CLINICAL STUDY REPORT

Dapagliflozin in type 2 diabetic nephropathy (DEER)

A study to investigate the potential renoprotective role of SGLT-2 antagonist Dapagliflozin in Type 2 diabetic patients with diabetic nephropathy

Sponsor Protocol Code:	King's Health Partners
EudraCT Number:	2013-004042-42
ClinicalTrials.gov Identifier:	
ISRCTN number:	
REC Number:	14/LO/0148 - London Westminster REC
Investigational Drugs (IMPs):	Dapagliflozin
Indication:	The potential renoprotective role of SGLT-2 antagonist Dapagliflozin in Type 2 diabetic patients with diabetic nephropathy
Development Phase:	3b
Study Begin (FPFV):	07/09/2015
Study End (LPLV):	20/11/2019
Report Version & Issue Date:	
Co-sponsor Name and Address:	King's College London - Strand, London WC2R 2LS Guy's and St Thomas' NHS Foundation Trust - Great Maze Pond, London SE1 9RT
Co-sponsor contact details:	King's College London - 020 7836 5454 Guy's and St Thomas' NHS Foundation Trust - 020 7188 7188
Chief Investigator:	Dr Janaka Karalliedde

SIGNATURE PAGE

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 for a licensing application.

Chief Investigator:

Printed name	**Signature**	**Date**
Janaka Karalliedde		

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1. Contents

APPENDICES

1. Ethics

Independent Ethics Committee or Institutional Review Board
The study protocol and amendments were reviewed and approved by a National Research Ethics Service London Westminster
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 patients provided written informed consent to participate in the study prior to being screened.

The patient information sheet detailed the procedures involved in the study (aims, methodology, potential risks and anticipated benefits) and the investigator explained these to each patient. The patient signed the consent form to indicate that the information had been explained and understood. The patients were then allowed time to consider the information presented before signing and dating the informed consent form to indicate that they fully understood the information, and willingly volunteered to participate in the study. The patients were given a copy of the informed consent form for their information. The original copy of the informed consent was kept in a confidential file in the Investigator's centre records.

2. Data Monitoring

There was no DMC for this trial

3. Sponsors, Investigators and Trial Sites

Co-Sponsors	
Guy's and St Thomas NHS Foundation Trust (co-sponsor)	King's College London (Leader sponsor)
Chief Investigator	Dr Janaka Karalliedde

4. Co-Investigator(s), Statistician, Laboratories, Database Management

Statistical and Data analysis coordinating centre **Statisticians** **Dr Salma Ayis and Dr Anastasion Mangelis**	Division of Health and Social Care at King's College London
Co-Investigator **Professor Lugi Gnudi Cardiovascular Division King's College London**	

5. Study Synopsis

Title of clinical trial	A study to investigate the potential renoprotective role of SGLT-2 antagonist Dapagliflozin in Type 2 diabetic patients with diabetic nephropathy
Protocol Short Title/Acronym	Dapagliflozin in type 2 diabetic nephropathy (DEER)
Study Phase	3B
Sponsor name	King's College London and Guy's and St Thomas' NHS Foundation Trust
Chief Investigator	Dr Janaka Karalliedde
Eudract number	2013-004042-42
REC number	14/LO/0148
IRAS project ID:	126755
Medical condition or disease under investigation	Type 2 diabetic patients with diabetic nephropathy
Purpose of clinical trial	The potential renoprotective role of SGLT-2 antagonist Dapagliflozin in Type 2 diabetic patients with diabetic nephropathy
Primary objective	To demonstrate whether the combination of Dapagliflozin and Ramipril significantly reduces albuminuria as compared to Ramipril alone in patients with type-2 diabetes with preserved renal function and residual microalbuminuria despite optimal renin-angiotensin-aldosterone system (RAAS) blockade.
Secondary objective (s)	To investigate whether Dapagliflozin and Ramipril significantly changes markers of arterial stiffness, RAAS

	components, markers of arterial ageing, glycaemic control, lipid profile, serum electrolytes, renal function, inflammatory markers, hemoglobin and haematocrit as compared to Ramipril alone in patients with type 2 diabetes with preserved renal function and residual microalbuminuria despite optimal renin-angiotensin-aldosterone system (RAAS) blockade.
Trial Design	Prospective randomised parallel group open label trial.
Endpoints	**Primary endpoint:** Change in albuminuria as measured by albumin excretion ratio (AER) from three timed urine collections collected within 7-10 days before baseline and final study visit at week 24 For the primary endpoint analysis, a median of 3 AER results is ideal, however a median of two AER results (minimum) is acceptable. **Exploratory secondary endpoints:** 1. Change in central aortic blood pressure and central arterial stiffness; 2. Change in brachial blood pressure; 3. Change in plasma renin activity, aldosterone, ACE-2 and Angiotensin 1-7/1-9 levels; 4. Change in total body water and extracellular fluid volumes by bio-impedance as previously described; 5. Change in highly sensitive CRP;

	6. Change in HbA1c, fasting c-peptide, glucose; 7. Change in lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides); 8. Change in serum electrolytes (sodium, magnesium, potassium), and renal function (serum creatinine, and estimated GFR; 9. Change in plasma albumin and liver function tests (ALT, ALP GGT); 10. Change in serum uric acid, serum calcium, serum phosphate, and haemoglobin; 11. Change in renal tubular markers L-FABP levels and retinol binding protein; 12. Change in 24 hr urine sodium, urine magnesium, urine uric acid, urine calcium, urine phosphate and urine potassium excretion; 13. Change in vascular cell adhesion molecule-1, Von Willebrand factor, oxidized low density lipoprotein and endothelin-1, Klotho; Change in Quality of life (EQOL5).
Withdrawal	Patients were free to withdraw from the study at any time without giving a reason. Patients were informed that if they requested to withdraw from the study, at any time during the trial, then this would have no negative consequences. The investigator could also withdraw patients from the trial if they deemed it appropriate for safety or ethical reasons or if it was considered detrimental to the well-being of the patient. Patients who withdrew or were withdrawn underwent

	a final evaluation at time convenient to the patient Full documentation was made of any withdrawals that occurred during the study in the CRF. The Investigator documented the date and time of the withdrawal and results of any assessments made at this time
Planned number of subjects	40
Summary of eligibility criteria	**Inclusion criteria:** 1. Patients with a diagnosis of T2DM with residual albuminuria (defined as a urine albumin creatinine ratio >3 mg/mmol in the preceding 12 months) on a maximum tolerated dose of ACE-inhibitor or ARB, and preserved renal function (estimated GFR >60 ml/min) 2. Patients on a stable dose of ACE-inhibitors or ARB in the preceding 3 months 3. Patients aged 35 to 75 years old (inclusive) 4. Written informed consent to participate in the study prior to any study procedures 5. Ability to communicate and comply with all study requirements. **Exclusion criteria:** 1. Patients with impaired renal function (eGFR<60 ml/min) 2. Patients with recent (6 months) history of cardiovascular or cerebrovascular disease event 3. Patients on thiazolidinediones (e.g. Pioglitazone) 4. Patients who have started drugs, which could affect sodium, balance (e.g. diuretics, non-steroidal anti-inflammatory drugs (NSAID), cyclo-oxygenase (Cox) 2 inhibitors, beta blockers or Calcium channel antagonists) within the previous month 5. Patients with uncontrolled

	hypertension defined as systolic blood pressure and diastolic blood pressure greater than 160 and 100 mmHg respectively 6. Pregnancy and lactating females 7. Pre-menopausal female patients not using contraception 8. Patients with very poorly controlled diabetes defined as HbA1c >12% 9. Patients with non-diabetic renal disease 10. Patients with a history of connective tissue disease or inflammatory arthritis 11. Recent (within 3 months) or current use of SGLT2 receptor blocker 12. Patients not willing to use appropriate contraception (see section 3.7) 13. Patients on loop diuretics 14. Recent history of (within 3 years of screening visit) or active malignancy 15. Patients with New York Heart Association class 3 or 4 cardiac disease 16. Abnormal Liver function tests defined as ALT or AST levels >3 times the upper limit of normal at screening 17. History of hereditary glucose-galactose malabsorption or primary renal glycosuria 18. History of one or more severe hypoglycaemic episodes within 6 months of screening (Severe hypoglycaemic episodes is as defined by ADA criteria (24) 19. Previous hypersensitivity to the active substance or to any of the excipients (see section 3.3) 20. Patients with an insufficient understanding of the trial 21. Patients with a history of DKA or at high risk of DKA (T2DM patients with known low C-peptide (<0.25nmol/l), patients with a history of pancreatitis, patients with conditions that lead to restricted food intake or severe dehydration.
IMP, dosage and route of administration	Dapagliflozin 10 mg od, per os.
Active comparator product(s)	Ramipril 10 mg once daily, per os

