (AER)  
estimated glomerular filtration rate (eGFR)  
Renin angiotensin aldosterone system (RAAS)  
Aortic Pulse wave velocity (Ao-PWV)  
Flow mediated dilation (FMD)  
high sensitive C- reactive protein (hsCRP)  
Vascular cell adhesion molecule 1 (VCAM)  
Endothelin 1 (ET-1)

## **7. Publication (reference)**

None to date

## **8. Study period (years)**

31 January 2017 to 06 July 2023  
Interruptions due to Covid -19 pandemic 2020 to 2021

## **9. Phase of development**

Phase IV

## **10.Objectives**

To evaluate if Ursodeoxycholic acid reduces albuminuria in patients with type 1 diabetes mellitus (T1DM) who had residual albuminuria despite established standard care.

## **11.Background and Context**

The aim of this research was to evaluate whether Ursodeoxycholic acid reduced albuminuria in patients with type 1 diabetes mellitus (T1DM) who had residual albuminuria despite established standard care. In the UK, diabetic nephropathy (DN) is the leading cause of patients requiring dialysis or renal transplantation [1,2]. One of the earliest manifestations of DN is albuminuria (increased urinary albumin excretion) which indicates high risk of progression of renal disease towards end stage renal disease (ESRD) that requires dialysis or transplantation. Albuminuria is also an index of endothelial dysfunction which characterises DN and a powerful independent predictor of cardiovascular disease (CVD)[1].

Patients with T1DM and albuminuria (urine albumin creatinine ratio  $\geq 30$  mg/mmol or albumin excretion rate  $\geq 200$  mcg/min) are at enhanced risk (up to 20 fold increased risk) of progression towards ESRD [3]. There is a linear relationship between albuminuria and risk of renal disease and there is substantial evidence that any

degree of reduction in albuminuria will be of benefit in terms of delaying progression towards ESRD and reducing CVD [1,3].

The number of patients with T1DM in the UK is approximately 400,000. DN develops in 30-40% of these patients of whom up to 40% (estimated number 64,000) have albuminuria [1]. Despite recent improvements in clinical care and treatment between 35 and 52% patients with T1DM and albuminuria progress to ESRD over 10-15 years follow up in European and US studies [4] and if these figures are replicated in the UK nearly 32,000 T1DM subjects will develop ESRD.

This indicates that more effective novel therapies are urgently needed to either prevent or slow down the inevitable progression to ESRD in this large number of patients. Treatments that reduce albuminuria result in significant reduction in the progression towards ESRD [1]. In patients with DN and macroalbuminuria a 50% reduction in albuminuria in the first 24 weeks of treatment translates to a 45% reduction in the long term risk of ESRD[5-7] and recent data suggests that in high risk patients any degree of reduction in albuminuria would delay progression towards ESRD and may reduce CVD [6,7].

Ursodeoxycholic acid is a naturally occurring bile acid secreted in human bile, currently used for the treatment of gallstones and liver disease associated with cholestasis. Laboratory work on rodent models of DN demonstrate that Ursodeoxycholic acid treatment reduces albuminuria and improves the histological changes of DN (manuscript submitted) by reducing endoplasmic reticular (ER) stress and insulin resistance novel pathways that drive renal damage [8]. Increased ER stress was also confirmed in renal tissue of patients with DN. Interestingly Ursodeoxycholic acid at the dose we wish to study improves endothelial function in patients with CVD, independent of effects on blood pressure and lipids, has good systemic bio-availability and is well tolerated with no serious adverse effects or patient withdrawals [9,10].

Endothelial dysfunction is implicated in the pathogenesis of albuminuria in patients with diabetes [10]. It is well established that, in diabetes, metabolic and haemodynamic perturbations (and their interaction) activate various intracellular pathways such as the polyol and hexosamine pathway, increase production of advanced glycation end products, protein kinase C and p38 mitogen-activated protein kinase, and promote an increase in oxidative stress. These pathways have been linked to the dysregulation of different vascular/endothelial growth factors that have been implicated in the pathogenesis of diabetic kidney disease [10,15].

Moreover, various conditions (such as, diabetes, sepsis and inflammatory bowel disease), in which systemic endothelial dysfunction and enhanced oxidative stress are associated with macroalbuminuria, provide strong evidence that a glomerular endothelial defect contributes to macroalbuminuria [15].

Cell and tissue injury as a result of excessive oxidative stress has been implicated in the aetiology of endothelial cell dysfunction in the glomerulus and tubules, before the manifestation of albuminuria [15]. To handle the increased oxidative stress, predominantly endoplasmic reticulum (ER) stress, metabolic turnover and protein-synthesis is increased in cells. In parallel adaptive cytoprotective mechanisms, directed at reduction in protein synthesis, defined as “unfolded protein response” (UPR), are activated. UPR is characterised by activation of several signalling pathways, increased expression of protein-chaperons, and increased protein ubiquitination [16].

The up regulation of chaperons to facilitate protein folding, to favour the UPR response, has been proposed as a therapeutic application as chaperons can restore the ER-dysfunction and metabolic impairment [17].

Ursodeoxycholic acid can act as a chaperon and in clinical practice is used to promote the resolution of gallstones and to treat liver disease associated with cholestasis.

