

An experimental pilot study to investigate changes in catecholamine synthesis and metabolism in patients with molecularly profiled pheochromocytoma and paraganglioma taking Belzutifan

IRAS Ref: Insert

Date and Version No: V1 19/11/2025

Chief Investigator: Dr Ruth Casey

Joint sponsors: Cambridge University Hospitals NHS
Foundation Trust and University of Cambridge

AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
V1	V1		Dr Ruth Casey	

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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

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

Chief Investigator:

Signature:

.....

Date:

...../...../.....

Name: (please print):

.....

KEY STUDY CONTACTS

Chief Investigator	Dr Ruth Casey
Study Co-ordinator	Dr Ruth Casey
Sponsor	Cambridge University Hospitals NHS Foundation Trust
Joint sponsor	University of Cambridge
Funder(s)	NIHR Cambridge BRC-wide Pump Priming funds 2025

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SYNOPSIS

Study Title	An experimental pilot study to investigate changes in catecholamine synthesis and metabolism in patients with molecularly profiled pheochromocytoma and paraganglioma taking Belzutifan.
Internal ref. no.	A096498
Study Design	Experimental single arm pilot interventional study
Study Participants	Patients with localised or metastatic catecholamine secreting pheochromocytoma or paraganglioma
Planned Sample Size (if applicable)	12 patients
Follow-up duration (if applicable)	9 days after finishing the medication
Planned Study Period	14 days
Primary Objective	Identify changes in the amino acid precursor of catecholamine synthesis during and after 5 days of taking Belzutifan 120mg once a day
Secondary Objectives	Associated changes in catecholamine metabolites during and after 5 days of taking Belzutifan 120mg once a day

FIGURE 1: STUDY FLOW CHART

See attached.

1. BACKGROUND AND RATIONALE

Background: Pheochromocytomas and paraganglioma (PPGL) are catecholamine secreting neuroendocrine tumours arising from the adrenal medulla or extra adrenal sympathetic or parasympathetic ganglion, with unpredictable malignant potential. Approximately 20% of all PPGL are metastatic but the most common morbidity caused by these tumours is cardiovascular compromise, driven by the excess catecholamine production. Symptoms of catecholamine excess include headache, palpitations, paroxysmal hypertension, or resistant hypertension, anxiety and excessive sweating. A catecholamine crisis is defined as acute and severe haemodynamic instability and collapse and is estimated to affect 11% of patients presenting with PPGL. At present the standard of care treatment in the UK and Europe for all patients with catecholamine secreting PPGL preparing for surgery and including those presenting with life threatening catecholamine crises, is alpha-adrenergic receptor blockade. Alpha-adrenergic receptor blockers attenuate the effects of elevated catecholamine's but do not impact the concentration of circulating catecholamine's. The use of alpha-adrenergic receptor blockers requires careful consideration in patients with catecholamine induced intravascular volume depletion or catecholamine induced cardiomyopathy, which contribute to hypotension and can make initiation of alpha-adrenergic receptor blockers challenging to manage. These medications typically require careful step wise up titration over 7-14 days to achieve hemodynamic stability ahead of planned curative surgery or in the event of a catecholamine crisis and therefore do not provide rapid stabilisation for patients. Furthermore, the use and cumulative dose of alpha-adrenergic receptor blockers has been demonstrated to impact on the severity and duration of post-operative hypotension for patients undergoing surgery for PPGL. Metyrosine (α -methyl-paratyrosine) is a tyrosine hydroxylase inhibitor that blocks the conversion of tyrosine to 3, 4-dihydroxyphenylalanine (dopa), the rate-limiting step in catecholamine synthesis. This medication is not licensed for pheochromocytoma in the UK or Europe but is available in the US. It is licensed in the UK for von Hippel-Lindau disease associated tumours. Aside from the limited availability, this medication has several dose dependent adverse effects including CNS depression, extrapyramidal side effects, psychosis and diarrhoea.