Maximum duration of treatment of a subject	24 weeks
Version and date of protocol amendments	V1.2 15OCT2015 V1.3 19JUL2016 V2 21AUG2017 V2.1 20NOV2017

6. Glossary of terms

Not used or available for this report **Publication (reference)**

1. Standards of medical care in diabetes--2012. Diabetes care. 2012 Jan;35 Suppl 1:S11-63. PubMed PMID: 22187469. Epub 2012/01/04. eng.

2. Sibal L, Home PD. Management of type 2 diabetes: NICE guidelines. Clin Med. 2009 Aug;9(4):353-7. PubMed PMID: 19728510. Epub 2009/09/05. eng.

3. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009 May 5;150(9):604-12. PubMed PMID: 19414839. Pubmed Central PMCID: 2763564. Epub 2009/05/06. eng.

4. Krimholtz MJ, Karalliedde J, Thomas S, Bilous R, Viberti G. Targeting albumin excretion rate in the treatment of the hypertensive diabetic patient with renal disease. Journal of the American Society of Nephrology : JASN. 2005 Mar;16 Suppl 1:S42-7. PubMed PMID: 15938033. Epub 2005/06/07. eng.

5. Karalliedde J, Gnudi L. Future strategies to prevent renal microvascular disease complications in diabetes. Future cardiology. 2008 Jan;4(1):77-83. PubMed PMID: 19804273. Epub 2008/01/01. eng.

6. Forsblom C, Harjutsalo V, Thorn LM, Waden J, Tolonen N, Saraheimo M, et al. Competing-risk analysis of ESRD and death among patients with type 1 diabetes and macroalbuminuria. Journal of the American Society of Nephrology : JASN. 2011 Mar;22(3):537-44. PubMed PMID: 21335512. Pubmed Central PMCID: 3060447. Epub 2011/02/22. eng.

7. Nelson RG. Is treatment of nephropathy in type 1 diabetes efficacious but ineffective? Journal of the American Society of Nephrology : JASN. 2011

Mar;22(3):402-4. PubMed PMID: 21355059. Epub 2011/03/01. eng.

8. Karalliedde J, Viberti G. Microalbuminuria and cardiovascular risk. American journal of hypertension. 2004 Oct;17(10):986-93. PubMed PMID: 15485765. Epub 2004/10/16. eng.

9. Ruggenenti P, Perticucci E, Cravedi P, Gambara V, Costantini M, Sharma SK, et al. Role of remission clinics in the longitudinal treatment of CKD. Journal of the American Society of Nephrology : JASN. 2008 Jun;19(6):1213-24. PubMed PMID: 18354029. Pubmed Central PMCID: 2396935. Epub 2008/03/21. eng.

10. Christlieb AR, Long R. Renin-angiotensin system in phlorhizin compared with alloxan diabetes in the rat. Diabetes. 1979 Feb;28(2):106-9. PubMed PMID: 421968. Epub 1979/02/01. eng.

11. Calado J, Sznajer Y, Metzger D, Rita A, Hogan MC, Kattamis A, et al. Twentyone additional cases of familial renal glucosuria: absence of genetic heterogeneity, high prevalence of private mutations and further evidence of volume depletion. Nephrol Dial Transplant. 2008 Dec;23(12):3874-9. PubMed PMID: 18622023. Epub 2008/07/16. eng.

12. Burrell LM, Johnston CI, Tikellis C, Cooper ME. ACE2, a new regulator of the renin-angiotensin system. Trends in endocrinology and metabolism: TEM. 2004 MayJun;15(4):166-9. PubMed PMID: 15109615. Epub 2004/04/28. eng.

13. Liu CX, Hu Q, Wang Y, Zhang W, Ma ZY, Feng JB, et al. Angiotensinconverting enzyme (ACE) 2 overexpression ameliorates glomerular injury in a rat model of diabetic nephropathy: a comparison with ACE inhibition. Mol Med. 2011 Jan-Feb;17(1-2):59-69. PubMed PMID: 20844835. Pubmed Central PMCID: 3022989. Epub 2010/09/17. eng.

14. Tikellis C, Bialkowski K, Pete J, Sheehy K, Su Q, Johnston C, et al. ACE2 deficiency modifies renoprotection afforded by ACE inhibition in experimental diabetes. Diabetes. 2008 Apr;57(4):1018-25. PubMed PMID: 18235039. Epub 2008/02/01. eng.

15. Soler MJ, Wysocki J, Batlle D. Angiotensin-converting enzyme 2 and the kidney. Experimental physiology. 2008 May;93(5):549-56. PubMed PMID: 18223023. Epub 2008/01/29. eng.

16. Ye M, Wysocki J, Naaz P, Salabat MR, LaPointe MS, Batlle D. Increased ACE 2 and decreased ACE protein in renal tubules from diabetic mice: a renoprotective combination? Hypertension. 2004 May;43(5):1120-5. PubMed PMID: 15078862. Epub 2004/04/14. eng.

17. Vallon V, Richter K, Blantz RC, Thomson S, Osswald H. Glomerular

hyperfiltration in experimental diabetes mellitus: potential role of tubular reabsorption.

Journal of the American Society of Nephrology : JASN. 1999 Dec;10(12):2569-76.

PubMed PMID: 10589696. Epub 1999/12/10. eng.

18. Williams B, Lacy PS. Central haemodynamics and clinical outcomes: going

beyond brachial blood pressure? European heart journal. 2010 Aug;31(15):1819-22.

PubMed PMID: 20472919. Epub 2010/05/18. eng.

19. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, et

al. Expert consensus document on arterial stiffness: methodological issues and clinical applications. European heart journal. 2006 Nov;27(21):2588-605. PubMed PMID:

17000623. Epub 2006/09/27. eng.

20. Karalliedde J, Buckingham R, Starkie M, Lorand D, Stewart M, Viberti G. Effect

of various diuretic treatments on rosiglitazone-induced fluid retention. Journal of the

American Society of Nephrology : JASN. 2006 Dec;17(12):3482-90. PubMed PMID:

17093067. Epub 2006/11/10. eng.

21. Karalliedde J, Smith A, DeAngelis L, Mirenda V, Kandra A, Botha J, et al.

Valsartan improves arterial stiffness in type 2 diabetes independently of blood pressure lowering. Hypertension. 2008;51(6):1617-23.

22. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al.

Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. AnnInternMed.

2006;145(4):247-54.

23. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular

filtration rate with standardized serum creatinine values. Clinical chemistry. 2007

Apr;53(4):766-72. PubMed PMID: 17332152. Epub 2007/03/03. eng.

24. https://www.nice.org.uk/guidance/ng28

25. Standards of medical care in diabetes--2010. Diabetes care. 2010 Jan;33 Suppl

1:S11-61. PubMed PMID: 20042772. Pubmed Central PMCID: 2797382. Epub

2010/01/29. eng.

26. Smith A, Karalliedde J, De AL, Goldsmith D, Viberti G. Aortic pulse wave velocity and albuminuria in patients with type 2 diabetes. J AmSocNephrol. 2005;16(4):1069-75.