The effects of Ursodeoxycholic acid on endothelial function in patients with cardiovascular disease has been evaluated. In a double blind placebo controlled cross over study of 17 patients with stable chronic heart failure (stage II/III) Ursodeoxycholic acid treatment at 500mg bid for 4 weeks improved endothelial function [12]. In another trial of 11 patients with ischaemic heart disease 6 weeks Ursodeoxycholic acid (dose 13-19mg/kg/day ~1000mg/day) improved endothelium function [11]. In both trials where patients were on RAAS blockers and statins, Ursodeoxycholic acid was well tolerated, had good systemic bioavailability and improved endothelial function independent of blood pressure or lipid levels. To date there have been no studies evaluating the effects of Ursodeoxycholic acid in patients with diabetic nephropathy. However, an enhanced ER-stress response is clearly detected in the kidney tissue of patients with diabetic nephropathy and in T1DM mice (Streptozotocin induced). Experiments in T1DM mice conducted by Prof. Isermann, (co-applicant) demonstrate that Ursodeoxycholic acid treatment for 12 weeks modifies the ER stress response in the kidney, resulting in amelioration of experimental diabetic nephropathy with reduction of albuminuria towards levels observed in healthy animals. These results were independent of changes in blood pressure, lipids or glucose. These data establish the scientific rationale for a proof of concept clinical trial to assess the efficacy of Ursodeoxycholic acid on reducing macroalbuminuria, and improving endothelial and renal function in patients with T1DM and nephropathy. Importantly Ursodeoxycholic acid will target pathways not addressed by traditional renoprotective drugs such RAAS blockers.

Treatments that delay/prevent ESRD all reduce albuminuria and data from patients with macroalbuminuria and diabetes indicate that a 50% reduction in albuminuria in the first 24 weeks of treatment translates to a 45% reduction in the long term risk of ESRD[8,19]. In fact some have argued that there is a linear relationship between

reduction in albuminuria in high risk patients and cardio-renal protection which indicates that any degree of reduction in albuminuria will be of benefit in terms of delaying progression towards ESRD and reducing CVD events[8,20]. If we are able to demonstrate in this 24 week double blind placebo controlled cross over trial that Ursodeoxycholic acid as an add on treatment to established standard care reduces albuminuria it would establish the rationale and platform for further research funding to investigate the longer term effects and potential benefits of this drug in preventing or delaying the progression towards DN in this high risk patient group.

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## 12.Methodology

**Trial Objectives** To evaluate if Ursodeoxycholic acid reduces albuminuria in patients with type 1 diabetes mellitus (T1DM) who had residual albuminuria despite established standard care

### Primary endpoints

The primary endpoint was the change in albuminuria measured by timed urine albumin excretion rate (AER) after 24 weeks treatment with Ursodeoxycholic acid as compared to placebo.

### Secondary endpoints

Secondary endpoints included blood pressure and estimated glomerular filtration rate (eGFR), and other independent predictors and biomarkers of renal and CVD risk;

### Inclusion Criteria

- ❑ T1DM patients aged 20 to 75 years, with residual albuminuria (defined as an urine albumin to creatinine ratio >3 mg/mmol or proteinuria in the preceding 6 months on a maximum tolerated and stable dose of RAAS blockade (ACE-inhibitor or angiotensin receptor blocker-ARB).
- ❑ Estimated GFR (by MDRD equation)  $\geq 30$  ml/min.
- ❑ Written informed consent to participate in the study prior to any study procedures.
- ❑ Ability to communicate and comply with all study requirements.

### Exclusion Criteria

- ❑ History of intolerance to Ursodeoxycholic acid.
- ❑ Active gastrointestinal disease (such as gall stones, inflammatory bowel disease, primary sclerosing cholangitis).
- ❑ Non-diabetic renal disease.
- ❑ Absence of diabetic retinopathy (as this would suggest non diabetic renal disease).
- ❑ Pregnancy.
- ❑ Insufficient understanding of the trial
- ❑ Lactating females

Following the screening visit and a 2-week run-in phase, patients were randomly allocated to receive either Ursodeoxycholic acid (500mg bid) for the first 24 weeks, 4 weeks wash out period followed by placebo for 24 weeks, or placebo for the first 24 weeks, 4 week wash out period followed by Ursodeoxycholic acid (500mg bid) for 24 weeks. Randomisation was done by the Division of Health and Social Care at King's College London, Patients screened were allocated a screening number, and if randomised, a randomisation number was allocated (distinct in format from screening number). Randomisation was by concealed envelopes or, if the facility was available, by the KCL clinical trials unit as per their SOP.

Monitoring of the trial was performed by the King's Health Partners Clinical Trial Office, and the Division of Health and Social Care at King's College London provided statistical/data analysis support. The randomisation records for participants were kept in the Department of Pharmacy Guy's and St Thomas Hospital NHS Trust. Patients and any health care provider involved in the trial were blinded to the group assignment. Individual treatment codes were supplied to the clinicians by clinical trials pharmacy only when clinically indicated.

Treatment codes will be supplied to the clinicians by clinical trials pharmacy if clinically indicated.

