

CLINICAL STUDY REPORT

Lixisenatide Arterial Stiffness Trial (LAST)

Lixisenatide on arterial stiffness in patients with diabetic nephropathy.

Sponsor Protocol Code:	King's Health Partners
EudraCT Number:	2016-001758-17
ClinicalTrials.gov Identifier:	
ISRCTN number:	ISRCTN97699312
REC Number:	16/LO/1947 - London Bloomsbury REC
Investigational Drugs (IMPs):	Lixisenatide
Indication:	To evaluate if 24 weeks treatment with Lixisenatide, reduces arterial stiffness as measured by aortic pulse wave velocity (Ao-PWV) in T2DM patients with diabetic nephropathy (DN)
Development Phase:	IV
Study Begin (FPFV):	02/10/2013
Study End (LPLV):	29/01/2020
Report Version & Issue Date:	05/01/2024
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
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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 or a licensing application.

Chief Investigator:**Printed name****Signature****Date**

Janaka Karalliedde



9/05/2025 (9 May 2025)

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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.

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

All data analyses were performed blinded to group allocation. All patient data were anonymised. Analyses were performed and supervised by Division of Health and Social Care at King's College London, which will be the statistical and data analysis coordinating centre. The change in Ao-PWV was analysed using an analysis of covariance (ANCOVA). The least squares means, 95% confidence interval and p value for treatment difference are 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 were made prior to unblinding treatment codes for analyses. Secondary endpoints were analysed using an ANCOVA model and least squares means, 95% confidence interval and p value for treatment difference is displayed. Missing data were not included in analyses. The data set for analyses was the ITT population.

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	Division of Health and Social Care at King's College London

5. Study Synopsis - Protocol V6.2 07JUN2022

Title of clinical trial	Lixisenatide on arterial stiffness in patents with diabetic nephropathy
Protocol Short Title/Acronym	Lixisenatide Arterial Stiffness Trial (LAST)
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	2016-001758-17
REC number	16/LO/1947 - London Bloomsbury REC
IRAS project ID:	209757
Medical condition or disease under investigation	Type 2D Diabetes patients Nephrology
Purpose of clinical trial	To evaluate if 24 weeks treatment with Lixisenatide, reduces arterial stiffness as measured by aortic pulse wave velocity (Ao-PWV) in T2DM patients with diabetic nephropathy (DN)
Primary objective	To evaluate if treatment with Lixisenatide for 24 weeks reduces Ao-PWV in T2DM with DN
Secondary objective (s)	To evaluate if treatment with Lixisenatide reduces albumin excretion rate (AER), central aortic pressure, augmentation index, sodium balance, ANP, post prandial sodium, brachial artery pressure and other secondary exploratory objectives
Trial Design	Proof of concept 24-week single centre, randomized, double-blind parallel group placebo-controlled study
Endpoints	Primary Endpoint <ul style="list-style-type: none"> The primary end point will be change from baseline in Ao-PWV. The primary end point is change in Ao-PWV following 24 weeks with

	<p>Lixisenatide as compared to 24 weeks of placebo treatment. The primary population used in this assessment will be the intention to treat population.</p> <p>Secondary Endpoints Exploratory secondary endpoints include changes in</p> <ul style="list-style-type: none"> • Albumin Excretion Ratio (AER), • central aortic pressure, • augmentation index, • sodium balance, • ANP, • post prandial sodium (at 2hrs and area under curve), • brachial artery pressure <p>a panel of vascular and inflammatory markers and advanced glycation end products (AGE).</p>
Planned number of subjects	Total 120; 60 patients per treatment group
Summary of eligibility criteria	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> • Written informed consent • T2DM patients aged ≥ 40 years with DN defined as a history of an elevated AER [albumin: creatinine ratio (ACR) ≥ 2.5mg/mmol in men and ≥ 3mg/mmol in women or AER ≥ 20mcg/min] or positive urine dipstick result for proteinuria or urine protein creatinine ratios (PCR)>15 mg/mmol or clinical evidence of diabetic nephropathy] in the absence of other causes of renal damage or urinary tract infections. • Estimated glomerular filtration rate (eGFR)* ≥ 30 ml/min; • On anti-hypertensive therapy with renin angiotensin system (RAS) inhibitor at a stable dose for at least 1 month prior to randomisation • HbA1c $\geq 6.5\%$ on anti-diabetic medications

