CLINICAL STUDY REPORT

Improving understanding of Heroin Overdose Testing (HOT-Treated)

Improving understanding of Heroin Overdose Testing: diamorphine dose-escalation testing in a treated population.

Sponsor Protocol Code:	3562
EudraCT Number:	2016-001877-34
ClinicalTrials.gov Identifier:	N/A
ISRCTN number:	N/A
REC Number:	16/LO/1765
Investigational Drugs (IMPs):	Diamorphine
Indication:	Addiction
Development Phase:	IV
Study Begin (FPFV):	12-FEB-2018
Study End (LPLV):	11-MAR-2022
Report Version & Issue Date:	Version 1.0, Date: 11-JUN-2024
Co-sponsor Name and Address:	South London and Maudsley NHS Foundation Trust & King's College London
Co-sponsor contact details:	Address: Ann Marie Murtagh KHP-CTO, F16 Tower Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT Email: QM.KHPCTO@kcl.ac.uk Tel: 02071885732
Chief Investigator:	Professor Sir John Strang

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: John Strang

Printed name John Strang **Signature**  **Date 17/6/24**

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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 (South East London REC).

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

Relevant patients (in this case, patients who are on an injectable diamorphine prescription) were approached by clinical care staff associated with the patient. Patients were based within SLaM and other allocated PIC sites. Potential participants were then pre-screened in the study site (King's Clinical Research Facility) where consent was taken.

2. Data Monitoring

N/a – there were no data monitoring and steering committee meetings for this study

3. Sponsors, Investigators and Trial Sites

Co-Sponsors	
South London and Maudsley NHS Foundation Trust and King's College London ***Ann Marie Murtagh*** ***King's Health Partners Clinical Trials Office*** ***F16 Guy's Tower, Guy's Hospital, Great Maze Pond, London SE1 9RT*** ***02071885732***	
Chief Investigator ***Professor Sir John Strang***	

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

Dr Basak Tas ***Research Fellow***	
Dr Caroline Jolley ***Reader & Honorary Respiratory Consultant***	

5. Study Synopsis

Title of clinical trial	Improving understanding of Heroin Overdose Testing: diamorphine dose escalation testing in a treated population.
Protocol Short Title/Acronym	Improving Understanding of Heroin Overdose Testing (HOT-Treated)
Study Phase	IV
Sponsor name	South London and Maudsley NHS Foundation Trust and King's College London
Chief Investigator	Professor Sir John Strang
Eudract number	2016-001877-34
REC number	16/LO/1765
IRAS project ID:	172751
Medical condition or disease under investigation	Opioid Overdose
Purpose of clinical trial	For the improved understanding of opioid overdose
Primary objective	To investigate respiratory depression and hypoxaemic response to intravenous (IV) or intramuscular (IM) higher-than-regular doses of heroin as a marker for overdose.
Secondary objective (s)	To investigate effect of variations in heroin dose on subjective drug effect and whether these are correlated to physiological changes. To investigate the unique arms movements of injecting heroin using wearable devices (motion signature) To monitor variation in breathing patterns (rhythm) using wearable devices (Apple Watch or similar & sensor on chest) 3: To record changes in blood oxygen as measured by commercial wearable devices (Apple Watch or similar) 4: To investigate whether a different environmental setting has an impact on physiological and psychological measures of heroin administration
Trial Design	Single-blind, dose escalation, single centre clinical trial

Endpoints	Primary Endpoints: • Blood Oxygen saturation (SpO_2) • End-tidal carbon dioxide ($ETCO_2$), • Transcutaneous carbon dioxide ($TcCO_2$), and • Intercostal parasternal electromyography to measure neural respiratory drive Secondary Endpoints: • Pupil size • Subjective drug effects • Staff rating of drug effects • Arm movements using the three-axis gyroscope, accelerometer, and magnetometer embedded in the wrist watch (Apple Watch or similar) • Respiratory pattern using the microphone embedded in the wrist watch (Apple Watch or similar) • Respiratory pattern using the gyroscope, accelerometer embedded within a small biosensor attached to surface of chest (Altair Medical) • Blood oxygen measure embedded in the wrist watch (Apple Watch or similar)
Planned number of subjects	12
Summary of eligibility criteria	Diamorphine-injecting subjects above the age of 18
IMP, dosage and route of administration	4 study sessions examining either IV or IM administration. A further 4 study sessions were implemented via the other injecting route if possible. 12 subjects were assigned to a session in the following order: 1) Diamorphine 100% of maintenance dose 2) Diamorphine 110% of maintenance dose 3) Diamorphine 120% of maintenance dose 4) Diamorphine 100% of maintenance dose
Active comparator product(s)	n/a
Maximum duration of treatment of a subject	12 weeks per set of sessions (with subjects