27. Talluri T. Qualitative human body composition analysis assessed with bioelectrical impedance. Collegium antropologicum. 1998 Dec;22(2):427-32. PubMed PMID: 9887598. Epub 1999/01/15. eng.

28. Nakamura T, Sugaya T, Kawagoe Y, Ueda Y, Osada S, Koide H. Effect of pitavastatin on urinary liver-type fatty acid-binding protein levels in patients with early diabetic nephropathy. Diabetes Care. 2005 Nov;28(11):2728-32. PubMed PMID: 16249547. Epub 2005/10/27. eng.

29. Shimizu H, Negishi M, Shimomura Y, Mori M. Changes in urinary retinol binding protein excretion and other indices of renal tubular damage in patients with noninsulin dependent diabetes. Diabetes research and clinical practice. 1992 Dec;18(3):207-10. PubMed PMID: 1289022. Epub 1992/12/01. eng.

30. Kum F, Karalliedde J. Critical appraisal of the differential effects of antihypertensive agents on arterial stiffness. Integrated blood pressure control. 2010;3:63-71. PubMed PMID: 21949622. Pubmed Central PMCID: 3172069. Epub 2010/01/01. eng

7. Study period (years)

Study Begin (FPFV):	07/09/2015
Study End (LPLV):	05/12/2019

8. Phase of development

3B

9. Objectives

Primary Objective

To demonstrate whether the combination of Dapagliflozin and Ramipril significantly reduces albuminuria as compared to Ramipril alone in patients with type-2 diabetes with preserved renal function and residual microalbuminuria despite optimal RAAS blockade.

Secondary Objectives

Secondary objectives included Change in HbA1c, fasting c-peptide, fasting glycaemia. Other secondary objective are listed below

- Change in lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides)
- Change in serum electrolytes (sodium, potassium), and renal function (serum creatinine, and estimated GFR)
- Change in Quality of life (EQOL5).
- Change in brachial blood pressureChange in plasma renin activity, aldosterone, ACE-2 and Angiotensin 1-7/1-9 levels
- Change in total body water and extracellular fluid volumes by bio-impedance;
- Change in highly sensitive CRP
- Change in plasma albumin and liver function tests (ALT, ALP GGT)
- Change in serum uric acid, serum calcium, serum phosphate, serum magnesium and haemoglobin
- Change in renal tubular markers L-FABP levels and retinol binding protein, soluble Klotho;
- Change in 24 hr urine sodium, urine magnesium, urine uric acid, urine calcium, urine phosphate, and urine potassium excretion
- Change in vascular cell adhesion molecule-1, Von Willebrand factor, oxidized low density lipoprotein and endothelin-1

10. Background and Context

11.1 AIM OF THE STUDY

To test in a prospective open label parallel group trial that the combination of Dapagliflozin and Ramipril significantly reduces albuminuria as compared to Ramipril alone in patients with type-2 diabetes (T2DM) being managed according to established standards of care, preserved renal function and residual microalbuminuria despite renin angiotensin aldosterone system (RAAS) blockade. The study was conducted in T2DM patients aged 35- 75 years, with residual albuminuria (defined as a urine albumin creatinine ratio >3 mg/mmol in the preceding 12 months) on 10mg od of Ramipril or another ACE-inhibitor or angiotensin receptor blocker (ARB), in a dose equivalent to 10mg od of Ramipril and estimated GFR >60 ml/min. Patients were on a stable dose of ACE-inhibitors or ARB in the preceding 3 months. The fundamental entry criterion was that the patient's own doctor considers there to be no clear indication for, or clear contraindications to, any of the trial treatments.

11.2 RATIONALE FOR THE STUDY

Over a lifetime diabetic nephropathy occurs in approximately 30-35 per cent of type-1 and type-2 diabetic patients. These patients are at heightened risk of premature cardiovascular death and progression to end stage renal disease. One of the earliest bed side clinical manifestations of diabetic renal injury is the detection of small amounts of albumin in the urine (albuminuria)(5). Albuminuria is an early sign of renal microvascular disease and serves as a surrogate bio-marker of renal and vascular injury in diabetes. Although the terms normoalbuminuria, microalbuminuria and macroalbuminuria (clinical albuminuria) describe different categories of urinary albumin excretion rates (AER) it is important to remember that they are part of a continuum in the relationship between albumin excretion and cardio-renal risk. Diabetes and in particular diabetic renal disease is characterised by activation of the RAAS. Despite the development and increased use of inhibitors of the RAAS, in recent decades there remains an unmet need for novel treatments to address the growing global burden of diabetic renal disease.

SGLT2 and the RAAS

In the kidney, glucose is freely filtered at the glomerulus and is reabsorbed via active transport mechanisms in the proximal convoluted tubule (one molecule of glucose is absorbed with 1 molecule of sodium). SGLT2 is the sodium-glucose co-transporter, expressed exclusively in the S1 segment of the proximal tubule that accounts for ~90% of glucose reabsorption. The sodium (Na)/ ATPase pump drives, in an energy dependent manner, the glucose transport back into the blood via the GLUT2 glucose transporter. Studies in rodents have suggested that, in non-diabetic rats treated with the competitive inhibitor of renal glucose transport Phlorizin, plasma renin activity (PRA) was significantly increased.

The inhibition of proximal tubule sodium reabsorption by SGLT2 inhibitors is likely to be corrected by a possible compensatory activation of the RAAS that will stimulate sodium reabsorption mainly in the distal convolute tubuli. Supporting this hypothesis is data from human subjects with familial renal glycosuria (a condition caused by mutation of the gene coding for SGLT2, and a relatively benign disease state with no metabolic or haemodynamic adverse sequelae), demonstrating markedly elevated PRA (between 3-5.7 times greater than normal) and aldosterone levels are 1.8-4.5 fold higher.

These results confirm that compensatory mechanisms are activated in response to the increased delivery of sodium to the distal nephron that accompanies glycosuria when SGLT2 is blocked / non-functional.

ACE-2 and Angiotensin 1-7: Novel mediators of the beneficial effects of RAAS blockade in diabetes

Angiotensin converting enzyme (ACE)-2 is a newly described enzyme found mainly in heart and kidney. ACE-2 cleaves a single residue from angiotensin-1 to generate Ang 1-9, and degrades Angiotensin-II, the main effector of the RAAS, to the vasodilator Ang 1-7. ACE-2 therefore acts in a counter-regulatory manner to ACE, modulating the balance between vasoconstrictors and vasodilators within the heart and kidney, and playing a significant role in regulating cardiovascular and renal function.

We hypothesise that the increase inhibition of proximal tubule sodium reabsorption and concomitant increased delivery of urinary sodium to the distal nephron induced by SGLT2

inhibitor Dapagliflozin would trigger the RAAS and, in patients treated with ACE-inhibitors or ARB, this would result in an increase in angiotensin-I and II levels. Both angiotensin-I and II are substrates for ACE-2, the combination treatment with Dapagliflozin + ACE-inhibitor (Ramipril) would result in increased ACE-2 activity and excess production of angiotensin 1-9 and 1-7 which will be beneficial as these isoforms have cardiovascular-renal protective effects.

Furthermore, over expression of ACE-2 in the diabetic kidney gives protection from diabetic kidney injury/ damage and has comparable effects as ACE-inhibitors on reduction of albuminuria. Conversely, the use of ACE-2 inhibitors appears to increase albuminuria and worsen the structural changes in animal models of diabetic kidney injury.
The proposed mechanism of these beneficial effects of ACE-2 include reduced levels of Angiotensin II (1-8) levels, increased levels of Angiotensin 1–7 and 1-9 levels, reduced oxidative stress, and reduced TGF-β1 and VEGF-A. Moreover, recent data indicates a synergistic effect of increased ACE-2 and decreased ACE in the kidney, as this combination results in greater reno-protection in diabetic mice than that afforded individually. Furthermore, the increased distal delivery of sodium due to SGLT2 inhibition by Dapagliflozin treatment may also lead to a reduction in intraglomerular pressure (a key initiator and factor that promotes progression of renal damage) by increasing tubulo-glomerular feedback and reducing sodium delivery to the macula densa.