	<ul style="list-style-type: none"> • Body mass index ≥ 30 kg/m² or ≥ 27 kg/m² (people from black, Asian and other minority ethnic groups and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities) <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Patients with eGFR < 30 ml/min; • Patients with recent (within 1 year) history of CVD event; • Patients with uncontrolled hypertension defined as systolic BP and diastolic BP greater than 180 and 110 mmHg respectively; • Pregnancy or lactation; • Females of child bearing potential or males able to father a child who do not agree to use suitable methods of contraception (as specified in section 4.7 of the Protocol) • Patients with non-diabetic renal disease; • Patients expected to receive an increase in the dose of RAS inhibitors during the course of study; • History of pancreatitis; • Active gastrointestinal (GI) or biliary disease; • Planned major GI surgery that can/could affect upper GI function; • History or family history of thyroid cancer or multiple endocrine neoplasia 2; • Known allergy/intolerance to GLP-1 receptor agonist treatment, metacresol or any of the IMP or placebo components. • Subjects involved in current research or have recently (within 30 days) been involved in any research involving an IMP prior to recruitment.
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	Subjects with insufficient understanding of the Trial or unable to comply with study requirements
IMP, dosage and route of administration	Lixisenatide
Active comparator product(s)	NA
Maximum duration of treatment of a subject	24 weeks
Version and date of protocol amendments	V1.0 11DEC2014 V2.0 18SEP2015 V3.0 25AUG2016 V4.0 19OCT2016 v6.0 20NOV2017 V6.1 06Aug2019 V6.2 07JUN2022

6. Glossary of terms

NA

7. Publication (reference)

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8. Study period (years)

Recruitment opened: 18/01/2017

Recruitment ended: 25/10/2021

04 Apr 2017 FPFV

LPLV 26 May 2022

9. Phase of development

IV

10. Objectives

Primary objective

To evaluate if treatment with Lixisenatide for 24 weeks reduces Ao-PWV in T2DM with DN

Secondary objectives

To evaluate if treatment with Lixisenatide reduces albumin excretion rate (AER), central aortic pressure, augmentation index, sodium balance, ANP, post prandial sodium, brachial artery pressure and other secondary exploratory objectives

11. Background and Context

Diabetic nephropathy (DN) develops in nearly 40% of patients with type 2 diabetes (T2DM), and is the leading cause of end stage renal disease in Europe and is associated with premature CVD morbidity and mortality (1). Despite increased use of inhibitors of the renin angiotensin system (RAS) and more rigorous glycaemic, blood pressure and lipid targets there remains an unmet need for novel treatments to address the burden of DN the major cause of chronic kidney disease in the UK which costs the NHS 1.4 billion pounds a year (1, 2). Emerging observational data suggest that GLP-1 receptor agonists may potentially improve cardiovascular outcomes in patients with T2DM (3, 4). The putative mechanisms explaining these data are unclear, however they are likely to involve the effects of GLP-1 receptor agonists on the vascular and renal system, which may be manifested by changes in arterial stiffness and albuminuria established predictors and bio-markers of cardio-renal disease. Lixisenatide has a significant effect on reducing post-prandial blood glucose excursions, an effect which is more pronounced than other GLP-1 agonists (5). Moreover, increased post-prandial glucose is an independent risk factor for the development of CVD (6, 7) and is associated with increased arterial stiffness and vascular dysfunction (8, 9). In recent years it is apparent that independent of the effects on glucose control, GLP-1 based therapies may have effects on the cardiovascular system (3). The receptor for GLP1 is expressed in cardiac cells, vascular cell and renal cells (4). In animal studies GLP-1 receptor agonists improve cardiac and vascular function through both glucose dependent and independent pathways (4, 10). GLP-1 receptor agonists suppress the potent inflammatory mediator nuclear factor kappa B (NFκB) and reduce monocyte chemoattractant protein-1 (MCP-1) and cell adhesion

molecules such as, vascular cell adhesion molecule (VCAM)-1, intracellular cell adhesion molecule (ICAM)-1 which have been associated with abnormalities in vascular function/arterial stiffness (11, 12).

In mice Lixisenatide treatment by activating anti-inflammatory and vascular protective pathways and improves CVD outcomes post myocardial infarction (13). In a recent clinical trial in 24 patients with T2DM, 12-week treatment with Exenatide significantly reduced the levels of plasma matrix metalloproteinase (MMP), a key mediator of arterial stiffness, an effect which was independent of weight loss (11). Increased arterial stiffness, involving accelerated vascular ageing of the aorta, as determined by the gold standard technique of aortic pulse wave velocity (Ao-PWV) is a powerful and independent risk factor for CVD and all-cause mortality (14). Ao-PWV provides prognostic information above and beyond traditional CVD risk factors such as BP itself, age, gender, diabetes, smoking, albuminuria and cholesterol (14, 15). In recent years it has been established that reversibility of Ao-PWV, independent of changes in BP or other conventional CVD risk factors, is an important modifiable risk factor for survival (15). We have previously demonstrated that 24 weeks treatment with valsartan can reduce Ao-PWV to a significantly greater extent than amlodipine in face of similar attained BP in patients with T2DM and DN (16). In previous studies we have observed that patients with microalbuminuria had higher Ao-PWV of ~1 metre/second than those with normoalbuminuric and that there was a close biological relationship between the two markers of CVD risk (17). The observed differences in Ao-PWV described are clinically relevant as an Ao-PWV rise of approximately 1 metre/second is associated with between 15%-34% increased CVD and all-cause mortality risk (18). Lixisenatide treatment is associated with BP reduction (by 3-5 mmHg) and effect that may be independent of changes in metabolic control and weight (4, 5). The mechanism(s) for this BP reduction which is also observed with other GLP-1 receptor agonists are unclear but recent data described in brief below may provide some answers (4, 10, 19). The RAS is the key pathophysiology pathway in the pathogenesis and progression of DN (1).