Belzutifan is a first in class, second generation, small-molecule inhibitor of hypoxia inducible factor 2 α (HIF-2 α). Belzutifan selectively disrupts the heterodimerization of the HIF transcription complex, preventing downstream target gene transcription. To date much of the

focus has been on the anti-proliferative effect of this drug in patients with tumours impacted by molecular aberrations which promote expression of the hypoxia inducible factor 2 α transcription factor such as VHL. The safety and efficacy of Belzutifan was first investigated in a phase 2, open-label, single-group trial, investigating patients with VHL associated renal cell carcinoma ([NCT03401788](#)). In this study, Belzutifan was associated with predominantly grade 1 and 2 adverse events, the most common side effects were anaemia and fatigue. There were no deaths from a treatment-related adverse event. A drop in haemoglobin from baseline of 1.9g/dl occurred in all patients in this study; however, intervention was rarely required and the time frame for the development of anaemia in this study was longer than the proposed treatment protocol for this study (5 days). The maximum EPO suppression from Belzutifan has been observed to occur following 2 weeks of consecutive dosing of Belzutifan. Mean EPO levels gradually returned to baseline values after 12 weeks of treatment. Belzutifan has subsequently been evaluated for safety and efficacy compared to Everolimus in patients with advanced renal cell carcinoma and no new safety signals were identified ([NCT04195750](#)). The Medicine and Healthcare products Regulatory Agency (MHRA) have approved Belzutifan in the UK for treating specific tumors associated with von Hippel-Lindau (VHL) disease and the European Medicines Agency have approved Belzutifan for use in patients with renal cell carcinoma and VHL associated tumours. Finally, in May 2025, the US Food and Drug Administration approved Belzutifan for adult and paediatric patients 12 years and older with locally advanced, unresectable, or metastatic pheochromocytoma or paraganglioma.

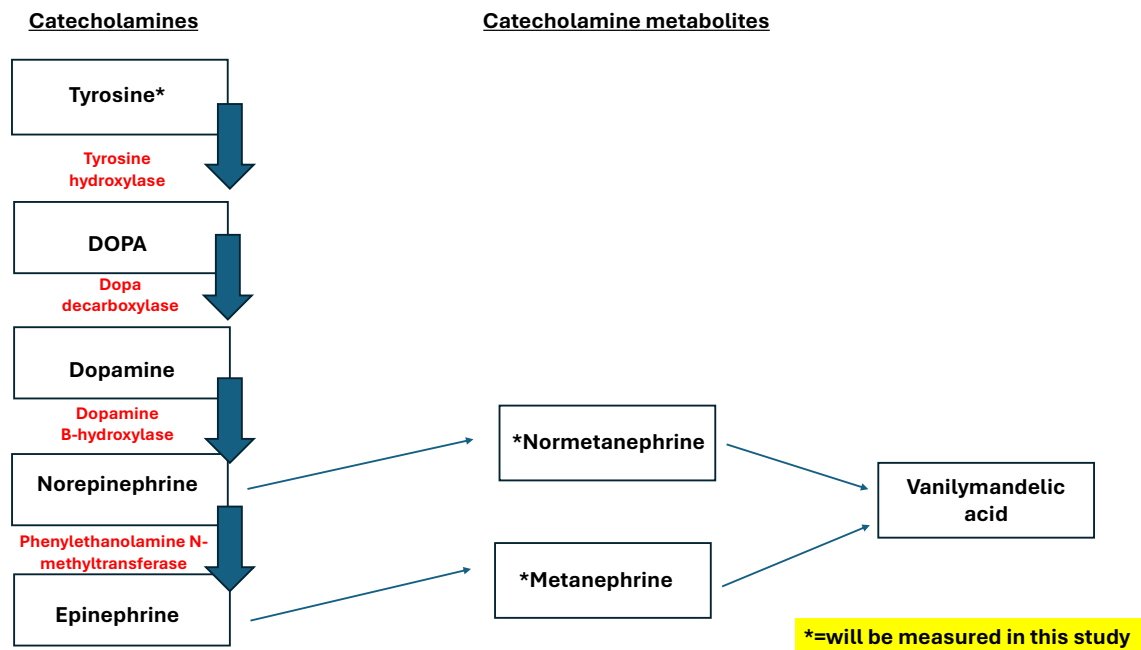
A case report has demonstrated a rapid anti-secretory benefit of Belzutifan in a patient with a metastatic PPGL driven by a gain of function mutation in the *EPAS1* gene. In this patient, a reduction of circulating catecholamines was noted on first use within 5 days and on re-use within 3 hours of starting Belzutifan 80-120mg daily. Improvement in haemodynamic parameters were observed within 48 hours. Preliminary mechanistic studies by the same group, suggest that Belzutifan inhibits catecholamine synthesis by reducing phosphorylated tyrosine hydroxylase levels which should disrupt catecholamine metabolism as the rate controlling enzyme in catecholamine synthesis. This proposed mechanism of action suggests that Belzutifan may only have an anti-secretory benefit in patients with PPGL harbouring cluster 1 gene mutations. Cluster 1 genes include *VHL*, *SDHB*, *SDHA*, *SDHC*, *SDHD*, *SDHAF2*, *FH*, *MDH2*, *SLC25A11*, *IDH1*, *EPAS1* and germline or somatic variants in these genes are found in up to 30% of all PPGL cases.