	receiving treatment as per standard of care pre-study, between visits and after the study).
Version and date of protocol amendments	Version 1.0, 19 July 2016 Version 1.1, 26 August 2016 Version 1.2, 19 December 2016 Version 1.3, 02 June 2017 Version 1.4, 07 March 2018 Version 1.5, 04 December 2018 Version 1.6, 12 August 2019 Version 1.7, 05 January 2021 Version 1.8, 07 December 2021

6. Glossary of terms

BMI	Body Mass Index
CI	Chief Investigator
CRF	Case Report Form/ Clinical Research Facility
EMG	Electromyography
EMG_{para}	Parasternal intercostal electromyogram
EMG_{para}%max	EMG_{para} as a percentage of maximum
EMG_{para}%index	Product of EMG_{para}%max and respiratory rate (V_f)
$ETCO_2$%	End-tidal carbon dioxide: percentage of CO_2 at the end of an exhaled breath
FEV_1	Forced expiratory volume in 1 second
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
KCH	King's College Hospital NHS Foundation Trust
NHS R&D	National Health Service Research & Development
REC	Research Ethics Committee
HRA	Health Research Authority
PI	Principal Investigator
RIOTT	Randomised Injectable Opiate Treatment Trial
SLaM	South London and the Maudsley
SpO_2%	Peripheral oxygen saturation: percentage reflecting level of oxygen in blood

$TcPCO_2$	Transcutaneous carbon dioxide
VAS	Visual Analogue Scale
VC	Vital capacity
V_f	Respiratory rate
V_T	Tidal volume
V_E	Minute ventilation

7. Publication (reference)

Bauer, S. M., Loipl, R., Jagsch, R., Gruber, D., Risser, D., Thau, K., & Fischer, G. (2008). Mortality in opioid-maintained patients after release from an addiction clinic. *European Addiction Research*, *14*(2), 82–91.

Comer, S. D., Sullivan, M. A., Whittington, R. A., Vosburg, S. K., & Kowalczyk, W. J. (2008). Abuse liability of prescription opioids compared to heroin in morphine-maintained heroin abusers. *Neuropsychopharmacology*, *33*(5), 1179–91.

Curran, H. V, Bolton, J., Wanigaratne, S., & Smyth, C. (1999). Additional methadone increases craving for heroin: a double-blind, placebo-controlled study of chronic opiate users receiving methadone substitution treatment. *Addiction*, *94*(5), 665–674.

Darke, S. (2011). The Life of the Heroin User: Typical Beginnings, Trajectories and Outcomes.

Darke, S. (2014). Opioid overdose and the power of old myths: what we thought we knew, what we do know and why it matters. *Drug & Alcohol Review*, *33*(2), 109–114. http://doi.org/10.1111/dar.12108

Darke, S., Duflou, J., & Torok, M. (2010). A reduction in blood morphine concentrations amongst heroin overdose fatalities associated with a sustained reduction in street heroin purity. *Forensic Science International*, *198*(1–3), 118–120.

Darke, S., & Farrell, M. (2014). Would legalizing illicit opioids reduce overdose fatalities? Implications from a natural experiment. *Addiction (Abingdon, England)*, *109*(8), 1237–1242.

Davidson, P. J., McLean, R. L., Kral, A. H., Gleghorn, A. A., Edlin, B. R., & Moss, A. R. (2003). Fatal heroin-related overdose in San Francisco, 1997-2000: a case for targeted intervention. *Journal of Urban Health*, *80*(2), 261–273.

Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M., & McLaren, J. (2011). Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies. *Addiction*, *106*(1), 32–51.

Dowling, J., Isbister, G. K., Kirkpatrick, C. M. J., Naidoo, D., & Graudins, A. (2008). Population pharmacokinetics of intravenous, intramuscular, and intranasal naloxone in human volunteers. *Therapeutic Drug Monitoring*, *30*(4), 490–496.