There is emerging evidence that central aortic blood pressures may be clinically more relevant and provide information on cardio-renal outcome above and beyond brachial blood pressure. The observed reduction in brachial blood pressure (between 2-4 mmHg) with Dapagliflozin has not been correlated with changes, if any, on central aortic pressures (which influence coronary perfusion and if raised result in left ventricular hypertrophy) or central arterial stiffness.

Importantly changes in central arterial stiffness as assessed by aortic pulse wave velocity is an independent predictor of cardio-renal end points and we have previously demonstrated a blood pressure independent effect of RAAS blockade on these measures.
Altogether, these animal data and the human data establish the scientific rationale to test the

cardiovascular-renal protective effects of Dapagliflozin, which we hypothesise, potentiates the effect of RAAS blockade in patients with diabetes on ACE inhibition and the resultant increase in cardiovascular-renal protective Angiotensin 1-9 and 1-7 isoforms mediates a reduction in albuminuria and improve vascular function.

11. Methodology

The primary endpoint will be albuminuria measured by albumin excretion rate (AER) after 24 weeks treatment with Dapagliflozin and Ramipril compared to Ramipril only. Analysis will follow the intention to treat approach

The null hypothesis that was tested is H0: µRamipril+Dapagliflozin - µRamipril=0, where µ's are the mean endpoint values for AER for the Ramipril+Dapagliflozin and Ramipril only group.

The primary end point will be albuminuria measured by albumin excretion rate. The primary population used will be the intention to treat population. Endpoint will be defined as the last available post- randomisation measurement of AER in treatment phase of 24 weeks. For the primary endpoint analysis, a median of 3 AER results is ideal, however a median of two AER results (minimum) is acceptable.

The change in AER was analysed using an analysis of covariance (ANCOVA) with baseline AER as covariate. The least squares means, 95% confidence interval and p value for treatment difference were displayed. To assess for potential interaction of treatment by baseline, supplementary analysis of the primary outcome/endpoint was performed by adding the interaction term to the primary ANCOVA model. Additional ANCOVA for the primary variables was performed for potential baseline prognostic factors. The list of potential prognostic variables at baseline was made prior to final analysis plan. Secondary endpoints were analysed using an ANCOVA model and least squares means. There were no interim or sub study analyses. Analysis will follow the intention to treat approach

DETERMINATION OF SAMPLE SIZE

Power calculation: We estimated that 14 patients per treatment group would provide 90% power, at the 5% level (two-sided), to detect a difference in AER of 10% between groups. Assuming a dropout rate of 20%, 20 patients per group would be required.

Data from animal studies demonstrate a blood pressure independent change in AER of 50-

75% with ACE-2 activation (15, 16). We have previously demonstrated a blood pressure independent reduction in albuminuria of a similar or greater magnitude (10-30%) with potentiation of RAAS blockade (ARB + thiazide diuretic) and combination of ACE-inhibitors or ARB in diabetes (4, 30).

We estimated that 14 patients per treatment group would provide 90% power, at the 5% level (two-sided), to detect a difference in AER of 10% between groups i.e. 28 patients in total needed. Assuming a dropout rate of 20%, 20 patients per group would have been required. However, as the dropout rate was much lower than anticipated (<5%) the study was powered to detect primary endpoint with 33 participants randomised (17 patients in the Dapagliflozin and Ramipril arm and 16 patients in the Ramipril only arm) eligible for analyses as per ITT approach

12. Number of patients (planned and analysed /evaluable)

13.1 Planned 33

13.2 Analysed

33 patients

Arm	Dapagliflozin and Ramipril	Ramipril only
# patients screened	68 in total	
# patients randomised/treated/ study arm	17	16
# patients completed/ study arm	17	14
Reasons for non-completion if applicable		Unrelated to AE

The reasons for patient withdrawal from the study- see Diagram of study flow

13. Diagnosis and main criteria for inclusion

1. Patients with a diagnosis of T2DM with residual albuminuria (defined as a urine albumin creatinine ratio >3 mg/mmol in the preceding 12 months) on a maximum

tolerated dose of ACE-inhibitor or ARB, and preserved renal function (estimated GFR >60 ml/min)

2. Patients on a stable dose of ACE-inhibitors or ARB in the preceding 3 months
3. Patients aged 35 to 75 years old (inclusive)
4. Written informed consent to participate in the study prior to any study procedures
5. Ability to communicate and comply with all study requirements.

14. Test product, dose and mode of administration

IMP

Dapagliflozin 10 mg od, *per os*.
Individual and Overall Drug Accountability was performed by Guy's and St Thomas' clinical trials pharmacy and verified by the CRA during site visits and at the completion of the trial. Patients were asked to return all unused medication at the end of the study.

Records of study medication administered and dispensed, medication returned, and intervals between visits will be kept during the study. Patients will be asked to return all previously dispensed medication containers, even if empty, to the site personnel at each scheduled visit. Treatment compliance will be assessed by the site personnel comparing the number of tablets/capsules dispensed and number of tablets/capsules returned at subsequent visits. If compliance is found to be less than 90% patients will receive additional counseling/instruction on the importance of taking the medication as per study protocol. Remaining capsules will be counted when further study medication is dispensed and at the final treatment visit.

15. Duration of treatment

24 weeks

16. Reference therapy, dose and mode of administration

Ramipril 10mg

17. Criteria for evaluation: Endpoints

T

17.1 Efficacy

The primary endpoint

The primary endpoint will be albuminuria measured by albumin excretion rate (AER) after 24 weeks treatment with Dapagliflozin and Ramipril compared to Ramipril only. Analysis will follow the intention to treat approach

The null hypothesis that was tested is H0: µRamipril+Dapagliflozin - µRamipril=0, where µ's are the mean endpoint values for AER for the Ramipril+Dapagliflozin and Ramipril only group.

The primary end point will be albuminuria measured by albumin excretion rate. The primary population used will be the intention to treat population. Endpoint will be defined as the last available post- randomisation measurement of AER in treatment phase of 24 weeks. For the primary endpoint analysis, a median of 3 AER results is ideal, however a median of two AER results (minimum) is acceptable.

Secondary endpoints were changes in markers of arterial stiffness, RAAS components, markers of arterial ageing, glycaemic control, lipid profile, serum electrolytes, renal function, inflammatory markers, hemoglobin and haematocrit with Dapagliflozin and Ramipril as compared to Ramipril alone in patients with type 2 diabetes with preserved renal function and residual microalbuminuria despite optimal renin-angiotensin-aldosterone system (RAAS) blockade.

17.2 Safety

Listing of adverse events and evaluation of their relationship to the IMP. See section 20.3 page 31 and appendix

18. Statistical Methods

The primary endpoint will be albuminuria measured by albumin excretion rate (AER) after 24 weeks treatment with Dapagliflozin and Ramipril compared to Ramipril only. Analysis will follow the intention to treat approach

The null hypothesis that was tested is H0: µRamipril+Dapagliflozin - µRamipril=0, where µ's are the mean endpoint values for AER for the Ramipril+Dapagliflozin and Ramipril only group.

The primary end point will be albuminuria measured by albumin excretion rate. The primary population used will be the intention to treat population. Endpoint will be defined as the last available post- randomisation measurement of AER in treatment phase of 24 weeks. For the primary endpoint analysis, a median of 3 AER results is ideal, however a median of two AER results (minimum) is acceptable.

The change in AER was analysed using an analysis of covariance (ANCOVA) with baseline AER as covariate. The least squares means, 95% confidence interval and p value for treatment difference were displayed. To assess for potential interaction of treatment by baseline, supplementary analysis of the primary outcome/endpoint was performed by adding the interaction term to the primary ANCOVA model. Additional ANCOVA for the primary variables was used for potential baseline prognostic factors. The list of potential prognostic variables at baseline was made prior to final analysis plan. Secondary endpoints were analysed using an ANCOVA model and least squares means. There are no planned interim or sub study analyses.