There is preliminary data to suggest that Belzutifan may impact catecholamines synthesis and or metabolism (Figure 2) and this potential impact on catecholamine metabolism needs to be further probed in an experimental pilot study focused on examining the precursor amino acid tyrosine, from which catecholamine synthesis is initiated, as an experimental primary endpoint. The hypothesis of this experimental study is that this amino acid will increase serially, if Belzutifan impacts catecholamine synthesis by disrupting the enzyme tyrosine hydroxylase.

The licensed dose of Belzutifan is 120mg daily, taken as three 40 mg tablets administered orally once daily, with or without food. Tablets should be swallowed whole. Belzutifan was licensed for clinical use in 2021 for patients with VHL associated tumours and later in 2023 for patients with advanced sporadic renal cell carcinoma, which has progressed through multiple lines of treatment and most recently in May 2025 for children and adults with metastatic pheochromocytoma and paraganglioma. Belzutifan has been investigated in clinical trials as a front- and later-line therapy, and in combination with other anti-cancer drugs such as tyrosine kinase inhibitors. It has been well tolerated, but anaemia and hypoxia have been observed as common ‘on target’ side-effects of Belzutifan and require monitoring during treatment.

This experimental medicine study will include patients from a single centre with localised or metastatic, catecholamine secreting PPGL. The aim of this pilot study is to identify if Belzutifan disrupts catecholamine synthesis and metabolism and will be investigated through serial measurements of the amino acid tyrosine and by measuring the metabolites of catecholamine metabolism in patients with secretory phaeochromocytoma/paraganglioma taking with Belzutifan 120mg daily for five days.

Figure 2: This image illustrates the catecholamine synthesis pathway.



2. OBJECTIVES

2.1 Primary Objective

To investigate the impact of Belzutifan on catecholamine synthesis as evidenced by the change in the experimental amino acid precursor of catecholamine synthesis; tyrosine in patients before, during and after 5 days of taking Belzutifan 120mg daily.

2.2 Secondary Objectives

To investigate the impact of Belzutifan on catecholamine metabolites, determined by changes in serial plasma metanephrines measured before, during and after 5 days of taking Belzutifan 120mg daily.

2.3 Outcome

The measured outcomes including tyrosine (catecholamine synthesis amino acid precursor) and plasma metanephrines (catecholamine metabolites) will provide insights into the potential impact that Belzutifan has on catecholamine metabolism.

3. STUDY DESIGN AND METHODS

3.1 Study design

This is a single centre, single arm, pilot interventional study aimed at identifying alterations in catecholamine synthesis and metabolism in patients taking Belzutifan 120mg daily for five days.

As this is a pilot and experimental study of a rare disease, sample size was not calculated. A study recruitment target of 8-12 patients was established based on the annual incidence of patients with catecholamine secreting PPGL attending our tertiary referral centre. There is an estimated annual incidence of 100-150 patients across all of England and an annual incidence of 15-20 patients attending Cambridge University Hospital per year.

3.2 Study protocol

The study protocol is 14 days (Figure 2: Schedule of events). All patients will be recruited by the PI after informed consent and review of the study inclusion and exclusion criteria.

Germline genetic results performed as part of routine clinical care will be recorded for all patients. For those patients with negative germline genetic test results, tumour sequencing of available tissue or tumour tissue later removed (after the end of the study protocol) during surgery will be performed to investigate for somatic variants in cluster 1 genes which may influence how Belzutifan impacts catecholamine synthesis and metabolism.

The study protocol is 14 days including five days of intervention with Belzutifan 120mg daily for all patients. Baseline plasma tyrosine and plasma metanephrines will be performed on all patients (day 0) and at several time points after starting Belzutifan 120mg daily to examine for alterations in catecholamine metabolism. Recruited patients will attend daily for seven days and again on day 10 and day 14 and will be reviewed by the PI.

Plasma tyrosine and metanephrines will be performed using liquid chromatography mass spectroscopy using published research methods and a percentage reduction in catecholamine metabolites and a percentage increase in tyrosine will be calculated for every patient at the end of the 14-day protocol.

Safety measures will include monitoring of full blood count, liver function tests and by measuring blood pressure and heart rate at baseline and at day 1-7, day 10 and day 14 in all

patients recruited to the study. Any changes in blood pressure during the study protocol will be reviewed by the PI and all changes to existing medications will be performed by the PI and recorded. All recruited patients will be interviewed daily from day 0 to day 7 and again on day 10 and day 14 and all symptoms reported will be recorded by the PI.