If at any time the (pregnancy) test did not come back negative (that is, it demonstrates that patient is pregnant), the patient was withdrawn from participation in the study. Patients were free to withdraw from study treatment or from the study at any time for any reason. Information collected during the trial could still be used. If patients decided to withdraw, at any time, they were asked for consent to use all of the data collected up to the time they decided to leave the study. We would also ask for patient consent to use all the frozen blood samples which had not been analysed until withdrawal from the trial

### **Procedures for Assessing Efficacy Parameters /endpoints**

The primary endpoint was the change in mean urine albumin excretion rate (AER) after 24 weeks treatment with Ursodeoxycholic acid as compared to placebo.

The primary end point was AER after 24 weeks treatment with Ursodeoxycholic acid as compared to placebo. AER data were log-transformed for analyses. The null hypothesis tested was  $H_0: \mu_{\text{Ursodeoxycholic acid}} - \mu_{\text{placebo}} = 0$ , where  $\mu$ 's are the mean endpoint values for log AER for Ursodeoxycholic acid and placebo.

AER values were analysed using analysis of covariance (ANCOVA), with baseline AER as covariate. In order account for the cross-over design, analyses estimated the effects of treatment and period. The least square means, 95% confidence interval and p value for the intervention effect were estimated. The possibility of an interaction between treatment and period, which might indicate a carry-over effect, was evaluated graphically to inform future trial design. A potential interaction of treatment by baseline AER value was similarly be evaluated.

Secondary endpoints were evaluated in the same framework. Additional analyses evaluated potential baseline prognostic factors associated with AER changes over time. The list of potential prognostic variables at baseline was made prior to final analysis plan.

Table : Schedule of events

Study visit number	1	2	2S	3*	4	4S	5
Week	-2	0 (±5 days)	4 (±5 days)	24 (±5 days)	28 (±5 days)	32 (±5 days)	52 (±5 days)
	Screening	Baseline					End of study
<b>Study procedures</b>							
Informed consent, review medical history and demographic questions	x						
Randomisation		x					
Asks questions regarding changes in health/ medications	x	x		x	x		x
Assess eligibility							
Height	x						
Weight	x	x		x	x		x
Waist circumference		x		x	x		x
Physical examination	x	x		x	x		x
Brachial blood pressure and heart rate	x	x		x	x		x
ECG		x					x
Measures of arterial stiffness (Ao-PWV and central aortic pressure) and endothelial function		x		x	x		x
Compliance				x			x
Dispensing of IMP		x			x		
Overnight urine collections for albumin excretion rate, urine sodium, urine magnesium, uric acid, calcium, phosphate, and potassium excretion.		x		x	x		x
Liver profile, bone profile, renal profile (including eGFR)		x		x	x		x
Safety visit for liver profile blood test and telephone monitoring			x			x	
Lipid profile		x		x	x		x
HbA1c, Full blood count		x		x	x		x
Endothelial and renal risk markers		x		x	x		x
Urine pregnancy test		x		x			x
Health related quality of life questionnaire		x		x	x		x

**Trial Medication**

Ursodeoxycholic acid the investigational product and matched placebo were supplied by the Pharmacy Manufacturing Unit of Guy's and St Thomas NHS foundation Trust. IMP was Ursofalk 500mg film-coated tablets and be in bottles. IMP was dispensed by Guy's clinical trial pharmacy department staff. The labelling and packaging were done by Guy's and St Thomas NHS foundation Trust pharmacy department.

The content of the labelling was in accordance with the local regulatory specifications and requirements.

**Dosing Regimen**

Patients received Ursodeoxycholic acid 500mg bid or matched placebo. Patients were 24 weeks on one and then 24 weeks on the other.

The SmPC for Ursodeoxycholic acid was the reference document.

<http://www.medicines.org.uk/emc/medicine/27444/SPC/Ursofalk+500mg+film-coated+tablets/#furtherInfo>

Ursodeoxycholic acid has generally been well tolerated when used in clinical practice for more than several decades. Common side effects (occurring in less than 1 in 10 but more than 1 in 100 patients) are soft, loose stools or diarrhoea. Very rare side effects (occurring in less than 1 in 10,000 patients) are: during the treatment of patients with liver disease abdominal pain, has been reported along with worsening of liver cirrhosis which partially eases after treatment is discontinued, hardening of gallstones due to build-up of calcium and rash.

Individual and Overall Drug Accountability were performed by Guy's and St Thomas' clinical trials pharmacy and verified by the KHP-CTO Clinical Research Associate during site visits and at the completion of the trial. Patients were asked to return all unused medication at the end of the study.

**13. Number of patients (planned and analysed)**

Number of patients planned was 30 (recruited n=32) and number of patients analysed n=31.

**Table: The reasons for patient withdrawal from the study see consort diagram above**

Patient	Comments
n=3	Participant no longer wishes to take part
n=2	Lost to follow up
n=2	Other (personal matter, times too difficult and can't commit)



## 14. Diagnosis and main criteria for inclusion

### Inclusion Criteria

- ❑ T1DM patients aged 20 to 75 years, with residual albuminuria (defined as an urine albumin to creatinine ratio >3 mg/mmol or proteinuria in the preceding 6 months on a maximum tolerated and stable dose of RAAS blockade (ACE-inhibitor or angiotensin receptor blocker-ARB).
- ❑ Estimated GFR (by MDRD equation)  $\geq 30$  ml/min.
- ❑ Written informed consent to participate in the study prior to any study procedures.
- ❑ Ability to communicate and comply with all study requirements.