DETERMINATION OF SAMPLE SIZE

Power calculation: We estimated that 14 patients per treatment group would provide 90% power, at the 5% level (two-sided), to detect a difference in AER of 10% between groups. Assuming a dropout rate of 20%, 20 patients per group would be required.

Data from animal studies demonstrate a blood pressure independent change in AER of 50-75% with ACE-2 activation (15, 16). We have previously demonstrated a blood pressure independent reduction in albuminuria of a similar or greater magnitude (10-30%) with potentiation of RAAS blockade (ARB + thiazide diuretic) and combination of ACE-inhibitors or ARB in diabetes (4, 30).

We estimated that 14 patients per treatment group would provide 90% power, at the 5% level (two-sided), to detect a difference in AER of 10% between groups i.e. 28 patients in total needed. Assuming a dropout rate of 20%, 20 patients per group would have been required.

However, as the dropout rate was much lower than anticipated (<5%) the study was powered to detect primary endpoint with 33 participants randomised (17 patients in the Dapagliflozin and Ramipril arm and 16 patients in the Ramipril only arm) eligible for analyses.

Analysis of Safety Variables

Listing of AE/SAEs

19. Changes in the Trial Plan

15th October 2015	DEER study protocol, Version 1.2:
19th July 2016	DEER study protocol, Version 1.3:
21st August 2017	DEER study, Version 2.0:
20th November 2017	DEER study, Version 2.1:

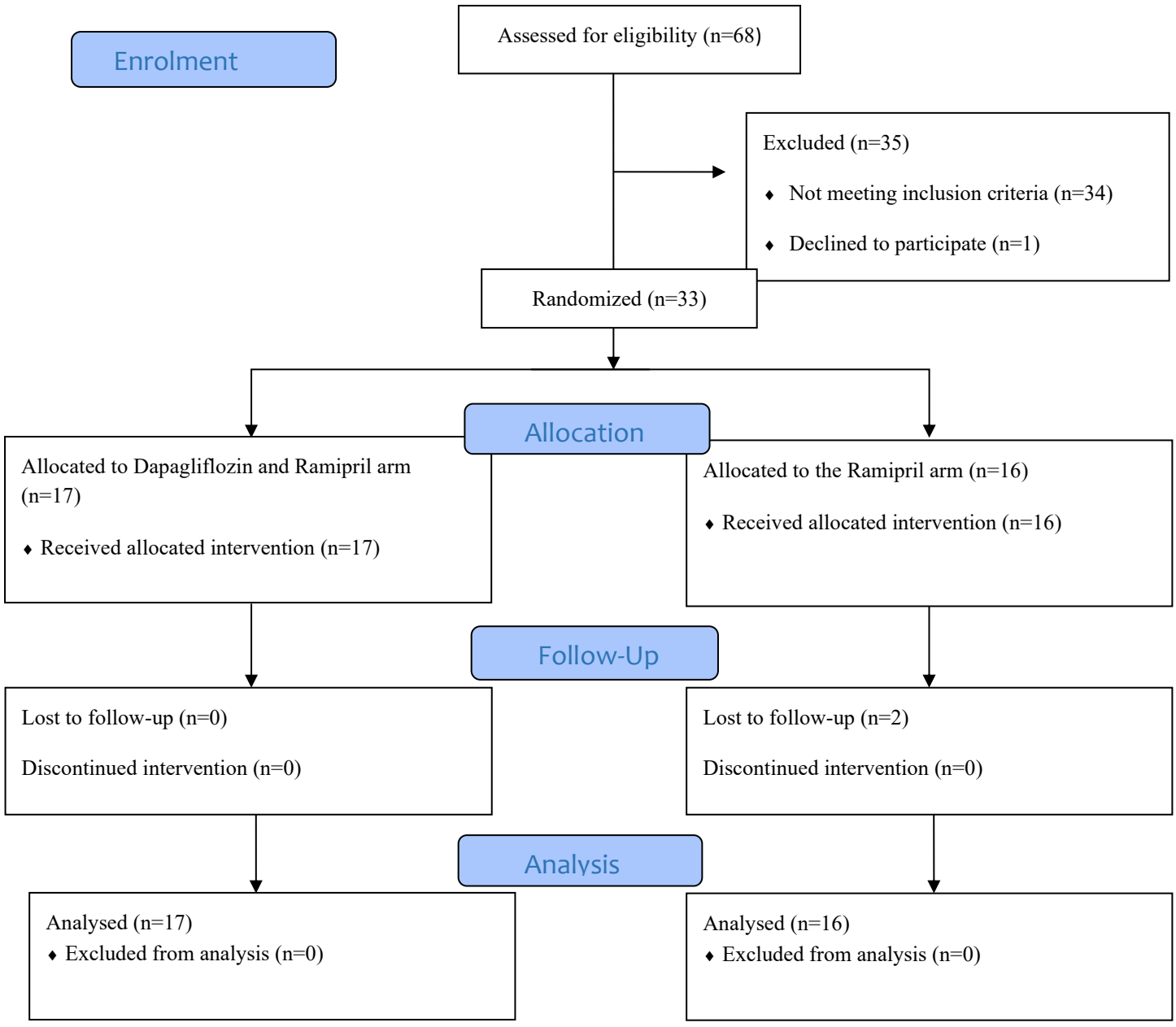
20.1 Protocol Deviations

Screening numbers were not sequential and there were issues with some participants attending for visits not fully fasted and not all participants could attend all visits and some visits were delayed outside trial visit window due to circumstances outside the control of the study team. As this was an ITT approach we included in analyses people with at least one follow up visits post randomization. One participants did not return IMP so we are unable to fully determine adherence. One participant had missing concomoitant medcatication that was not recorded In the opinion of the study team these dviations are unlikely to cause significant impact on the primary outcome of the study and related results.

20. Summary – Conclusions

Screening included 68 patients, of whom thirty-three were randomised: 17 patients in the Dapagliflozin and Ramipril arm and 16 patients in the Ramipril only arm. All patients completed the study except for two patients in the Ramipril arm who withdrew after visit 5 and 6 respectively. Of the cohort, 72.7% (n=24) were males and 27.3% females (n=9) with type 2 diabetes, mean age of 58 years (range 42 – 75 years) and of African/ Afro-Caribbean 48.5% (n=16), Caucasian 42.4% (n=14) and Asian 9.1% (n=3) ethnicity. Mean duration of diabetes was 13 years (range 1.5 – 25 years). Please see figure below for CONSORT Flow diagram of the progress through the phases of a parallel randomised trial of two groups Baseline differences between groups that were clinically important were adjusted for in analyses in ANCOVA model. Analysis followed the intention to treat approach

Patient Flow Diagram



21.1 Demographic data

The following tables summarise the demographics of the study population:
Se next page)

Table 1: Selected baseline data of 33 patients who were eligible for analyses of primary and secondary endpoints randomised to Ramipril or Ramipril+ Dapagliflozin treatment groups

Parameters	**Ramipril only (n=16)**	**Ramipril + Dapagliflozin (n=17)**
Gender	Females: 5 (31.2%) Males: 11 (68.8%)	Females: 4 (23.5%) Males: 13 (76.5%)
Ethnicity	African/ Afro-Caribbean: 11 (68.8%) Caucasian: 3 (18.8%) Asian: 2 (12.4%)	Caucasian: 11 (64.7%) African/ Afro-Caribbean: 5 (29.4%) Asian: 1 (5.9%)
Mean Age (years)	60 (8.3)	55.5 (9.7)
Mean duration of diabetes (years)	14.2 (4.9)	14.4 (3.9)
Weight (kg)	91.5 (13.7)	99.0(15.05)
Body Mass Index (kg/m^2)	30.9 (4.1)	32.9 (3.9)
Systolic Blood Pressure (mmHg)	138.2 (20.8)	139.1 (14.1)
Diastolic Blood Pressure (mmHg)	78.9 (7.4)	83.3 (9.4)
Pulse Wave Velocity (m/s)	9.9 (2.1)	9.1 (1.91)
Central Systolic Blood Pressure (mmHg)	127.8 (17.2)	120.1 (15.2)
Central Diastolic Blood Pressure (mmHg)	81.1 (8.2)	82.4 (9.3)