3.3. Data management

Data on recruited patient demographics, clinical history, genetic results, medications (including any changes to medication over the study protocol), baseline and sequential urinary VMA and plasma catecholamine metabolites and FBC and liver function results, reported symptoms, blood pressure, heart rate and pulse oximetry, will be recorded as per the schedule of events (Figure 2).

Source documents are the documents where data are first recorded, and from which participants' data are obtained. These include, but are not limited to, electronic hospital records (from which medical history and previous and concurrent medication may be obtained) clinical and office charts, laboratory and pharmacy records.

The data will be collected by the PI or a named co-investigator and will be anonymised and stored on an NHS secure computer platform and will be stored for 18 months after completion of the study. After 18 months the data will be permanently deleted.

Direct access will be granted to authorised representatives from the Sponsor, and host institution only.

Figure 2: Schedule of events:

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 10	Day 14
Review inclusion/exclusion criteria	*									
Review germline genetic test results from patient records	*									
If no germline pathogenic variant, arrange research tumour sequencing*	*									
Review of concomitant medication	*	*	*	*	*	*	*	*	*	*
Pregnancy test for females aged 18-50 years	*									
Administration of Belzutifan 120mg daily		*	*	*	*	*				
Lying blood pressure check after 20 mins of supine rest	*	*	*	*	*	*	*	*	*	*
Heart rate check after 20mins of supine rest	*	*	*	*	*	*	*	*	*	*

Pulse oximetry	*	*	*	*	*	*	*	*	*	*
FBC	*		*	*	*	*	*			*
Liver function	*		*	*	*	*	*			*
Fasted plasma metanephrines	*		*	*	*	*	*			*
Fasted plasma tyrosine	*					*				*
Symptom check		*	*	*	*	*	*	*	*	*

- Tumour sequencing should be performed using DNA extracted from paraffin embedded tissue samples using TSO 500 or Sanger sequencing for known hot spots in *EPAS1* gene (exon 9, 12)

3.4 Study Participants

3.4 a) Inclusion Criteria

- Adult patients > 18 years
- Patients must have a biochemically confirmed diagnosis of a pheochromocytoma or paraganglioma using plasma metanephrines or 24- hour urinary metanephrines and plasma or urinary metanephrines should be at least 1.5 times the upper limit of the normal reference range.
- Female patients of child-bearing potential must have a negative serum pregnancy test result within 3 days before first administration of study drug
- Able to provide informed consent

3.4 b) Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Has hypoxia, or requires intermittent supplemental oxygen, or requires chronic supplemental oxygen.
- Has clinically significant cardiac disease, including unstable angina, acute myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass graft surgery (CABG) $\leq$ 6 months from Day 1 of study drug administration, or New York Heart Association Class III or IV congestive heart failure. Medically controlled arrhythmia stable on medication is permitted.
- Has a co-existing malignancy (in addition to PPGL)
- Has a Hb < 100g/dL
- Is on medications which may interfere with belzutifan pharmacokinetics and that cannot be stopped for the duration of the study and for 7 days after the study period (everolimus, omeprazole, esomeprazole, Fluconazole, fluoxetine, Voriconazole, Sirolimus)
- Has a known diagnosis of HIV, hepatitis B or hepatitis C

4. STUDY PROCEDURES AND INTERVENTIONS

4.1 Recruitment

This study does not include randomisation into a specific arm of a study. Patients will either be recruited and entered into the study, or if they do not or cannot provide informed consent or do not meet inclusion criteria, they will not be entered into the study.

Study recruitment will be aided by an existing hospital database and a dedicated clinic for patients with PPGL led by Dr Casey. Cambridge University Hospital is one of three European centres recognised as ‘centres of excellence’ for the management of PPGL and as a result CUH review about 20-25% of all newly diagnosed PPGL patients in England per year.

All patients with catecholamine secreting PPGL, who meet inclusion criteria and who have no exclusion criteria and can provide informed consent are eligible for recruitment to the study.

4.2 Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any data can be retrieved for that individual, either electronically or on paper. Written or electronic versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study, what it will involve for the participant; how and where the data will be stored and to whom the anonymised data may be made available.

It will be clearly stated that the participant is free to withdraw consent at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal. The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate.

Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participant if they wish. The original signed form will be retained at the study

site. If a person loses the ability to provide informed consent, they will be removed from the study.