Moreover, patients with DN are characterised by activation of the RAS, and increased salt sensitivity with sodium retention which are associated with this groups enhanced cardiorenal risk (1). Exciting recent data highlight the close relationship between GLP-1 receptor activation, sodium balance and the RAS. In mice Liraglutide acting on cardiac GLP-1 receptors promotes atrial natriuretic peptide (ANP) release (20). In an animal model of hypertension, the effects of angiotensin II (a known vasoconstrictor and pro inflammatory mediator) was abolished by Liraglutide treatment (21). This effect is mediated by GLP-1 receptors in the atria as mice lacking the GLP-1 receptor did not have a fall in BP. In elegant studies the authors further demonstrated that a GLP-1 receptor agonist Liraglutide is an ANP secretagogue acting via GLP-1R/Epac2 signalling pathway mechanism that leads to vasodilation of the aorta and natriuresis (21).

ANP is a known direct inhibitor of renin and prevents activation of the RAS (20, 22); data in animals and in vitro provide new information on the mechanisms underlying the BP lowering effects of GLP-1 agonists and describe further mechanistic pathways that would explain the potential cardio-renal benefits of Lixisenatide. Moreover, this heart-gut-renal axis is a potential therapeutic target for DN currently not addressed.

It is feasible to hypothesise Lixisenatide may improve aortic wall structure and function, by reducing vessel wall inflammation and extracellular matrix turnover, reducing RAS activity and salt sensitivity, and increasing aortic vasodilation which are manifested by reduction in Ao-PWV and central aortic pressures which translates to a reduction in BP.

In support of this patients with T2DM treated with Exenatide for 24 weeks had significant reductions in augmentation pressure and augmentation index (an indirect measure of AoPWV) which were independent of glycaemic control as compared with insulin glargine (23). However, in this study Ao-PWV, was not measured and to date no study has been conducted on the effect of GLP-1 receptor agonists on Ao-PWV in patients with DN nor has its potential effect on albuminuria been evaluated. Albuminuria is an early marker of renal microvascular injury in diabetes (24). Although the terms normoalbuminuria, microalbuminuria and macroalbuminuria 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 and that albuminuria indicates significant endothelial damage (1, 25). In a recent study in an animal model of type 1 diabetes, GLP-1 receptor agonist exendin 4 ameliorated albuminuria and glomerular structural changes of DN, an effect independent of changes in BP, blood glucose and weight loss (26). To date the effects, if any, of GLP-1 receptor agonists on Ao-PWV and albuminuria (two predictors of cardio-renal risk) in patients with DN remain unknown.

We therefore propose a proof of concept 24-week single centre, randomized, double-blind parallel group placebo-controlled study to evaluate if 24 weeks treatment with Lixisenatide, in addition to established stable oral anti-diabetic and anti- hypertensive medications, reduces Ao-PWV (primary endpoint) in T2DM patients with DN.

12. Methodology

All data analyses were performed blinded to group allocation. All patient data was anonymised. Analyses were performed and supervised by Division of Health and Social Care at King's College London, which were the statistical and data analysis coordinating centre. The change in Ao-PWV was analysed using an analysis of covariance (ANCOVA). The least squares means, 95% confidence interval and p value for treatment difference was 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 unblinding treatment codes for analyses. Secondary endpoints were analysed using an ANCOVA model and least squares means, 95% confidence interval and p value for treatment difference was displayed. Missing data was not included in analyses. The data set for analyses was the ITT population.

It was estimated that 60 patients per treatment group would provide 90% power at the 5% level (two-sided) to detect a difference in Ao-PWV between Lixisenatide and placebo of 1.0

meter /second with a population standard deviation of 1.5 m/s and assuming a 20% drop out rate during the study. We have previously demonstrated a blood pressure independent 1 meter/second reduction in Ao-PWV is detectable following 24 weeks in T2DM patients with DN (16). Recent data demonstrated that Exenatide reduced augmentation index by 2-3% (23) a degree of change associated with a reduction in Ao-PWV of between 1 to 1.5 meter/second in our previous work and by others.