Central pulse pressure (mmHg)	46.6 (12.66)	37.8 (11.32)
Augmentation index at HR75 %	19.5 (8.25)	18.9 (6.11)
Albumin excretion rate (µg/min)*	108.0 (72.4, 316)	35.3 (27.1, 71.5)
eGFR (ml/min/1.73 m^2)	94.6 (23.53)	98.2 (20.94)
HbA1c (%)	9.2 (1.21)	8.9 (1.08)
Serum creatinine (umol/l)	79.7 (19.49)	74.1 (15.35)
Total cholesterol (mmol/l)	4.2 (0.96)	4.1 (1.33)
LDL cholesterol (mmol/l)	2.3 (0.86)	1.9 (1.12)
Triglycerides (mmol/l)	1.8 (1.65)	2.1 (1.26)
Haemoglobin (g/L)	128.1 (13.93)	140.9 (15.81)
Haematocrit (vol%)	38.7 (3.87)	41.1 (5.08)

*Median (interquartile range) for Albumin excretion rate. All other data reported as mean (SD).

20.2 Primary outcome

The primary outcome was change in Albumin Excretion Rate (AER) in Dapagliflozin + Ramipril compared to Ramipril only. The difference was statistically significant, with lower AER in the Dapagliflozin + Ramipril group. (Table 1). Analysis followed the intention to treat approach

Table 1. Primary outcome was change in Albumin Excretion Rate in Dapagliflozin + Ramipril compared to Ramipril only.

Primary outcome	Difference ([Dapagliflozin + Ramipril] - Ramipril only)
Albumin excretion rate (AER) mcg/min	Log mean difference (95% CI): -0.544 (-1.07, -0.02). p-value = 0.042

Table 2: Selected endpoints that demonstrated statistically significant end of study differences between arms (adjusted for baseline)

HbA1c %	mean difference (95% CI): -1.7 (-2.6, -0.9) p-value < 0.001
Fasting glucose mmol/l	mean difference (95% CI): -3.9 (-7.4, -0.5) p-value = 0.025
Serum sodium mmol/l	mean difference (95% CI): 3.6 (2, 5.2) p-value < 0.001
Angiotensin 1,7 ng/l	Log mean difference (95% CI): -0.393 (-0.71, -0.07) p-value = 0.017
Haematocrit %	Log mean difference (95% CI): 0.05 (0, 0.11) p-value 0.051

Table 3: Changes in selected variables including primary endpoint (AER) during trail (baseline to end of study visit) within Ramipril or Ramipril+ Dapagliflozin treatment groups

Parameters	Ramipril only (n=16)	Ramipril + Dapagliflozin (n=17)
Albumin excretion rate (AER) (mcg/min)		
Baseline, median (IQR)	108.0 (72.4, 316.0)	35.3 (27, 71.1)
End of study, median (IQR)	98.8 (42.3, 184.0)	17.9 (7.8, 119.2)
Percentage of difference of geometric mean (95% CI)	-26.1 (-39, -179)	-27.5 (-114, -11)
p-value	0.36	< 0.001
Weight (kg)		
Baseline, mean (SD)	91.5 (13.7)	99.0 (15.1)
End of study, mean (SD)	91.2 (15.1)	97.6 (13.9)
Difference between visits, mean (95% CI)	-0.24 (-1.96, 1.49)	-1.44 (-3.02, 0.14)
p-value	0.78	0.07
Body Mass Index (kg/m^2)		
Baseline, mean (SD)	30.9 (4.1)	32.9 (3.9)
End of study, mean (SD)	30.9 (4.7)	32.6 (3.8)
Difference between visits, mean (95% CI)	0.06 (-0.62, 0.75)	-0.38 (-0.92, 0.17)
p-value	0.85	0.16
Systolic Blood Pressure (mmHg)		
Baseline, mean (SD)	138 (21)	139 (14)
End of study, mean (SD)	137 (18)	136 (15)
Difference between visits, mean (95% CI)	-1.65 (-12.52, 9.22)	-2.69 (-13.27, 7.90)
p-value	0.75	0.60
Diastolic Blood Pressure (mmHg)		
Baseline, mean (SD)	79 (7)	83 (9)
End of study, mean (SD)	81 (6)	81 (6)
Difference between visits, mean (95% CI)	1.71 (-3.26, 6.67)	-2.81 (-6.88, 1.25)
p-value	0.48	0.16
Aortic Pulse Wave Velocity (m/s)		
Baseline, mean (SD)	9.88 (2.12)	9.06 (1.91)
End of study, mean (SD)	10.00 (1.84)	9.13 (2.03)
Difference between visits, mean (95% CI)	0.12 (-0.89, 1.13)	0.06 (-0.96, 1.08)
p-value	0.81	0.90
Central Diastolic Blood Pressure (mmHg)		
Baseline, mean (SD)	81 (8)	82 (9)
End of study, mean (SD)	82 (6)	80 (8)
Difference between visits, mean (95% CI)	0.65 (-4.61, 5.91)	-2.44 (-6.09, 1.22)
p-value	0.80	0.18
Central pulse pressure (mmHg)		
Baseline, mean (SD)	47 (13)	38 (11)
End of study, mean (SD)	44 (11)	40 (16)
Difference between visits, mean (95% CI)	-2.47 (-8.03, 3.09)	2.31 (-5.11, 9.73)
p-value	0.36	0.52
Augmentation index (%)		
Baseline, mean (SD)	19.5 (8.3)	18.9 (6.1)
End of study, mean (SD)	20.7 (8.3)	20.9 (8.9)
Difference between visits, mean (95% CI)	1.20 (-2.23, 4.62)	1.07 (-4.01, 6.15)
p-value	0.47	0.66
eGFR (ml/min/1.73 m^2)		
Baseline, mean (SD)	94.6 (23.5)	98.2 (20.9)
End of study, mean (SD)	93.4 (20.78)	97.3 (24.0)
Difference between visits, mean (95% CI)	-1.21 (-9.26, 6.83)	-0.96 (-8.79, 6.87)
p-value	0.75	0.80