### Exclusion Criteria

- ❑ History of intolerance to Ursodeoxycholic acid.
- ❑ Active gastrointestinal disease (such as gall stones, inflammatory bowel disease, primary sclerosing cholangitis).
- ❑ Non-diabetic renal disease.
- ❑ Absence of diabetic retinopathy (as this would suggest non diabetic renal disease).
- ❑ Pregnancy.
- ❑ Insufficient understanding of the trial
- ❑ Lactating females

Following the screening visit and 2 weeks run in phase patients were randomly allocated to receive either Ursodeoxycholic acid (500mg bid) for the first 24 weeks, 4 weeks wash out period followed by placebo for 24 weeks, or placebo for the first 24 weeks, 4 week wash out period followed by Ursodeoxycholic acid (500mg bid) for 24 weeks. Randomisation was done by the Division of Health and Social Care at King's College London. Patients screened were allocated a screening number, and if randomised, a randomisation number was allocated (distinct in format from screening number). Randomisation was by concealed envelopes or, if the facility was available, by the KCL clinical trials unit as per their SOP.

Monitoring of the trial was performed by the King's Health Partners Clinical Trial Office, and the Division of Health and Social Care at King's College London provided statistical/data analysis support. The randomisation records for participants were kept in the Department of Pharmacy Guy's and St Thomas Hospital NHS Trust. Patients and any health care provider involved in the trial were blinded to the group assignment. Individual treatment codes were supplied to the clinicians by clinical trials pharmacy only if clinically indicated.

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time for any reason. Information collected during the trial could still be used. If patients decided to withdraw, at any time, they were asked for consent to use all of the data collected up to the time they decided to leave the study. We were also asking for patient consent to use all the frozen blood samples which had not been analysed until withdrawal from the trial.

### **Procedures for Assessing Efficacy Parameters /endpoints**

The primary endpoint was change in mean urine albumin excretion rate (AER) after 24 weeks treatment with Ursodeoxycholic acid as compared to placebo.

The primary end point was AER after 24 weeks treatment with Ursodeoxycholic acid as compared to placebo. AER data were log-transformed for analyses. The null hypothesis tested was  $H_0: \mu_{\text{Ursodeoxycholic acid}} - \mu_{\text{placebo}} = 0$ , where  $\mu$ 's are the mean endpoint values for log AER for Ursodeoxycholic acid and placebo.

AER values were analysed using analysis of covariance (ANCOVA), with baseline AER as covariate. In order account for the cross-over design, analyses estimated the effects of treatment and period. The least square means, 95% confidence interval and p value for the intervention effect were estimated. The possibility of an interaction between treatment and period, which might indicate a carry-over effect, was evaluated graphically to inform future trial design. A potential interaction of treatment by baseline AER value was similarly evaluated.

Secondary endpoints were evaluated in the same framework. Additional analyses evaluated potential baseline prognostic factors associated with AER changes over time. The list of potential prognostic variables at baseline was made prior to final analysis plan.

## **15. Test product, dose and mode of administration**

### ***Trial Medication***

Ursodeoxycholic acid, the investigational product, and matched placebo were supplied by the Pharmacy Manufacturing Unit of Guy's and St Thomas NHS foundation Trust. IMP was UrsOfalk 500mg film-coated tablets provided in bottles. IMP was dispensed by Guy's clinical trial pharmacy department staff. The labelling and packaging were done by Guy's and St Thomas NHS foundation Trust pharmacy department. The content of the labelling was in accordance with the local regulatory specifications and requirements.

### **Dosing Regimen**

Patients received Ursodeoxycholic acid 500mg bid or matched placebo. Patients were 24 weeks on one and then 24 weeks on the other.

## **16. Duration of treatment**

48 weeks

## 17. Criteria for evaluation: Endpoints

### Procedures for Assessing Efficacy Parameters /endpoints

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Secondary endpoints were evaluated in the same framework. Additional analyses evaluated potential baseline prognostic factors associated with AER changes over time. The list of potential prognostic variables at baseline was made prior to final analysis plan

## 18. Safety

Physical examination, laboratory assessments (blood and urine tests) and adverse event monitoring from screening to last visit were performed. Visit 2 S (week 4) and 4S (week 32) were additional safety visits for liver profile blood test and subsequent telephone call for monitoring

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

**Adverse Event (AE):** Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

**Adverse Reaction (AR):** Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

**Unexpected Adverse Reaction (UAR):** An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

- The summary of product characteristics (SmPC) for that product (for products with a marketing authorisation)

**Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR):** Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

- Results in death;
- Is life-threatening;
- Required hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect.

### **Important Medical Events (IME) & Pregnancy**

Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

- Reporting Responsibilities

King's College London (KCL) and Guy's and St Thomas' NHS Foundation Trust as the sponsors have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use Clinical Trials, Regulations 2004) to the Kings Health Partners Clinical Trial Office.

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately by the Chief Investigator to the Kings Health Partners Clinical Trial Office in accordance with the current Pharmacovigilance Policy.

Death as a result of disease progression and other events that are primary or secondary outcome measures are not considered to be SAEs and should be reported in the normal way, on the appropriate CRF

The Kings Health Partners Clinical Trial Office will report SUSARs and other SARs to the regulatory authorities (MHRA, competent authorities of other EEA-European Economic Area) states in which the trial is taking place.