4.2 Study Assessments/Interventions

All recruited patients will receive 120mg once a day of Belzutifan for five days (day1 to 5).

4.3 Definition of End of Study

The study end is defined as the final visit (day 14) of the study protocol.

5. SAFETY REPORTING

The study will be conducted in accordance with the protocol, GCP, relevant regulations and standard operating procedures.

This study is an experimental study and is not assessing safety or efficacy. Safety and efficacy have already been investigated for the intervention (Belzutifan) (NCT04195750, NCT03401788) and this drug is licenced for use in the UK.

Safety will be monitored in accordance with the agreed precautions and side effects outlined by the British National Formulary including anaemia; dizziness; dyspnoea; fatigue; hypoxia; nausea.

Anaemia will be screened for using a full blood count at day 0, 2-7, day 10 and day 14.

Hypoxia will be screened for using pulse oximetry at day 0, 1-7, day 10 and day 14

Symptoms including dizziness, fatigue and dyspnoea will be screened for through interview of recruited patients performed by the PI on day 1-7, day 10 and day 14.

Liver function will be checked at day 0 and day 1-7, day 10 and day 14 to screen for any mild derangements in liver function that has been described in safety studies to date.

Abnormalities of laboratory test results (e.g. FBC) may or may not, in the opinion of the Investigator, be considered clinically significant. All clinically significant abnormal laboratory test results will be reported on the Adverse Event CRF and will be followed until a

return to normal or baseline levels. Abnormal laboratory values that require intervention must be reported on the Adverse Event CRF. Any laboratory test result that is abnormal during the study but not considered clinically significant will be followed at the discretion of the Investigator.

Changes in blood pressure or heart rate will be monitored for by measuring blood pressure and heart rate at day 0, 1-7, day 10 and day 14.

Belzutifan will be permanently discontinued and reported as an adverse event if

- A patient has a drop in Hb < 80g/dl
- A patient has recorded oxygen saturations < 90% on room air
- A patient has an elevation in Alanine aminotransferase (ALT) > 3 times the starting ALT value
- A female patient becomes pregnant

5.1 Definition of Serious Adverse Events

A serious adverse event is any event that is considered

- Is life-threatening
- Requires inpatient hospitalisation
- Requires discontinuation of the intervention as listed above

5.2 Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant will be reported to the REC if in the opinion of the Chief Investigator the event was: ‘related’ – that is, it resulted from administration of the intervention. Reports of related SAEs will be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES report of serious adverse event form.

6. STATISTICS

6.1 The Number of Participants

This study is a pilot proof of concept experimental study, and 12 patients will be recruited.

6.2 Sampling

This is a pilot experimental study measuring a continuous variable (precursor amino acid of catecholamine synthesis and catecholamine metabolites) and therefore a definite sample size and power calculation is not appropriate, but a cohort of 8-12 patients is typically recommended for pilot studies with the aim of informing the standard deviation for future larger studies and therefore a cohort of 8-12 was selected.

6.3 Analysis of Endpoints

The study end points are continuous variables (plasma tyrosine, plasma metanephrines). Descriptive statistics will be used to describe the baseline data and variables at the described study timepoints and inferential statistical tests including t-tests and ANOVA will be employed to calculate differences in variables from baseline to the end of the study.

7. ETHICAL AND REGULATORY COMPLIANCE

7.1 Data Protection and Patient Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely on an NHS computer and will only be accessible by study staff (PI and co-investigators).

The PI will be the data custodian, and the data will be stored for 18 months after the study protocol is completed for every patient and data archiving will be performed in line with institutional policy or permanently deleted.

7.2 Sponsorship, Financial and Insurance

The study is sponsored by Cambridge University Hospitals NHS Foundation Trust and University of Cambridge. The trial will be funded by NIHR Cambridge BRC-wide Pump Priming funds 2025.

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the study caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the study, but no-one has acted negligently.

The University of Cambridge will arrange insurance for negligent harm caused as a result of protocol design and for non-negligent harm arising through participation in the clinical trial.

8. DISSEMINATION POLICY

The study data belongs to the Chief Investigator and the study sponsors and dissemination of the study data will follow the framework laid out by Cambridge University. On completion of the study and data analysis, a final study report will be drafted as an abstract and final manuscript. The abstract will be submitted to national and or international scientific meetings and the final manuscript will be submitted for publication in an open access journal and the Cambridge University repository.

The chief Investigator will liaise with the relevant patient and public involvement group- AMEND (<https://www.amend.org.uk>) and if the study findings are of interest, will arrange for a summary of the study to be published in the patient newsletter.

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