HbA1c (%)		
Baseline, mean (SD)	9.2 (1.2)	8.9 (1.1)
End of study, mean (SD)	9.8 (1.7)	7.8 (1.3)
Difference between visits, mean (95% CI)	0.72 (0.08, 1.36)	-1.03 (-1.55, -0.51)
p-value	0.03	< 0.001
Fasting glucose (mmol/l)		
Baseline, mean (SD)	9.7 (4.0)	10.8 (3.3)
End of study, mean (SD)	12.8 (5.3)	9.2 (3.5)
Difference between visits, mean (95% CI)	2.94 (-0.26, 6.13)	-1.34 (-2.93,0.26)
p-value	0.07	0.09
Serum sodium (mmol/l)		
Baseline, mean (SD)	138.5 (3.4)	137.8 (2.7)
End of study, mean (SD)	136.8 (3.9)	139.8 (2.4)
Difference between visits, mean (95% CI)	-1.76 (-3.18, -0.35)	2.00 (1.09, 2.91)
p-value	0.02	< 0.001
Serum potassium (mmol/l)		
Baseline, mean (SD)	4.4 (0.4)	4.4 (0.5)
End of study, mean (SD)	4.5 (0.4)	4.5 (0.4)
Difference between visits, mean (95% CI)	0.14 (-0.04, 0.31)	0.13 (-0.01, 0.26)
p-value	0.12	0.07
Serum creatinine (umol/l)		
Baseline, mean (SD)	80.0 (19.5)	74.1 (15.4)
End of study, mean (SD)	79.5 (16.3)	81.9 (29.7)
Difference between visits, mean (95% CI)	-0.12 (-6.90, 6.66)	7.75 (-6.46, 21.96)
p-value	0.97	0.26
Haemoglobin (g/L)		
Baseline, mean (SD)	128.1 (13.9)	140.9 (15.8)
End of study, mean (SD)	129.2 (18.6)	144.2 (11.9)
Difference between visits, mean (95% CI)	1.18 (-2.65, 5.00)	3.25 (-1.60, 8.10)
p-value	0.52	0.17
Haematocrit (vol%)		
Baseline, mean (SD)	38.7 (3.9)	41.1 (5.1)
End of study, mean (SD)	39.4 (5.3)	43.2 (3.3)
Difference between visits, mean (95% CI)	0.71 (-0.27, 1.70)	2.08 (-0.06, 4.21)
p-value	0.14	0.06
Angiotensin Converting Enzyme 2 (ng/L)		
Baseline, mean (SD)	29.01 (45.42)	25.83 (32.41)
End of study, mean (SD)	38.38 (39.32)	32.81 (39.71)
Difference between visits, mean (95% CI)	7.90 (-14.89, 30.70)	6.98 (-9.87, 23.83)
p-value	0.47	0.39
Aldosterone (ng/L)		
Baseline, mean (SD)	99.03 (45.36)	84.75 (43.06)
End of study, mean (SD)	116.04 (59.04)	94.48 (41.58)
Difference between visits, mean (95% CI)	16.26 (-13.12, 45.65)	9.73 (-15.54, 35.00)
p-value	0.26	0.42
Angiotensin 1-7 (ng/l)		
Baseline, mean (SD)	54.29 (22.97)	86.26 (31.74)
End of study, mean (SD)	60.98 (17.30)	76.08 (37.16)
Difference between visits, mean (95% CI)	5.72 (-4.94, 16.38)	-10.17 (-21.34, 0.99)
p-value	0.27	0.07
Angiotensin 1-9 (ng/l)		
Baseline, mean (SD)	166.56 (36.33)	207.55 (91.29)
End of study, mean (SD)	181.95 (60.94)	182.85 (52.15)
Difference between visits, mean (95% CI)	16.16 (-20.12, 52.43)	-24.71 (-83.50, 34.09)
p-value	0.36	0.38

Active Renin (ng/L)		
Baseline, mean (SD)	27.13 (38.46)	48.10 (42.64)
End of study, mean (SD)	30.91 (40.29)	51.71 (45.78)
Difference between visits, mean (95% CI)	2.54 (-23.23, 28.31)	3.61 (-23.60, 30.82)
p-value	0.84	0.78
s-Klotho (ng/L)		
Baseline, mean (SD)	851.00 (433.02)	795.45 (437.94)
End of study, mean (SD)	739.37(337.88)	729 (321.96)
Difference between visits, mean (95% CI)	-34.09 (-38.22, 106.41)	-65.69 (-174.2, 42.8)
p-value	0.33	0.22
FGF-23 (pg/ml)		
Baseline, mean (SD)	12.95 (11.27)	11.67 (13.17)
End of study, mean (SD)	11.78 (15.25)	9.27 (10.71)
Difference between visits, mean (95% CI)	-1.31 (-3.81, 6.43)	-2.41 (-5, 0.19)
p-value	0.59	0.07

20.3 Safety results

Table: List of AEs observed

Randomisation Number	**Arm**	**Event Name** (enter conditions, not symptoms)	**Intensity**	**Study Drug Action**	**Outcome**	**Relationship to Study Drug**
1047	Ramipril	cough	Mild	None	Resolved	Likely
1047	Ramipril	pins and needles, numbness at his feet	Moderate	None	Not resolved	Unlikely
1047	Ramipril	Diabetic Neuropathy	Moderate	None	Not resolved	Unlikely
1047	Ramipril	Flu	Moderate	None	Resolved	Unlikely
1047	Ramipril	Cough	Moderate	None	Not resolved	Unlikely
1048	Dapagliflozin and Ramipril	Skin abrasion and Rash	Mild	None	Resolved	Unlikely
1051	Ramipril	Vomiting	Mild	None	Resolved	Unlikely
1052	Dapagliflozin and Ramipril	Weakness	Mild	None	Resolved	Unlikely
1053	Ramipril	Foul smelling urine	Mild	None	Not resolved	Unlikely
1053	Ramipril	Pain in the legs	Moderate	None	Not resolved	Unlikely
1053	Ramipril	Urinary tract infection	Mild	None	Resolved	Unlikely
1054	Ramipril	Palpitations	Moderate	None	Not resolved	Unlikely
1055	Dapagliflozin and Ramipril	Diarrhoea,gas,belching	Mild	None	Resolved	Unlikely
1055	Dapagliflozin and Ramipril	Lichen Sclerosis	Mild	None	Resolved	Unlikely

1058	Dapagliflozin and Ramipril	Angina	Mild	None	Not resolved	Unlikely
1061	Dapagliflozin and Ramipril	Urinary frequency exacerbation	Moderate	None	Not resolved	Possibly
1061	Dapagliflozin and Ramipril	Mild bilateral pretibial pitting oedema.	Mild	None	Resolved	Unlikely
1062	Dapagliflozin and Ramipril	Right upper quadrant pain	Moderate	None	Resolved	Unlikely
1062	Dapagliflozin and Ramipril	Constipation	Moderate	None	Not resolved	Possibly
1062	Dapagliflozin and Ramipril	Fungal genital infection	Moderate	None	Resolved	Possibly
1062	Dapagliflozin and Ramipril	Respiratory tract infection	Moderate	None	Not resolved	Unlikely
1062	Dapagliflozin and Ramipril	Hand joint stiffness	Moderate	None	Not resolved	Unlikely
1062	Dapagliflozin and Ramipril	Low blood glucose	Mild	None	Resolved	Unlikely
1063	Dapagliflozin and Ramipril	Dry mouth	Mild	None	Not resolved	Likely
1063	Dapagliflozin and Ramipril	Involuntary movement of four limbs	Mild	None	Resolved	Unlikely
1065	Ramipril	Iron deficiency anaemia	Mild	None	Not resolved	Unlikely
1065	Ramipril	Gastritis	Moderate	None	Not resolved	Unlikely
1065	Ramipril	Gastric polyps	Moderate	None	Not resolved	Unlikely
1065	Ramipril	helicobacter pylori infection	Moderate	None	Resolved	Unlikely
1065	Ramipril	sigmoid colon polyp	Moderate	None	Not resolved	Unlikely

1066	Ramipril	Macroscopic haematuria	Moderate	Temporarily interrupted	Resolved	Unlikely
1071	Ramipril	Cold	Mild	None	Resolved	Unlikely
1071	Ramipril	Flu-like symptoms	Mild	None	Resolved	Unlikely
1072	Dapagliflozin and Ramipril	Back pain	Moderate	None	Not resolved	Possibly
1072	Dapagliflozin and Ramipril	Night cough	Moderate	None	Not resolved	Possibly
1074	Ramipril	Fall	Moderate	None	Resolved	Unlikely
1074	Ramipril	knee pain left and right	Moderate	None	Not resolved	Unlikely
1074	Ramipril	Hypoglycaemia	Mild	None	Resolved	Unlikely
1075	Ramipril	Swelling of the face and eyes	Mild	None	Resolved	Unlikely
1076	Dapagliflozin and Ramipril	Peptic ulcer disease	Moderate	None	Not resolved	Unlikely
1076	Dapagliflozin and Ramipril	Candidiasis at Lower oesephagus	Moderate	None	Not resolved	Unlikely
1077	Ramipril	Gastritis/Epigastric pain	Moderate	None	Resolved	Unlikely
1079	Dapagliflozin and Ramipril	Cough	Moderate	None	Not resolved	Unlikely
1081	Ramipril	Urinary frequency	Mild	None	Resolved	Unlikely
1082	Ramipril	Pedal edema	Mild	None	Resolved	Unlikely
1082	Ramipril	Diarrhea	Mild	None	Resolved	Unlikely
1082	Ramipril	Rash	Mild	None	Resolved	Unlikely
1084	Dapagliflozin and Ramipril	Hyperkalemia	Mild	None	Resolved	Unlikely
1085	Dapagliflozin and Ramipril	Trigger finger	Mild	None	Resolved	Unlikely