The Chief Investigator will report to the relevant ethics committees. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.
- The Chief Investigator and KHP-CTO (on behalf of the co-sponsors), will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

All AE and SAE will be reported and will be captured from the time of screening

## **19. Statistical Methods and trial plan changes**

No major changes to trial plan were done. Of note there was suspension in study recruitment and visits due to Covid -19 pandemic with related changes made to protocol to enable remote visits/assessments. The primary endpoint was not changed nor the methods for its assessment. No changes to secondary endpoints other than

due to limitations in sample collection/visits we could not collect all the required data for the secondary exploratory and exploratory endpoints

Patients were eligible to take part in this study if they had an albumin excretion rate > 30mg/24hrs. The mean value of AER in eligible patients was assumed to be 550 mg/24 hrs<sup>1</sup>. The analysis was undertaken on log-transformed data with an aim to detect a 30% reduction in the mean value as previously observed<sup>1-3</sup>. This equates to a difference in log values of:  $\ln(550) - \ln(385) = \ln(550/385) = 0.36$ .

Assuming a SD of 0.63 for the log AER values as reported<sup>4</sup> for 80% power and 5% significance level, 26 participants was required. Factoring in a 15% drop out rate (observed by our group and others in trial of similar duration in patients with diabetes and kidney disease<sup>1, 3</sup>) we aimed to recruit 30 patients in total.

The effect size of 30% in change in albumin excretion rate was a conservative estimate as compared to effect size for Ursodeoxycholic acid in reducing albuminuria (>50%) noted in animal studies. Previous cross-over trials in patients with T1DM and proteinuria and have been able to detect reductions in albuminuria of between 20-40% when a new therapy was added to standard care for renal disease, which includes ACE-Inhibitors as in our proposal.

## 20. Summary of Results and Conclusions

### Demographic data

#### Cumulative Subject Exposure to IMP/Placebo by age (at randomisation) and gender

Number of Subjects			
Age (years)	Male	Female	Total
Pre-term new-born infants (<37 weeks)	0	0	0
New-borns (0-27 days)	0	0	0
Infants and toddlers (28 days – 23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	17	8	25
Elderly (≥65 years)	4	2	6
<b>Total</b>	<b>21</b>	<b>10</b>	<b>31</b>

6.45% of subjects were Asian, 3.23% were black, 3.23% were mixed and 87.10% were White. For the study as a whole, 67.74% of subjects were male and 32.26 % were female. The following tables summarises the demographics of the study population:

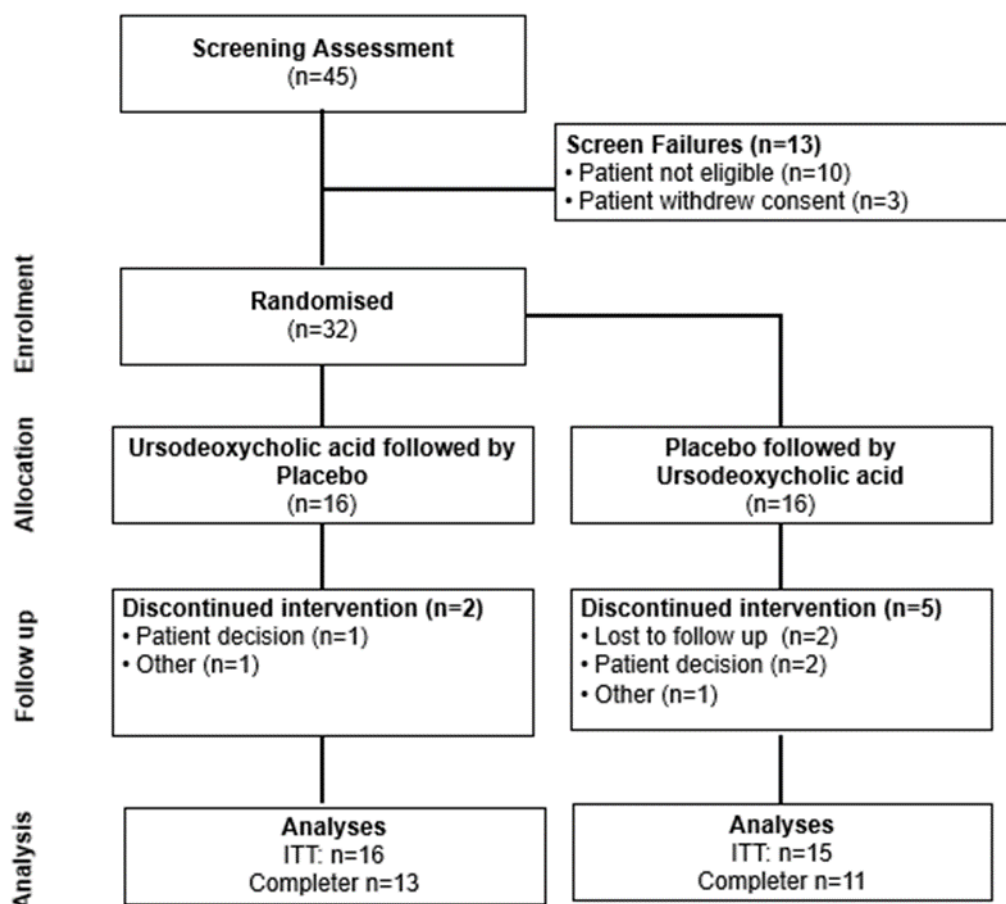
#### Cumulative Exposure by Ethnic Origin