13. Number of patients (planned and analysed)

13.1 Planned

101 patients

13.2 Analysed

90 patients

Arm	Active	Placebo
# patients screened	143 in total	
# patients randomised/treated/ study arm	Randomised 51/ treated 51	Randomised 50/ treated 50
# patients completed/ study arm	47	43
Reasons for non-completion if applicable	NA	NA

Number of withdrawals and reason:

1 did not attend (**following screening and randomization**) due to preference, 15 withdrew due to preference and 1 because of health reasons unrelated to IMP before the 24-week follow up (**during treatment phase**). Of the patients who withdrew, 7 were in the treatment arm and 10 in the placebo arm.

14. Diagnosis and main criteria for inclusion

- Written informed consent
- T2DM patients aged ≥ 40 years with DN defined as a history of an elevated AER [albumin: creatinine ratio (ACR) ≥ 2.5 mg/mmol in men and ≥ 3 mg/mmol in women or AER ≥ 20 mcg/min] or positive urine dipstick result for proteinuria or urine protein creatinine ratios (PCR) > 15 mg/mmol or clinical evidence of diabetic nephropathy] in the absence of other causes of renal damage or urinary tract infections.
- Estimated glomerular filtration rate (eGFR)* ≥ 30 ml/min.

- On anti-hypertensive therapy with renin angiotensin system (RAS) inhibitor at a stable dose for at least 1 month prior to randomization.
- HbA1c $\geq 6.5\%$ on anti-diabetic medications.
- Body mass index ≥ 30 kg/m² or ≥ 27 kg/m² (people from black, Asian and other minority ethnic groups and for whom insulin therapy would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities).

15. Test product, dose and mode of administration

IMP

Lixisenatide - Initially 10 micrograms once daily for 14 days, then increased to 20 micrograms once daily by subcutaneous injection.

16. Duration of treatment

24 weeks

17. Reference therapy, dose and mode of administration

NA

18. Criteria for evaluation: Endpoints

18.1 Efficacy

Primary end-point

Table 2: ANCOVA analysis results of Aortic pulse wave velocity at 24 weeks and least squares means (95% CI)

	Least squares means (95% CI)			P-value effect*	
	Overall mean baseline	Arm 01 (Lixisenatide)	Arm 02 (Placebo)	Treatment	Baseline measure
Aortic pulse wave velocity (m/s) (Ao-PWV) at 24 weeks	9.4	9.65 (9.17, 10.13)	9.96 (9.45, 10.46)	0.378	6.3e-19

*Results from ANCOVA model of Ao-PWV assessment for 24 weeks adjusting on the baseline Ao-PWV assessment and treatment arm.

*Least square means for 24 weeks Ao-PWV calculated from the model based on the overall mean of Ao-PWV assessment at baseline.

Secondary Efficacy Parameters

Table 3.: ANCOVA analysis results of each secondary endpoint at 24 weeks and least squares means (95% CI)

	Endpoint's least squares means (95% CI)			P-value effect*	
	Overall mean baseline	Arm 01 Lixisenatide	Arm 02 Placebo	Treatment	Baseline measure
Albuminuria excretion rate (AER) (mcg/min)	328.74	449.94 (253.54, 646.34)	208.26 (6.97, 409.56)	0.093	1.27E-05
Central systolic blood pressure (mmHg)	118.7	121.95 (117.97, 125.93)	118.11 (113.94, 122.27)	0.19	3.93E-07
Central diastolic blood pressure (mmHg)	78	78.83 (76.83, 80.83)	78.06 (75.97, 80.15)	0.601	2.63E-08
Seated brachial systolic blood pressure (mmHg)	132.71	136.57 (132.28, 140.86)	133.45 (128.97, 137.94)	0.322	2.04E-05
Seated brachial diastolic blood pressure (mmHg)	76.97	78.46 (76.48, 80.43)	77.43 (75.37, 79.5)	0.483	2.67E-07
Weight (Kg)	76.97	100.58 (98.63, 102.52)	100.58 (98.54, 102.62)	0.999	8.56E-42
eGFR/1.73m2 (mL/min)	66.99	67.83 (65.4, 70.27)	66.11 (63.56, 68.66)	0.339	1.36E-44

HbA1c log transformed (%) (geometric means)	9.02	8.94 (8.58, 9.30)	9.58 (9.12, 9.97)	0.038	3.46E-12
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*Results from ANCOVA model adjusting on the baseline assessment and on treatment arm.