Dursteler-Mac Farland, K. M., Stormer, R., Seifritz, E., Hug, I., Muller-Spahn, F., Ladewig, D., & Stohler, R. (2000). Opioid-associated effects on oxygen saturation. *Addiction*, *95*(2), 285–287.

Jolley, C. J., Bell, J., Rafferty, G. F., Moxham, J., & Strang, J. (2015). Understanding heroin overdose: A study of the acute respiratory depressant effects of injected pharmaceutical heroin. *PLoS ONE*, *10*(10), 1–14.

Kelly, A. M., Kerr, D., Dietze, P., Patrick, I., Walker, T., & Koutsogiannis, Z. (2005). Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *Medical Journal of Australia*, *182*(1), 24–27.

Lintzeris, N., Mitchell, T. B., Bond, A. J., Nestor, L., & Strang, J. (2007). Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose conditions in opioid dependent patients. *Drug Alcohol Depend*, *91*(2–3), 187–194. http://doi.org/10.1016/j.drugalcdep.2007.05.019

Lintzeris, N., Mitchell, T. B., Bond, A. J., Nestor, L., & Strang, J. (2007). Pharmacodynamics of diazepam co-administered with methadone or buprenorphine under high dose conditions in opioid dependent patients. *Drug and Alcohol Dependence*, *91*(2–3), 187–194.

Lintzeris, N., Mitchell, T. B., Bond, A., Nestor, L., & Strang, J. (2006). Interactions on mixing diazepam with methadone or buprenorphine in maintenance patients. *J Clin Psychopharmacol*, *26*(3), 274–283. http://doi.org/10.1097/01.jcp.0000219050.33008.61

Mitchell Mayet, S., Lintzeris, N., Spofforth, N., Forzisi, L. & Strang, J., T. B. (n.d.). Understand heroin overdose death risk: experimental study of acute hypoxaemia after heroin or methadone injection. *Manuscript for Submission, Available on Request*.

Murphy, P. B., Kumar, A., Reilly, C., Jolley, C., Walterspacher, S., Fedele, F., … Hart, N. (2011). Neural respiratory drive as a physiological biomarker to monitor change during acute exacerbations of COPD. *Thorax*, *66*(7), 602–608.

Nicholson, A. N. (1978). Visual analogue scales and drug effects in man. *British Journal of Clinical Pharmacology*, *6*(1), 3–4.

Oviedo-Joekes, E., Brissette, S., Marsh, D. C., Lauzon, P., Guh, D., Anis, A., & Schechter, M. T. (2009). Diacetylmorphine versus methadone for the treatment of opioid addiction. *New England Journal of Medicine*, *361*(8), 777–786.

Reilly, C. C., Jolley, C. J., Ward, K., MacBean, V., Moxham, J., & Rafferty, G. F. (2013). Neural respiratory drive measured during inspiratory threshold loading and acute hypercapnia in healthy individuals. *Exp Physiol*, *98*(7), 1190–1198.

Reilly, C. C., Ward, K., Jolley, C. J., Lunt, A. C., Steier, J., Elston, C., … Moxham, J. (2011). Neural respiratory drive, pulmonary mechanics and breathlessness in patients with cystic fibrosis. *Thorax*, *66*(3), 240–246.

Rook, E. J., Van Ree, J. M., Van Den Brink, W., Hillebrand, M. J. X., Huitema, A. D. R., Hendriks, V. M., & Beijnen, J. H. (2006). Pharmacokinetics and Pharmacodynamics of High Doses of Pharmaceutically Prepared Heroin, by Intravenous or by Inhalation Route in Opioid-Dependent Patients. *Basic & Clinical Pharmacology & Toxicology*, *98*(1), 86–96.

Sessler, C. N., Gosnell, M. S., Grap, M. J., Brophy, G. M., O'Neal, P. V., Keane, K. A., … Elswick, R. K. (2002). The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. *American Journal of Respiratory and Critical Care Medicine*, *166*(10), 1338–1344.