Ethnic origin Number of subjects	
Asian	2
Black	1
Mixed	1
White	27
<b>Total</b>	<b>31</b>

**Table 1: Demographic data for all patients (safety population)**

	Treatment groups		
	Placebo followed by Ursodeoxycholic acid	Ursodeoxycholic acid followed by Placebo	Total
	N=15	N=16	N=31
Mean age at randomisation (yrs)	53.4 (14.2)	54.8 (13.6)	54.1 (13.7)
Gender			
Male	10 (66.7%)	11 (68.8%)	21 (67.7%)
Female	5 (33.3%)	5 (31.2%)	10 (32.3%)
Ethnicity			
Asian	1 (6.7%)	1 (6.2%)	2 (6.5%)
Black - other	1 (6.7%)	0 (0.0%)	1 (3.2%)
White	13 (86.7%)	14 (87.5%)	27 (87.1%)
Mixed - excluding Afro-Caribbean	0 (0.0%)	1 (6.2%)	1 (3.2%)
Smoking status			
Current smoker	1 (7.1%)	2 (15.4%)	3 (11.1%)
Ex-smoker	7 (50.0%)	3 (23.1%)	10 (37.0%)
Never smoked	6 (42.9%)	8 (61.5%)	14 (51.9%)
Mean diabetic duration (yrs) <sup>#</sup>	30.9 (16.0)	36.5 (10.2)	33.8 (13.4)
Mean number of units of alcohol drunk per week	5.2 (6.0)	5.4 (6.4)	5.3 (6.1)
BMI (Kg/M <sup>2</sup> )	28.9 (6.4)	25.1 (3.5)	26.9 (5.4)
Mean Seated Systolic Blood Pressure (mmHg) <sup>*</sup>	132.1 (17.1)	131.4 (18.7)	131.7 (17.7)
Mean Seated Diastolic Blood Pressure (mmHg) <sup>*</sup>	77.9 (10.5)	75.8 (8.3)	76.8 (9.4)
Mean Seated Pulse Rate <sup>*</sup>	78.0 (16.2)	73.1 (8.0)	75.5 (12.6)
eGFR/173 M <sup>2</sup> (mL/min)	96.3 (63.4)	81.1 (27.3)	88.7 (48.5)
Mean Ln (AER) <sup>+</sup>	3.7 (1.4)	3.3 (1.5)	3.5 (1.4)

### Consort diagram for study



### Primary outcome results

#### Descriptive Statistics of primary endpoint

	Placebo followed by Ursodeoxycholic acid		Ursodeoxycholic acid followed by Placebo	
Mean of the Log transformed AER	Baseline	Week 24	Baseline	Week 24
N	15	11	13	13
Mean (SD)	3.72 (1.42)	4.73 (1.75)	3.29 (1.49)	3.71 (1.69)
Median (IQR)	3.40 (2.84 - 4.48)	4.09 (3.53 - 6.03)	3.13 (2.48 - 3.66)	3.17 (2.66 - 3.76)

Note: Mean of the log AER was calculated as taking the log of the individual AER measurements and then calculating the mean of the log transformed measurements of AER

**ANCOVA model at Week 24 adjusting for baseline values**

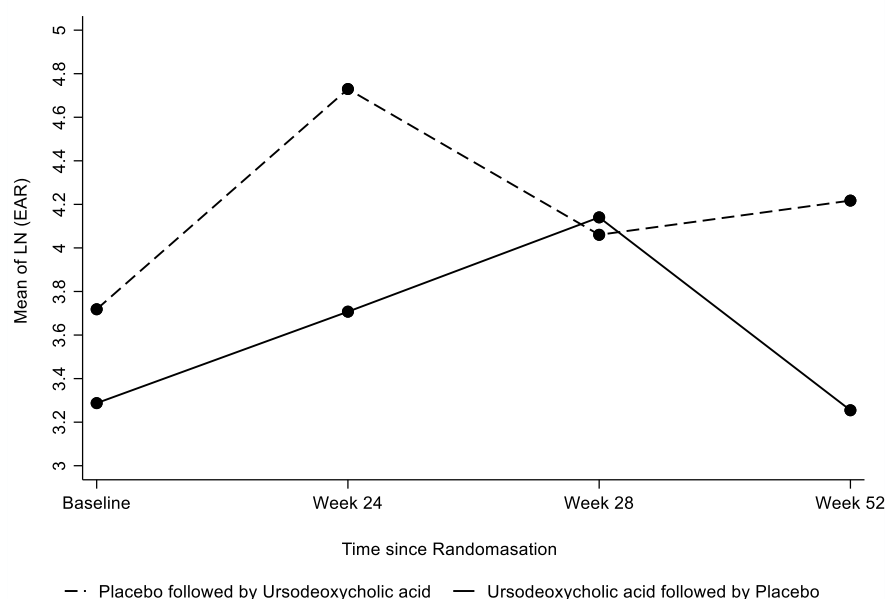
Mean of the Log transformed AER	Placebo followed by Ursodeoxycholic acid	Ursodeoxycholic acid followed by Placebo
N*	11	13
Least Square Mean (95%CI)	4.31 (3.96,4.66)	3.87 (3.51, 4.23)
Least Square Mean difference (95%CI)		-0.31 (-1.02, 0.41)
P-value		0.384
Adjusted R-Square	78.4%	

\*At week 24 there are some patients with no data

The primary endpoint was change in uAER after 24 weeks treatment with Ursodeoxycholic acid as compared to 24 weeks on placebo. As shown in table below of the people with data for the primary endpoint (n=24) there was a reduction in uAER however this did not reach statistical significance.

