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Buccal naloxone testing in healthy volunteers

Submission date
22/09/2025

Recruitment status
Recruiting

Registration date
06/11/2025

Overall study status
Ongoing

Last Edited
04/12/2025

Condition category
Injury, Occupational Diseases, Poisoning

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
This study addresses whether a novel ultra-portable buccal naloxone wafer can provide rapid drug absorption comparable to current naloxone formulations, improving emergency overdose response through better medication carriage and availability. Naloxone saves lives. As an emergency antidote medication, it rapidly reverses heroin/opioid overdose, preventing drug-related death, but only if administered promptly at the time of crisis. Deaths can occur before arrival of emergency services: so naloxone is now pre-provided to friends and families and those with active addiction problems (plus frontline staff, outreach workers, hostel staff, police officers). Naloxone has historically been provided as a pre-filled syringe for injection or, recently, as a nasal spray. But there are problems with these forms of naloxone (injection, nasal). With nasal naloxone, people need healthy nasal passages and no mucus/vomit. Naloxone also needs to be readily available, on their person, when an unanticipated future emergency occurs. A format is required that is as portable as a wallet or mobile phone (hopefully never needed, but there, just in case). Feasibility work demonstrated that rapid-dispersal naloxone wafers can be produced, disintegrating within seconds. These will fit into a wallet or purse, thereby remedying the current poor carriage rates for naloxone (only 15-20%). These now need testing on the mucosa inside the mouth (in the cheek cavity). This study will investigate the absorption of the different versions of naloxone in healthy volunteers.

Who can participate?
Healthy volunteers aged 18-60 years

What does the study involve?
Healthy volunteers will take part in the study. At the initial (baseline) visit, they will be interviewed and examined by a doctor, and undergo blood tests and urinalysis. Physical observations will be recorded regularly during each experimental visit, with nursing and medical support available throughout.

Participants will attend five experimental visits over three weeks, during which intensive blood sampling will be carried out. The aim is to compare the speed of absorption and optimal dosing of a new buccal wafer form of naloxone against existing formulations.

What are the possible benefits and risks of participating?
In addition to being paid for their time, participants may enjoy the experience of taking part in

research. Their participation in this trial will contribute to scientific progress and help improve overdose prevention strategies and access to life-saving medication.

The risks associated with the study are minimal. Naloxone is generally considered safe when used as directed. It is specifically designed to rapidly reverse opioid overdose and has a well-established safety profile.

Pregnancy: While naloxone is considered relatively safe during pregnancy, as it's used to treat opioid overdose in pregnant women, extra precautions will be taken. Female participants of child-bearing potential must use a highly effective method of contraception for the duration of the trial and for a specified period after the completion of the trial.

Cannula insertion: The participant may experience pain and discomfort at the insertion site of the cannula. However, the CRF has experienced research nurses who will prepare the participant and minimise the risk of pain and discomfort.

Confidentiality: The participant's confidentiality will be of utmost importance for this study, particularly since the study requires them to disclose their medical and psychiatric histories and personal drug use information. The study will not collect information that is not relevant to the research questions. All participants will be given an anonymised unique identification number, which will be used throughout the study whenever data is recorded. Personally identifiable information will be kept separately, in locked databases which only a limited number of relevant research personnel who have completed relevant training (Good Clinical Practice) will have access to.

Burdens include time spent on the study and potential discomfort from naloxone administration. The study design has been optimised to minimise the time required from participants while still collecting necessary data. Any potential discomfort from naloxone administration will be closely monitored and addressed by the medical team.

Where is the study run from?
at King's College Hospital Clinical Research Facility.

When is the study starting and how long is it expected to run for?
September 2025 to February 2026

Who is funding the study?
The Scottish Chief Scientist's Office, NHS Fife and Health Innovation South East Scotland (HISES), UK, with Supplement funding from Accord Healthcare, pharmaceutical partner.

Who is the main contact?
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Contact information

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Public

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
1011060

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
3644NalBuc

Study information

Scientific Title
Ultra-portable rapid-dispersal buccal lyophilised naloxone for constant carriage: testing in healthy volunteers

Acronym
NalBuc

Study objectives
This is a phase I pharmacokinetic study investigating a novel buccal lyophilised naloxone formulation in healthy volunteers. Naloxone is a potent opioid antagonist used to reverse the effects of opioid overdose. The study aims to characterize the pharmacokinetic profile of this ultra-portable rapid-dispersal formulation compared to approved naloxone formulations, with attention to absorption speed and appropriate dosing for future medicinal product development.