Stoermer, R., Drewe, J., Dursteler-Mac Farland, K. M., Hock, C., Mueller-Spahn, F., Ladewig, D., … Mager, R. (2003). Safety of injectable opioid maintenance treatment for heroin dependence. *Biological Psychiatry*, *54*(8), 854–861.

Stohler, R., Dursteler, K. M., Stormer, R., Seifritz, E., Hug, I., Sattler-Mayr, J., … Hock, C. (1999). Rapid cortical hemoglobin deoxygenation after heroin and methadone injection in humans: a preliminary report. *Drug & Alcohol Dependence*, *57*(1), 23–28.

Strang, J., Metrebian, N., Lintzeris, N., Potts, L., Carnwath, T., Mayet, S., … Forzisi, L. (2010). Supervised injectable heroin or injectable methadone versus optimised oral methadone as treatment for chronic heroin addicts in England after persistent failure in orthodox treatment (RIOTT): a randomised trial. *The Lancet*, *375*(9729), 1885–1895.

Walsh, S. L., Gilson, S. F., Jasinski, D. R., Stapleton, J. M., Phillips, R. L., Dannals, R. F., … al., et. (1994). Buprenorphine reduces cerebral glucose metabolism in polydrug abusers. *Neuropsychopharmacology*, *10*(3), 157–170.

White, J., Bell, J., Saunders, J. B., Williamson, P., Makowska, M., Farquharson, A., & Beebe, K. L. (2009). Open-label dose-finding trial of buprenorphine implants (Probuphine) for treatment of heroin dependence. *Drug Alcohol Depend*, *103*(1–2), 37–43.

8. Study period (years)

Study period was 4 years. FPFV was 12 February 2018, LPLV was 11 March 2022. End of study was 22 March 2022. This was the database lock date which was the definition of the end of study. Patient recruitment was ongoing with data collection. The study was paused due to the COVID-19 pandemic between 20 March 2020 and 29 October 2021.
The study was terminated prematurely because of the dwindling number of patients in the UK on diamorphine for their heroin addiction treatment and also because of a diamorphine shortage which affected the few patients who were on that treatment.

9. Phase of development

Phase IV

10. Objectives

1: To investigate respiratory depression and hypoxaemic response to intravenous (IV) or intramuscular (IM) higher-than-regular doses of heroin as a marker for overdose.

Secondary objectives

1: To investigate effect of variations in heroin dose on subjective drug effect and whether these are correlated to physiological changes.1: To investigate the unique arms movements of injecting heroin using wearable devices (motion signature)

2: To monitor variation in breathing patterns (rhythm) using wearable devices (Apple Watch or similar & sensor on chest)

3: To record changes in blood oxygen as measured by commercial wearable devices (Apple Watch or similar)

4: To investigate whether a different environmental setting has an impact on physiological and psychological measures of heroin administration.

11. Background and Context

Heroin and other opioids act by binding to mu opioid receptors which are present in areas of the brain involved with respiration. Death by overdose of heroin is usually caused by its depreciative and disruptive action on the regular breathing rhythm and respiratory drive. This can cause high levels of carbon dioxide (hypercapnia), low levels of oxygen (hypoxaemia) in the blood, and accumulation of fluid in the lungs.

It remains unclear why some people are more prone to experiencing hypercapnia and hypoxaemia than others. The aim of the project is to address whether changes in dose (equivalent to changes in purity) increase the risk of overdose, as measured by physiological markers.

It is received wisdom that purity is a risk factor for opioid overdose (Darke, 2014; Darke & Farrell, 2014). However, several issues complicate this simple explanation so that our understanding remains unclear and requires testing; firstly, street heroin is not consumed at doses, purities and frequencies that relate to any significant correlation of a heightened risk of overdose. This is strongly evidenced by, a) toxicological examinations, and b) demographic reports. A substantial number of fatal overdose cases have low blood morphine (metabolite of heroin that is tested) concentrations, often similar to, or even below, those of living intoxicated heroin users, or of heroin users who died from other causes (Darke, Duflou, & Torok, 2010; Darke & Farrell, 2014; Davidson et al., 2003). Demographic reports reveal that fatal overdose is most common among long-term, dependent, injecting drug users, often over the age of 30 (Bauer et al., 2008; Darke, 2011, 2014; Degenhardt et al., 2011). This bears no relevance to the inexperienced and intolerant (to variations in purity) user that one might expect.