Figure 1 showing the overtime mean of log AER measurement from baseline to Week 52 between the treatment arms.

Figure 1: Mean of log AER measurement from baseline to Week 52

**Safety results**

**Table 2: Listing of Adverse Events** for all patients 2019 version of the MedDRA to code the events)



<b>Adverse Events</b>	<b>Placebo</b>	<b>Ursodeoxycholic acid</b>
Total Number of AEs per Study Arm	15	22
Subjects affected by non-serious adverse events:	10	6

Table 2 above show the number of adverse events by treatment through the study. Of 37 events observed during the study, 33/37 (89.2%) were not serious adverse events, while 4/37 (10.8%) were serious adverse events. The 37 AEs were experienced by 16 patients, ten patients (15 events) in Placebo arm and 6 patients (22 events) in the Ursodeoxycholic acid arm, including three patients in Ursodeoxycholic acid arm experiencing four SAE events (Viral lower tract, Diabetic Ketoacidosis, Alcohol dependence syndrome, Bowel resection). One subject experienced two SAEs (Alcohol dependence syndrome, and Diabetic Ketoacidosis).

**Table 3: Adverse Events by Body System Class**

	<b>Treatment Groups</b>	
	<b>Placebo</b>	<b>Ursodeoxycholic acid</b>
	<b>Number of events (15)</b>	<b>Number of events (22)</b>
<b>Body system Code</b>		
Respiratory	3 (20.0%)	4 (18.2%)
Gastro-intestinal	1 (6.7%)	5 (22.7%)
Genito-urinary/renal	0 (0.0%)	5 (22.7%)
Musculo-skeletal	0 (0.0%)	1 (4.5%)
Dermatological	6 (40.0%)	4 (18.2%)
Eyes, ear, nose, throat	0 (0.0%)	1 (4.5%)
Other	0 (0.0%)	1 (4.5%)
<b>Ongoing</b>		
No	12 (80.0%)	21 (95.5%)
Yes (at end of study)	1 (6.7%)	1 (4.5%)
Yes (but not at study end yet)	2 (13.3%)	0 (0.0%)
<b>Outcome</b>		
Recovered	12 (80.0%)	19 (86.4%)
Recovered with sequelae	0 (0.0%)	2 (9.1%)
Continuing	3 (20.0%)	1 (4.5%)
<b>Intensity</b>		
Mild	3 (21.4%)	5 (23.8%)
Moderate	9 (64.3%)	13 (61.9%)
Severe	2 (14.3%)	3 (14.3%)
<b>Related to intervention</b>		
Definite	5 (33.3%)	5 (26.3%)
Probable	2 (13.3%)	0 (0.0%)

Remote	0 (0.0%)	3 (15.8%)
None	8 (53.3%)	11 (57.9%)

**Table 4: Adverse Events by treatment group**

Adverse Event	Treatment Groups	
	Placebo	Ursodeoxycholic acid
	Number of events (15)	Number of events (22)
ABNORMAL RENAL PROFILE	0 (0.0%)	1 (4.5%)
ACUTE ANTERIOR UVEITIS	1 (6.7%)	0 (0.0%)
Alcohol dependence syndrome	0 (0.0%)	1 (4.5%)
BACKACHE	0 (0.0%)	1 (4.5%)
BLADDER INFECTION	0 (0.0%)	3 (13.6%)
BRUISED LEFT KNEE AFTER FALLING	1 (6.7%)	0 (0.0%)
BRUISED LOWER RIGHT JAW DUE TO FALL	1 (6.7%)	0 (0.0%)
Back Pain	1 (6.7%)	0 (0.0%)
Big toe fracture	1 (6.7%)	0 (0.0%)
Bowel resection	0 (0.0%)	1 (4.5%)
Cellulitis	1 (6.7%)	0 (0.0%)
Covid Infection	1 (6.7%)	2 (9.1%)
DIARRHOEA	1 (6.7%)	1 (4.5%)
Diabetic Ketoacidosis	0 (0.0%)	1 (4.5%)
EXCESSIVE FLATULENCE	0 (0.0%)	1 (4.5%)
FLU-LIKE COLD SYMPTOMS	1 (6.7%)	0 (0.0%)
FLU-LIKE SYMPTOMS	1 (6.7%)	1 (4.5%)
LEG CRAMPS	1 (6.7%)	0 (0.0%)
LIPOHYPERTROPHY AT ABDOMINAL INJECTION SITES	1 (6.7%)	0 (0.0%)
LOWER BACK PAIN	1 (6.7%)	0 (0.0%)
LOWER STOMACH DISCOMFORT	0 (0.0%)	1 (4.5%)
Leg Swelling	0 (0.0%)	1 (4.5%)
NAUSEA	0 (0.0%)	1 (4.5%)
RIGHT SIDED PAIN	1 (6.7%)	0 (0.0%)
Riggt arm operation	0 (0.0%)	1 (4.5%)
Right arm fracture	0 (0.0%)	1 (4.5%)
TOOTHACHE	0 (0.0%)	1 (4.5%)
UPPER RESPIRATORY TRACT INFECTION	1 (6.7%)	0 (0.0%)
UTI	0 (0.0%)	1 (4.5%)
VIRAL LOWER TRACT I	0 (0.0%)	1 (4.5%)
WORSENING SKIN RASH	0 (0.0%)	1 (4.5%)