*Least square means for 24 weeks Ao-PWV calculated from the model based on the overall average of Ao-PWV assessment at baseline.

18.2 Safety

Table 4.1: Patient listing of reported AEs

Patient ID	Randomisation date (System)	Trial Arm	AE no.	Adverse Event (AE)	Body System code	Currently ongoing / ongoing at end of study? [(Complete also at end of study)	Outcome	Intensity	Relationship to study intervention
P010001	08/05/2017	Arm 02	01	Mild abdominal pain and nausea*	Gastro-intestinal	No	Recovered	Moderate	Possibly
			02	Nausea*	Gastro-intestinal	No	Recovered	Mild	Possibly
			03	Obesity	Endocrine	Yes (at end of study)	Continuing	Mild	Not related
			04	Reports vaginal bleeding	Genito-urinary/renal	Yes (at end of study)	Continuing	Mild	Not related
P010002	15/05/2017	Arm 01	01	Blood in left eye back area	Eyes, ear, nose, throat	No	Recovered	Mild	Not related
			02	Extrasystoles	Other cardiovascular events	Yes (but not at study end yet)	Continuing	Mild	Not related
			03	Obesity	Gastro-intestinal	Yes (but not at study end yet)	Continuing	Mild	Not related
			04	Hardly palpable pedal pulses	Other cardiovascular events	Yes (but not at study end yet)	Continuing	Mild	Not related
			05	Loss of protective sensation	Neurological	Yes (but not at study end yet)	Continuing	Mild	Not related
			06	Right foot callus on the plantar surface of first metatarsophalangeal joint	Musculo-skeletal	Yes (but not at study end yet)	Continuing	Mild	Not related
P010004	07/06/2017	Arm 02	01	Obesity	Endocrine	Yes (at end of study)	Continuing	Mild	Not related
			02	Mild oedema of RT lower leg	Haematological	Yes (but not at study end yet)	Continuing	Mild	Not related
			03	Pneumonia	Respiratory	No	Recovered	Moderate	Not related

Patient ID	Randomisation date (System)	Trial Arm	AE no.	Adverse Event (AE)	Body System code	Currently ongoing / ongoing at end of study? [(Complete also at end of study)	Outcome	Intensity	Relationship to study intervention
			04	Iron deficiency	Haematological	Yes (at end of study)	Continuing	Mild	Not related
P010005	20/06/2017	Arm 01	01	Obesity	Endocrine	Yes (but not at study end yet)	Continuing	Not available or not applicable	Not related
P010008	17/07/2017	Arm 02	01	Bruising at left flank	Dermatological	Yes (but not at study end yet)	Continuing	Mild	Not related
			02	Obesity	Endocrine	Yes (but not at study end yet)	Continuing	Mild	Not related
			03	Stomach-ache and vomits	Gastro-intestinal	No	Recovered	Mild	Possibly
P010011	01/08/2017	Arm 01	01	Obesity	Endocrine	Yes (but not at study end yet)	Continuing	Mild	Not related
P010012	04/08/2017	Arm 01	01	Obesity	Endocrine	Yes (but not at study end yet)	Continuing	Mild	Not related
			02	Boil left armpit	Dermatological	No	Recovered	Moderate	Not related
			03	Cold	Respiratory	Yes (at end of study)	Continuing	Mild	Not related
P010015	22/08/2017	Arm 02	01	Stasis dermatitis lower legs bilaterally	Dermatological	Yes (at end of study)	Continuing	Mild	Not related
			02	Infection	Dermatological	No	Recovered	Moderate	Not related
P010017	21/08/2017	Arm 01	01	Hypoglycemia	Endocrine	No	Recovered	Moderate	Possibly
			02	Chest infection	Chest infection	No	Recovered	Mild	Not related
P010020	16/10/2017	Arm 01	01	Diarrhoea	Gastro-intestinal	No	Recovered	Mild	Not related
P010026	06/11/2017	Arm 02	01	Flu	Flu	No	Recovered	Moderate	Not related
			02	Asthma attack	Respiratory	No	Recovered	Mild	Not related
			03	Asthma attack	Respiratory	Yes (at end of study)	Continuing	Mild	Not related
			04	Allergy	Immunological	Yes (at end of study)	Continuing	Mild	Not related
P010027	09/11/2017	Arm 01	01	Flu	Respiratory	No	Recovered	Mild	Not related
P010028	10/11/2017	Arm 02	01	Flu	Virus	No	Recovered	Mild	Not related
			02	Flu	Virus	No	Recovered	Mild	Not related