Our main objective is to measure and compare the pharmacokinetic profile (how quickly and effectively naloxone enters the bloodstream) of a novel buccal formulation of naloxone in healthy volunteers with approved formulations (naloxone ampoule) as the injectable form, and Nyxoid® as naloxone nasal spray comparison.

Our secondary objectives are:
To measure the dose-proportionality (whether higher doses produce proportionally higher blood levels) of the novel formulation by comparing the plasma exposure (amount of naloxone in the bloodstream) of two different buccal doses and one sublingual dose.
To assess the safety and tolerability of the novel buccal formulation.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 27/10/2025, London Bridge Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8229, (0)207 104 8140, (0)207 104 8055; londonbridge.rec@hra.nhs.uk), ref: 25/LO/0701

Study design
Phase I open-label within-subject five-way crossover study

Primary study design
Interventional

Study type(s)
Efficacy, Safety

Health condition(s) or problem(s) studied
Opioid overdose

Interventions

This study will employ an open-label, within-subject design with repeated sessions to evaluate the IMPs in a five-way crossover design, where each participant will receive all the considered treatment conditions in a random sequence. These five treatment arms are made up of three experimental IMPs. A novel rapid-dispersal ultra-portable formulation of naloxone at two test doses (2mg and 4mg) administered via buccal absorption in the cheek pouch, and a 2mg dose administered sublingually, and then two active comparator products; intramuscular naloxone via naloxone ampoule which contains 0.4mg/1ml naloxone hydrochloride, and an intranasal spray formulation (Nyxoid), containing 1.8mg/0.1ml naloxone hydrochloride dihydrate, equivalent to 2 mg of naloxone hydrochloride, per dose.

The order in which a participant receives each IMP across five study visits is randomised via the King's Clinical Trial Unit's randomisation system, in which each treatment is assigned a code from 01-05, each participant will automatically be assigned a random order of code, representing the order of drug products for each visit, at the point of enrolment on the clinical study once eligible and confirmed.

The time to reach maximum plasma concentration will be determined to characterise the rate of naloxone absorption. Tmax will be reported as the median and range for each treatment group, based on observations over the 4-hour post-dose period. This intensive sampling schedule, particularly in the first 15 minutes, is designed to accurately capture the early absorption phase and the precise determination of Tmax for each formulation and dose.

Time to 50% of maximum concentration (T50%)
A particularly important secondary endpoint will be the time taken to reach 50% of the observed Cmax, as the increase in plasma levels before reaching Cmax is unlikely to be linear, and the time taken to reach 50% with different formulations is likely to indicate the speed with which there may be a future benefit of reversal of opioid overdose. T50% will be reported as the median and interquartile range for each treatment group, based on observations over the 4-hour post-dose period.

Maximum Plasma Concentration (Cmax)
The maximum observed plasma naloxone concentration will be determined for each formulation and dose. Cmax will be reported as the mean and standard deviation for each treatment group, based on measurements taken over the 4-hour post-dose period.

Area Under the Curve from time zero to infinity (AUCinf)
The total systemic exposure to naloxone will be quantified by calculating the area under the plasma concentration-time curve extrapolated to infinity. AUCinf will be reported as the mean and standard deviation for each treatment group, calculated from time zero to infinity.

Area Under the Curve from time zero to 15 minutes (AUC0-15)
Early systemic exposure to naloxone will be assessed by calculating the area under the plasma concentration-time curve from administration to 15 minutes post-dose. AUC0-15 will be reported as the mean and standard deviation for each treatment group.

Elimination Half-life (t1/2)
The elimination half-life of naloxone will be calculated from the terminal slope of the log concentration-time curve. t1/2 will be reported as the mean and standard deviation for each treatment group.

Secondary endpoints will be evaluated from the same series of blood samples collected for the primary endpoint. These samples will allow calculation of T50% (time to 50% of maximum

concentration), Cmax (maximum plasma concentration), T1/2 (elimination half-life), AUC0-15 (area under the curve from zero to 15 minutes), and AUCinf (area under the curve from zero to infinity). Wafer disintegration time will be recorded immediately after administration. Visual Analogue Scale (VAS) assessments for taste and tolerability will be completed immediately following administration of each formulation.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Buccal naloxone wafer [Naloxone, Naloxone], Sublingual naloxone wafer [Naloxone], Naloxone 400 micrograms/ml solution for injection/infusion [Naloxone hydrochloride dihydrate], Nyxoid 1.8 mg nasal spray, solution in a single-dose container [Naloxone hydrochloride dihydrate]

Primary outcome(s)
Time to Maximum Plasma Concentration (Tmax) will be determined from blood samples collected at multiple timepoints over 4 hours following administration of each naloxone formulation. Blood samples will be collected pre-dose and at 2, 4, 6, 8, 10, 12.5, 15, 30, 45 minutes and 1, 1.5, 2, and 4 hours post-dose.