**Table 5: Listing of Serious Adverse Events for all patients**

<b>Serious Adverse Events</b>	<b>Placebo</b>	<b>Ursodeoxycholic acid</b>
Total Number of SAEs per Study Arm	0	4
Total number of all cause deaths per Study Arm	0	0
Total number of deaths resulting from adverse events per Study Arm	0	0

Within the per protocol population (n= 32), a total of 37 AEs, including 4 SAE, were identified as treatment-emergent and included in the safety analysis. Summary tables for AEs and SAEs are presented in the appendix of this synopsis.

Overall, 16/32 patients (50%) patients experienced at least one AE. The proportion that experienced at least one SAE was 12.5% (n=4/32).

**Incidence of adverse drug reactions (ADRs):** 15 (10 for definite; 2 for probable; 3 for remote)/37 AEs (40.5%) including SAEs were assessed as related or remotely to at least one study drug and 8 / 32 patients (25%) experienced 15 ADR, Table 3.

There were none Serious Adverse Reactions (SARs), zero unexpected SARs and zero SUSARs.

## **21.Conclusions**

In conclusion in this first ever human study investigating the potential reno-protective effects of Ursodeoxycholic acid on top of standard of care in people with T1DM and DN we observed a modest numerical reduction in uAER however this did not reach statistical significance. Further larger studies are required to clarify the potential long-term kidney benefits of Ursodeoxycholic acid for kidney disease.

## **22.Date of Report**

02 Sept 2024

## 23.APPENDICES

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### i) Summary of treatment-emergent AEs in the per protocol population

System Organ Class <i>(Current list of MedDRA SOC)</i>	Preferred Term	Number of Subjects Experiencing the AE in Ursodeoxycholic acid followed by Placebo <i>(ideally list number and percentage e.g. 10 /12 subjects would be listed as 10 (83.33%)</i>	Total Number of Occurrences of the AE <i>(10 subjects may have experienced the same AE multiple times throughout the trial e.g. there were 20 occurrences of the same event)</i>	Number of Subjects Experiencing the AE in Placebo followed by Ursodeoxycholic acid <i>(ideally list number and percentage e.g. 10 /12 subjects would be listed as 10 (83.33%)</i>	Total Number of Occurrences of the AE <i>(10 subjects may have experienced the same AE multiple times throughout the trial e.g. there were 20 occurrences of the same event)</i>
Blood and lymphatic system disorders					
Cardiac disorders					
Congenital, familial and genetic disorders					
Ear and labyrinth disorders	Acute anterior uveitis	0	0	1(6.3%)	1

Eye Disorders					
Gastro-intestinal		1(6.3%)	5	1(6.3%)	
	Bowel resection		1		0
	Diarrhoea		1		1
	Nausea		1		0
	Excessive flatulence		1		0
	LOWER STOMACH DISCOMFORT		1		
General disorders and administration site conditions					
Hepatobiliary disorders					
Immune system disorders					
Infections and infestations					
Injury, poisoning and procedural complications					
Investigations					
Metabolism and nutritional disorders					
Musculoskeletal and connective tissue disorders		2(12.5%)	4	5 (31.3%)	6
	Back pain		0		1
	Backache		1		0
	Big toe fracture		0		1
	Bruised left knee after falling		0		1
	Leg cramps		0		1
	Leg swelling		1		0
	Lower back pain		0		1
	Riggt arm operation		1		0

	Right arm fracture		1		0
	Right sided pain				1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Nervous system disorders					
Pregnancy, puerperium and perinatal conditions					
Product issues					
Psychological	Alcohol dependence syndrome	1(6.3%)	1		
Renal and urinary disorders		3 (18.75%)	5	0	0
	Bladder infection		3	0	0
	Abnormal renal profile		1	0	0
	UTI		1	0	0
Reproductive system and breast disorders					
Respiratory		3 (18.75%)	4	3 (18.75%)	3
	Covid infection		2		1
	Flu-like symptoms		1		1
	Upper respiratory tract infection		0		1
	VIRAL LOWER TRACT I		1		0
Skin and subcutaneous tissue disorders	Worsening skin rash	1(6.3%)	1	0	0
Social circumstances					
Surgical and medical procedures					
Vascular disorders					

Endocrine	Diabetic Ketoacidosis	1(6.3%)	1	0	0
Other		1(6.3%)		4 (25.0%)	4
	Toothache (mouth)		1		0
	Cellulitis(legs)		0		1
	Bruised lower right jaw due to fall (mouth)		0		1
	Flu-like cold symptoms (cold)		0		1
	Lipohypertrophy at abdominal injection sites (abdomen)		0		1