Patient ID	Randomisation date (System)	Trial Arm	AE no.	Adverse Event (AE)	Body System code	Currently ongoing / ongoing at end of study? [(Complete also at end of study)	Outcome	Intensity	Relationship to study intervention
P010030	04/12/2017	Arm 01	01	Tooth ache	Tooth	Yes (but not at study end yet)	Continuing	Moderate	Not related
P010037	01/03/2018	Arm 01	01	Pain and numbness of right thigh	Musculo-skeletal	Unknown	Continuing	Moderate	Not related
P010039	19/03/2018	Arm 01	01	Short term memory loss	Memory loss	Yes (but not at study end yet)	Continuing	Mild	Not related
			02	Chest infection	Respiratory	No	Recovered	Mild	Not related
P010043	24/04/2018	Arm 02	01	Inflammation of the skin	Dermatological	Unknown	Unknown	Moderate	Not related
			02	Boils/pilonidal cyst	Dermatological	Unknown	Unknown	Moderate	Not related
P010046	01/05/2018	Arm 01	01	Urinary tract bleeding	Genito-urinary/renal	No	Recovered	Mild	Not related
			02	Fall with bruise to left leg following hypoglycaemia	Musculo-skeletal	No	Recovered	Mild	Possibly
			03	Flatulence	Gastro-intestinal	Yes (but not at study end yet)	Continuing	Mild	Not related
			04	Folliculitis	Dermatological	Yes (but not at study end yet)	Continuing	Mild	Not related
			05	Hypoglycaemia	Endocrine	No	Recovered	Moderate	Possibly
P010047	16/05/2018	Arm 02	01	Macroscopic haematuria	Genito-urinary/renal	No	Recovered	Mild	Not related
			02	Pain lower abdomen	Musculo-skeletal	No	Recovered	Mild	Not related
P010061	28/08/2018	Arm 01	01	Forehead wound	Forehead wound	No	Recovered	Mild	Not related
P010064	19/09/2018	Arm 02	01	Diarrhoea	Gastro-intestinal	No	Recovered	Mild	Possibly
			02	Urine infection	Genito-urinary/renal	No	Recovered	Moderate	Not related
P010066	22/10/2018	Arm 02	01	Tooth extraction infection	Immunological	No	Recovered	Mild	Not related
P010068	31/10/2018	Arm 01	01	Back pain	Musculo-skeletal	Yes (but not at study end yet)	Continuing	Mild	Not related
			02	Knee pain	Musculo-skeletal	Yes (but not at study end yet)	Continuing	Mild	Not related
P010074	05/12/2018	Arm 01	01	Flu	Flu	No	Recovered	Moderate	Not related
P010075	11/12/2018	Arm 02	01	Dizziness, fell off and hit the floor and lost teeth	Dizziness	No	Recovered	Moderate	Not related

Patient ID	Randomisation date (System)	Trial Arm	AE no.	Adverse Event (AE)	Body System code	Currently ongoing / ongoing at end of study? [(Complete also at end of study)	Outcome	Intensity	Relationship to study intervention
P010076	25/01/2019	Arm 02	01	Low back pain	Musculo-skeletal	Yes (but not at study end yet)	Continuing	Mild	Not related
			02	Urine infection	Genito-urinary/renal	Yes (but not at study end yet)	Continuing	Moderate	Not related
P010082	11/03/2019	Arm 02	01	Exacerbation of chronic COPD	Respiratory	Yes (but not at study end yet)	Continuing	Moderate	Not related
P010096	11/06/2019	Arm 01	01	Nausea and constipation	Gastro-intestinal	Yes (but not at study end yet)	Continuing	Moderate	Possibly
P010112	23/10/2019	Arm 02	01	Tooth infection	Tooth infection	No	Continuing	Moderate	Not related
P010119	09/12/2019	Arm 02	01	Bones, inflammation	Musculo-skeletal	Yes (but not at study end yet)	Continuing	Moderate	Not related
P010127	04/03/2020	Arm 02	01	Body rash	Dermatological	Yes (at end of study)	Continuing	Moderate	Not related
P010138	15/06/2021	Arm 01	01	Hypoglycemia	Endocrine	Yes (but not at study end yet)	Unknown	Moderate	Definitely
			02	Right Shoulder Pain	Musculo-skeletal	Yes (but not at study end yet)	Unknown	Moderate	Not related
			03	Nausea	Gastro-intestinal	Yes (but not at study end yet)	Continuing	Mild	Definitely
			04	Light-headed	Other cardiovascular events	Yes (but not at study end yet)	Continuing	Mild	Possibly

* Action taken in relation to IMP was dose reduction

Table 4.2: Listing of patients with at least one serious AEs (SAE)