The idea that purity plays a role in overdose is challenged by the observation of overdoses in clinical settings as well as in an illicit drug market scenario, most strikingly in a heroin-assisted treatment clinic. Even where a pharmaceutical and titrated dose is administered, though rare, overdose events still occur (Jolley et al., 2015; Mitchell et al., n.d.; Strang et al., 2010). In the UK-based RIOTT clinic, the rate was reported to be around 1 in every 6,000 injecting events (Strang et al., 2010), and in the Canadian NAOMI clinic this figure was around 1 in 8,000 injecting events (Oviedo-Joekes et al., 2009). In previous related work, the level of participants' regular dose of diamorphine showed significant changes in oxygen saturation (blood oxygen level) in half of all testing sessions (Dursteler-Mac Farland et al., 2000; Mitchell et al., n.d.; Stoermer et al., 2003; Stohler et al., 1999). Clearly, respiratory depression can occur without variation in administered heroin doses.

To test this in a laboratory setting, a dose escalation study, with higher-than-regular doses, but still within the regular range of clinical care, was used as a comparative marker to address whether changes in dose (equivalent to changes in purity) truly increase respiratory depression.

The study incorporated a range of physiological measurements, including, but not limited to, peripheral oxygen saturation, ventilatory frequency, end-tidal carbon dioxide and neural respiratory

drive (NRD). Acquisition of the NRD is a novel technique which precisely assesses respiratory function; it was previously only possible to do this using impractical invasive techniques (Reilly et al., 2011). NRD analysis has not been conducted with this type of study before, and it will provide a unique method of measuring physiological responses of diamorphine in the testing conditions.

The study aimed to expand on the work already undertaken by further investigation and analysis of direct quantitative data in order to determine whether changes to dose (equivalent to changes of purity) of diamorphine is a risk factors for respiratory impairment and hypoxaemia, thus whether it can genuinely potentiate an overdose. The approaches used in this project aimed to accurately capture, in a laboratory context, the realistic scenarios that occur in the heroin-using community.

12. Methodology

Overview of the study design:

The study was a single-blind, dose escalation design in 12 subjects with four or eight testing sessions, in addition to two follow-up home visits.

Each set of four sessions comprised of an IV or IM administration of 100% OR 110% OR 120% of the regular dose of diamorphine. The following sequence of doses were self-administered on each study:

1. Diamorphine=100% (IV or IM)
2. Diamorphine=110% (IV or IM)
3. Diamorphine=120% (IV or IM)
4. Diamorphine=100% (IV or IM)

Each session consisted of 30 minutes of pre-monitoring analyses (drug test, breathalyser and pregnancy test, if applicable), 30 minutes for preparing the participant for monitoring and a minimum of 60 minutes of monitoring (maximum of 120 minutes). Participants did not remain at study facilities for longer than 180 minutes in total, per study day.

There was a wash-out period of at least 4 days to ensure that there was no presence of excess metabolites. Serial measurements of subjective drug effects and physiological responses were made prior to, and for one hour following drug administration.

Subjects normally self-administer their diamorphine in separate doses throughout the day. Subjects were screened prior to the first testing session (maximum 8 weeks between screen and first session), and during this process, the frequency of the subject's usual daily dosing were established. For example, a patient who is on 300mg daily may take this in 3 equal parts, each consisting of 100mg doses. The trial only affected one dose of diamorphine. And this was determined at the screening visit. The affected dose was selected depending on circumstances of the individual patient, for example, where a subject is required to commute a longer distance to the study site, it was more practical to affect their 2nd or 3rd dose of the day. In cases where the selected dose was not the first one of the day subjects were asked to attend 4 hours after their previous dose. Diamorphine has a half-life of 2-3 minutes, but, because of the action of active metabolites such as morphine, its effects can last up to 3 to 4 hours (when injected), thus, the 4-hour time window is sufficient to prevent interaction with

the trial dose.

A fourth session was implemented with the same dose as the first session to ensure that there were no effects on respiration due to the novel laboratory setting. A further two follow-up home visits were planned to occur for subjects who had completed study sessions at the study site.

5 subjects (n=5) on injectable diamorphine maintenance treatment, who are therefore, on a stable titrated dose of diamorphine were recruited for this study.