Key secondary outcome(s))
The following secondary outcome measures will be evaluated from the same series of blood samples collected for the primary endpoint: pre-dose and at 2, 4, 6, 8, 10, 12.5, 15, 30, 45 minutes and 1, 1.5, 2, and 4 hours after administration, unless otherwise stated:
1. Time to 50% of maximum concentration (T50%)
2. Maximum Plasma Concentration (Cmax)
3. Area Under the Curve from time zero to infinity (AUCinf)
4. Area Under the Curve from time zero to 15 minutes (AUC0-15)
5. Elimination Half-life (t1/2)
6. Wafer disintegration time will be measured immediately after administration
7. Taste and tolerability will be measured using a Visual Analogue Scale (VAS) immediately following administration of each formulation

Completion date
15/02/2026

Eligibility

Key inclusion criteria
1. Healthy volunteers. Defined as healthy based on medical examination, which includes: clinical history, physical examination, ECG, vital signs, and laboratory tests of blood and urine.
2. Aged 18-60
3. Able and willing to provide written informed consent
4. Adequate venous access and willingness for intravenous cannulation during each visit.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
60 years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Clinically relevant medical history, physical findings, ECG, or laboratory values at the pre-trial screening assessment that could interfere with the objectives of the trial or the safety of the participant.
2. Presence of acute or chronic illness or history of chronic illness sufficient to invalidate the volunteer's participation in the trial or make it unnecessarily hazardous.
3. Impaired endocrine, thyroid, hepatic, respiratory or renal function, diabetes mellitus, coronary heart disease, or history of any neurological or mental illness.
4. Surgery or medical condition that might affect the absorption of medicines.
5. Blood pressure and heart rate in the supine position at the screening examination outside the ranges: blood pressure 90–140 mm Hg systolic, 40–90 mm Hg diastolic; heart rate 40–100 beats /min. Repeat measurements are permitted if values are borderline (i.e. values that are within 5 mm Hg for blood pressure or 5 beats/min for heart rate) or if requested by the investigator. Subjects can be included if the repeat value is within range or still borderline but deemed not clinically significant by the investigator.
6. Loss of more than 400 mL of blood during the 3 months before the trial, e.g. as a blood donor.
7. Any prescribed medication (apart from contraceptives).
8. Use of any over-the-counter medications containing codeine or other opioids, prescribed opioid medication, or illicitly obtained opioids within the past 2 weeks (if the participant is taking a long-acting opioid, the period might, after consideration by the examining doctor, be extended to 4 weeks or longer according to the washout period).
9. BMI <18 or >30.0kg/m2.
10. Intake of more than 14 units of alcohol weekly.
11. Pregnant or breastfeeding.
12. Women of childbearing potential (as defined in CTFG guidelines, see 6.7 Concomitant Medication) not willing to use a highly effective form of contraception (as defined in CTFG guidelines, see section 6.7 Concomitant Medication) during participation in the study or male patients not willing to ensure the use of a condom during participation in the study.
13. eGFR≤ 70 ml/min.
14. Any liver function or renal function test abnormality. A repeat is allowed on one occasion for the determination of eligibility.
15. Urine drug screen positive for any substances.
16. Positive alcohol breath test, above 0.

17. Participant in any other clinical trial or experimental drug study in the past 3 months
18. Known hypersensitivity to naloxone and/or formulation excipients (gelatin, mannitol).
19. Not willing to ingest fish-derived gelatin.
20. Insufficient understanding of the trial.

Date of first enrolment
15/12/2025

Date of final enrolment
01/02/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
King’s College Hospital NHS Foundation Trust
1st Floor, Cheyne Wing
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Sponsor information

Organisation
Kings Health Partners

ROR
https://ror.org/01xcsye48

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Government

Funder Name
Chief Scientist Office, Scottish Government Health Directorate CSO

Alternative Name(s)
Chief Scientist Office, Scottish Government Health Directorate CSO, Chief Scientist Office, Scottish Government Health Directorates, Chief Scientist Office of the Scottish Government Health Directorates, Scottish Government Health and Social Care Directorate of the Chief Scientist Office, Scottish Government Health Directorate Chief Scientist Office, The Chief Scientist Office, CSO

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Accord Healthcare

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.1	11/09/2025	24/09/2025	No	Yes
Participant information sheet	version 1.2	21/10/2025	18/11/2025	No	Yes
Protocol file	version 1.2	11/09/2025	24/09/2025	No	No
Protocol file	version 2.0	24/10/2025	18/11/2025	No	No