1086	Dapagliflozin and Ramipril	Atrial Fibrillation	Moderate	None	Resolved	Unlikely
1086	Dapagliflozin and Ramipril	Hyperglycaemia with dehydration and paroxysmal AF	Moderate	None	Resolved	Unlikely

Table: List of SAEs

Arm	Randomisation Number	Event	Causality related to intervention	Outcome
Ramipril + Dapagliflozin	1069	Resection of endometrial fibroids	Unlikely	Resolved
	1086	Endophtalmitis after an eye injection	Unlikely	Resolved
	1086	Right Orbital Inflammatory Syndrome (orbital infection)	Unlikely	Resolved
Ramipril	1073	Hypersensitive airways disease on background of undiagnosed chronic airways disease	Unlikely	Resolved

Table: Listing of Adverse Events for all patients *(state which version of the MedDRA dictionary or other medical dictionary was used to code the events)*

Adverse Events	**Ramipril only (n=16)**	**Ramipril + Dapagliflozin (n=17)**
Total Number of AEs per Study Arm	28	27
Subjects affected by non-serious adverse events:	12	13

Table: Listing of Serious Adverse Events for all patients

Serious Adverse Events	**Ramipril only (n=16)**	**Ramipril + Dapagliflozin (n=17)**
Total Number of SAEs per Study Arm	1	3
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= 33), a total of 55 AEs, including 4 SAEs, 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, 25 patients (76%) patients experienced at least one AE. The proportion that experienced at least one SAE was 9% (n=3).

Incidence of adverse drug reactions (ADRs): 1 / 55 AEs (2 %) were assessed as related to at least one study drug and 1 / 33 patients (3%) experienced 1 ADR.

There were 0 Serious Adverse Reactions (SARs), 0 unexpected SARs and 0 SUSARs.

21. Conclusion

This study demonstrated that the combination of Dapagliflozin and Ramipril significantly

reduced urine albumin excretion rate (primary endpoint) as compared to Ramipril alone in patients with type-2 diabetes with preserved renal function and residual microalbuminuria despite optimal RAAS blockade.

For exploratory endpoints, we observed significant differences in mediators of the RAAS system (fall in Ang 1-7 levels) and a rise in serum sodium between treatment groups. As expected significant reduction in HbA1c fasting glucose and rise in haematocrit were observed with Dapagliflozin treatment.

In contrast to recent publications, which have used range of 'non-gold standard' methods of assessing arterial stiffness, we did not observe a significant reduction in indices of arterial stiffness (as measured by 'gold standard' methodology of applanation tonometry).

We also did not observe a significant difference between the two treatment groups on biomarkers of arterial ageing.

These results suggest that the observed cardio-renal benefits of SGLT-2 Inhibitors are unlikely to be related to improvements in arterial stiffness or markers of arterial ageing. Further larger studies are needed to confirm the preliminary observations we have made on changes in Ang 1-7 (a novel mediator of the RASS) and related clinical relevance.

22. Date of Report

This is version 1.0 of the Clinical Study Report synopsis, dated 18/FEB/2026.

APPENDICES

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

System Organ Class *(Current list of MedDRA SOC)*	**Preferred Term**	**Number of Subjects Experiencing the AE in Active Arm** *(ideally list number and percentage e.g. 10 /12 subjects would be listed as 10 (83.33%)*	**Total Number of Occurrences of the AE - Active Arm** *(10 subjects may have experienced the same AE multiple times throughout the trial e.g. there were 20 occurrences of the same event)*	**Number of Subjects Experiencing the AE in Control Arm** *(ideally list number and percentage e.g. 10 /12 subjects would be listed as 10 (83.33%)*	**Total Number of Occurrences of the AE - Control Arm** *(10 subjects may have experienced the same AE multiple times throughout the trial e.g. there were 20 occurrences of the same event)*
Blood and lymphatic system disorders	Blood and lymphatic system disorders	0	0	0	0
Cardiac disorders	Angina; Palpitations; Atrial fibrillation	2	2	1	1
Congenital, familial and genetic disorders	Congenital, familial and genetic disorders	0	0	0	0
Ear and labyrinth disorders	Ear and labyrinth disorders	0	0	0	0
Eye Disorders	Swelling of the face and eyes; Endophtalmitis after	2	2	1	1

	an eye injection; Right Orbital Inflammatory Syndrome (orbital infection)				
Gastrointestinal disorders	Diarrhoea, gas, belching; Right upper quadrant pain; constipation; gastritis; gastric polyps; helicobacter pylori infection; sigmoid colon polyp; peptic ulcer disease; diarrhoea; vomiting	3	4	4	7
General disorders and administration site conditions	Weakness; Pedal oedema; Dry mouth; Mild bilateral pretibial oedema	3	3	1	1
Hepatobiliary disorders	Hepatobiliary disorders	0	0	0	0
Immune system disorders	Immune system disorders	0	0	0	0
Infections and infestations	Flu; Urinary tract infection; Fungal genital infection; respiratory tract infection; flu-like symptoms; cold; candidiasis at lower oesophagus	4	3	3	4
Injury, poisoning and procedural complications	Fall	0	0	1	1
Investigations	Investigations	0	0	0	0
Metabolism and nutritional disorders	Low blood glucose; Hypoglycaemia; Iron deficiency anaemia	1	1	2	2
Musculoskeletal and connective tissue	Hand joint stiffness; back pain; knee pain left and	3	3	1	1

disorders	right; trigger finger				
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0
Nervous system disorders	Pins and needles, numbness at his feet; Involuntary movement of four limbs; Diabetic neuropathy	1	1	2	3
Pregnancy, puerperium and perinatal conditions	Pregnancy, puerperium and perinatal conditions	0	0	0	0
Product issues	Product issues	0	0	0	0
Psychiatric disorders	Psychiatric disorders	0	0	0	0
Renal and urinary disorders	Urinary frequency exacerbation; Urinary frequency; Macroscopic haematuria; Hyperkalaemia	2	2	3	3
Reproductive system and breast disorders	Resection of endometrial fibroids	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Cough; Night cough; Hypersensitive airways disease on background of undiagnosed chronic airways disease	2	2	2	3
Skin and subcutaneous tissue disorders	Skin abrasion and rash; Lichen Sclerosus	2	2	1	1
Social circumstances	Social circumstances	0	0	0	0
Surgical and medical procedures	Surgical and medical procedures	0	0	0	0
Vascular disorders	Vascular disorders	0	0	0	0

ii) Summary of treatment-emergent ARs in the per protocol population

In the active arm 25 treatment emergent AEs were recorded: infections and infestations (4 subjects; 4 events), gastrointestinal disorders (3; 4), general disorders and administration site conditions (3; 3), and musculoskeletal and connective tissue disorders (3; 3), with additional AEs in cardiovascular (2; 3), renal and urinary (2; 2), respiratory (2; 2), eye (2; 2), reproductive system (1;1) skin and subcutaneous tissue (2; 2), metabolism and nutritional (1; 1), and nervous system disorders (1; 1). In the control arm 28 treatment emergent AEs were recorded: gastrointestinal disorders (4; 7), infections and infestations (3; 5), and renal and urinary disorders (3; 3), metabolism and nutritional (2; 2) and nervous system disorders (2; 3), cardiovascular (1; 1), eye (1; 1), general disorders (1; 1), injury/poisoning/procedural complications (1; 1), musculoskeletal (1; 1), respiratory (1; 2), and skin (1; 1).

iii) Summary of treatment-emergent SAEs in the study population

4 treatment emergent SAEs were observed: 3 in the active arm (eye [2], reproductive [1] and 1 (respiratory) in the control arm.

iv) Summary of treatment-emergent SARs in the study population

No treatment-emergent SARs were observed