Patient ID	Randomisation date (System)	Trial Arm	AE no.	Adverse Event (AE)	Body System code	Currently ongoing / ongoing at end of study? ((Complete also at end of study)	Outcome	Intensity	Relationship to study intervention	Action taken in relation to IMP	Serious AE?
P010051	21/08/2018	Arm 01	01	Malignant hypertension	Other cardiovascular events	No	Recovered	Moderate	Not related	None	Requires hospitalisation or prolongation of existing hospitalisation
P010053	17/07/2018	Arm 02									
			01	Acute coronary syndrome (artery by-pass)	Other cardiovascular events	No	Recovered	Severe	Not related	Treatment stopped permanently	Requires hospitalisation or prolongation of existing hospitalisation
P010068	31/10/2018	Arm 01	01	Knee pain		No	Recovered	Unknown	Not related	None	Requires hospitalisation or prolongation of existing hospitalisation
P010069	14/11/2018	Arm 01	01	Acute coronary syndrome	Other cardiovascular events	No	Recovered	Severe	Not related	None	Requires hospitalisation or prolongation of existing hospitalisation
			02	Cerebrovascular Accident		No	Recovered	Unknown	Not related	None	Requires hospitalisation or prolongation of existing hospitalisation
P010070	13/11/2018	Arm 02	01	Benign female reproductive tract neoplasm		No	Recovered	Unknown	Not related	None	Requires hospitalisation or prolongation of existing hospitalisation

Patient ID	Randomisation date (System)	Trial Arm	AE no.	Adverse Event (AE)	Body System code	Currently ongoing / ongoing at end of study? [(Complete also at end of study)	Outcome	Intensity	Relationship to study intervention	Action taken in relation to IMP	Serious AE?
P010077	15/01/2019	Arm 01	01	Low back pain		No	Recovered	Unknown	Not Related	None	Requires hospitalisation or prolongation of existing hospitalisation
P010099	26/07/2019	Arm 02	01	Lower respiratory tract infection		No	Recovered	Unknown	Not Related	None	Requires hospitalisation or prolongation of existing hospitalisation
P010109	11/11/2019	Arm 02	01	Upper gastrointestinal bleeding			Continuing	Unknown	Not Related	None	Requires hospitalisation or prolongation of existing hospitalisation
P010136	Not randomised		01	Mini-Stroke		No	Resolved with sequelae	Unknown	Not Related	None	Requires hospitalisation or prolongation of existing hospitalisation
P010143	Not randomised		01	Unwell		No	Recovered	Unknown	Not Related	None	Requires hospitalisation or prolongation of existing hospitalisation
P010004	07/06/2017	Arm 02	01	Anaemia – Weight Loss		No	Recovered	Unknown	Not Related	None	Requires hospitalisation or prolongation of existing hospitalisation
P010046			01	Hyperglycaemia		No	Recovered	Unknown	Not Related	None	Requires hospitalisation or prolongation of existing hospitalisation
	01/05/2018	Arm 01	02	Hyperglycaemia		No	Recovered	Unknown	Unlikely	None	Requires hospitalisation or prolongation of existing hospitalisation

19. Statistical Methods

Analysis of Efficacy Variables

ANCOVA analysis results of each secondary endpoint at 24 weeks and least squares means (95% CI)

Analysis of Safety Variables

Listing of reported AE/SAE

20. Changes in the Trial Plan

101 patients were randomised among which one patient did not attend baseline visit and thus no baseline Ao-PWV was recorded. Among the 100 left patients, 17 patients didn't reach 24 weeks follow-up. 7/ 17 patients had their Ao-PWV assessment data at 12 weeks of follow-up.

20.1 Protocol Deviations

NA

21. Summary – Conclusions

21.1 Demographic data

Table 1.1: Baseline demographics overall and by treatment arm

	Arm 01 N=51 Lixisenatide	Arm 02 N=50 Placebo	Total (N=101)
Age at screening, mean (SD)	61.5 (10.2)	67.2 (11.9)	64.5(11.3)
Sex n (%)			
Male	32 (62.7)	34 (68)	66 (65.3)
Female	19 (37.3)	16 (32)	35 (34.7)

	Arm 01 N=51 Lixisenatide	Arm 02 N=50 Placebo	Total (N=101)
Ethnicity n (%)			
Asian	5 (9.8)	1(2)	6 (5.9)
Black - Afro-Caribbean	19 (37.3)	18 (36)	37 (36.6)
Black - other	5 (9.8)	4 (8)	9(8.9)
White	21 (41.2)	26 (50.9)	47 (46.5)
Mixed - including Afro-Caribbean	1 (2.1)	1 (2.3)	2 (19.8)

21.2 Primary outcome

Table 2: ANCOVA analysis results of Aortic pulse wave velocity at 24 weeks and least squares means (95% CI)

	Overall mean baseline	Least squares means (95% CI)		P-value effect*	
		Arm 01 (Lixisenatide)	Arm 02 (Placebo)	Treatment	Baseline measure
Aortic pulse wave velocity (m/s) (Ao-PWV) at 24 weeks	9.4	9.65 (9.17, 10.13)	9.96 (9.45, 10.46)	0.378	6.3e-19

*Results from ANCOVA model of Ao-PWV assessment for 24 weeks adjusting on the baseline Ao-PWV assessment and treatment arm.

*Least square means for 24 weeks Ao-PWV calculated from the model based on the overall mean of Ao-PWV assessment at baseline.

There wasn't a statistically significant reduction *in* Ao-PWV, hence primary outcome not met.

21.3 Safety Result

Table: Adverse events per study arm

Adverse Events	Treatment Arm	Placebo	Not randomised
Total Number of AEs per Study Arm	41	37	2
Subjects affected by non-serious adverse events:	16	16	0

Table: Listing of Serious Adverse Events for all patients

Serious Adverse Events	Treatment Arm	Placebo	Not randomised
Total Number of SAEs per Study Arm	5	7	2
Total number of all cause deaths per Study Arm	0	0	0
Total number of deaths resulting from adverse events per Study Arm	0	0	0

Within the per protocol population (n= 101), a total of 78 AEs, including 12 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, 44 randomised patients (42.7%) patients experienced at least one AE, of which 23 were in the placebo arm 21 in the treatment arm and 2 were not randomised. The proportion that experienced at least one SAE was 13.6% (n=14).

Incidence of adverse drug reactions (ADRs): 11/78 AEs (14.1%) were assessed as related to at least one study drug and 11 / 101 patients (11 %) experienced ADR.

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

22. Conclusion

The primary objective of the trial was not met, as there was no statistically significant reduction in Ao-PWV following 24-week treatment with Lixisenatide as compared to placebo. There were no significant medical events or unplanned pregnancy. There were no issues with IMP concordance. There were 14 SAEs in total as discussed in the relevant section and no SAR, SUSAR's or unexpected SAR.

23. Date of Report

This is version 3.0 of the Clinical Study Report synopsis, dated 09 May 2025

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	Total Number of Occurrences of the AE	Number of Subjects Experiencing the AE in Placebo Arm	Total Number of Occurrences of the AE
Blood and lymphatic system disorders	Hematological	0	3	2 (100%)	3
Cardiac disorders	Other cardiovascular disorders	2 (66.66%)	5	1 (67%)	5
Congenital, familial and genetic disorders	NA	0	0	0	0
Ear and labyrinth disorders	Eyes, ear, nose, throat	0	0	0	0
Eye Disorders	Eyes, ear, nose, throat	1(100%)	1	0	1
Gastrointestinal disorders	Gastrointestinal/ Tooth	4 (36%)	11	7 (64%)	11
General disorders and administration site conditions	NA	0	0	0	0
Hepatobiliary disorders	NA	0	0	0	0
Immune system disorders	Immunological	0	2	2 (100%)	2
Infections and	NA	0	0	0	0

infestations					
Injury, poisoning and procedural complications	Forehead wound	1(100%)	0	0	1
Investigations	NA	0	0	0	0
Metabolism and nutritional disorders	Endocrine	6 (60%)	11	4 (40%)	11
Musculoskeletal and connective tissue disorders	Musculoskeletal	8 (80%)	11	2 (20%)	11
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	NA	0	0	0	0
Nervous system disorders	Neurological/Dizziness/Memory loss	3 (100%)	3	0	3
Pregnancy, puerperium and perinatal conditions	NA	0	0	0	0
Product issues	NA	0	0	0	0
Psychiatric disorders	NA	0	0	0	0
Renal and urinary disorders	NA	0	0	0	0
Reproductive system and breast disorders	Genitourinary/Renal	0	6	6 (100%)	6
Respiratory, thoracic and mediastinal disorders	Respiratory/Virus/Flu/Chest infection/Lower respiratory tract infection	5 (42%)	14	7 (58%)	14
Skin and subcutaneous tissue disorders	Dermatological	3 (42%)	8	4 (58%)	8
Social circumstances	NA	0	0	0	0
Surgical and medical procedures	NA	0	0	0	0
Vascular disorders	Other cardiovascular disorders	2 (100%)	2	0	2

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

A total of 11 AEs were identified as adverse drug reactions. 6 gastrointestinal (nausea, constipation, diarrhoea), 3 endocrine (hypoglycaemia), 1 other cardiovascular (lightheadedness), 1 musculoskeletal (muscle injury due to fall related to hypoglycemia).

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

None

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

None