Permissible windows: Between study visits a minimum of 4 days is applicable, but no maximum amount of time.

Time from consent to first study visit: there was no minimum but we implemented a maximum time period of eight weeks.

After the first set of four sessions, participants were re-invited to undertake a further four testing sessions via the other injecting route, i.e. if the first four sessions were IV administration, the subsequent four sessions were IM. Participants whose intravenous route was unsuitable were not asked to conduct any extra sessions and were only tested via IM route. The second set of sessions had a planned minimum time frame of 4 days (same as the permissible window between visits) and no maximum time frame.

For participants who completed the 4 (or 8, if applicable) study sessions at the study site, follow-up home visits were planned to be conducted. These were planned to be conducted after suitability was assessed and consent obtained from the participant. Details on the home visits are in *Section 11 – Follow-up home visits*.

Each session consisted of 30 minutes of pre-monitoring analyses (vital signs, SpO_2%, drug test, breathalyser, and pregnancy test, if applicable), 30 minutes of preparing the participant for monitoring and a minimum of 60 minutes (and maximum of 120 minutes) of monitoring. Participants were not expected to remain at study facilities for longer than 180 minutes in total, per study day. This time was prolonged if adverse events occurred. The same timings were to be followed for the home visits.

Between study visits, subjects took their treatment of diamorphine maintenance as per standard care. Additionally, after the trial end, subjects were able to continue diamorphine maintenance treatment as per standard care.

Serial measurements of subjective drug effects and physiological responses were made prior to, and for one hour following drug administration.

IMP administration

IMP was self-administered intravenously on the study day, as a first choice and priority. Participants were encouraged to self-administer the IMP in under 1 minute, and timing of IMP administration was measured by one of the trial staff. Delegated trial staff (nurse or doctor) were available for assistance, and also, if self-administration was declined, a delegated trial staff member was able to administer the IMP (nurse or doctor administration). Additionally, a small cannula (e.g. blue) was inserted and used for administering any emergency medication. However, if venous access for cannula insertion or IMP administration was not possible for the study, intramuscular administration was chosen. Route

of administration had to remain the same for each study session, for each individual study subject.

Emergency medications naloxone and adrenaline were appropriate and licensed for intramuscular administration. As per safety procedures (section 13 of protocol), if an emergency situation were to occur in which an emergency medical intervention was deemed best administered intravenously, this could be in regions that would not be considered by us for use in the study (e.g. groin, central, etc.).

Thus, all participants were either:

1. A user who injects IV (either regularly or occasionally)
    i. With a cannula (for naloxone and adrenaline)
    ii. IV IMP administration for all four (+ 2 home visits, if applicable) sessions;

OR:

2. A user who injects IV (either regularly and occasionally) and where there is an issue finding surface veins on the initial study day
    i. Without a cannula (naloxone and adrenaline would be administered IM)
    ii. IM IMP administration for all four (+ 2 home visits, if applicable) sessions.

Schedule of Events:

Diamorphine (IMP) Administration, 100%, 110% or 120% of regular dose, IV

Assessment	Screening	All Study Days (4)									
Time (mins)		Pre-testing (on each study day)	Continuous (automatic recording)	-3	0	3	8	15	30	60	60+
Informed consent	x										
Pregnancy Status/Test	x	x									
Demographics, Medical History & BMI	x										
Concomitant medication check	x	x									
Eligibility Assessment	x	x									
Adverse Events Check		x		x	x	x	x	x	x	x	x
Breathalyser for alcohol		x									
Drug screen for additional drugs		x									
Spirometry	x										
Vital signs: HR, BP	x	x	x								
Diamorphine administration					x						
Airflow & $ETCO_2$%				x	x	x	x	x	x	x	x
EMG_{para}			x								
$TcPCO_2$			x								
SpO_2%	x	x	x								
Pupil size		x		x	x	x	x	x	x	x	
Subjective Drug Effects*				x	x	x	x	x	x	x	
Staff rating				x	x	x	x	x	x	x	
Motion Signature			x								
Breathing rhythm			x								

NB: 60+ denotes that monitoring after 60 minutes is optional. Up to a further 60 minutes of monitoring was only implemented with approval from participants.

*Subjective strength of drug effect measured at all timepoints. Subjective drug liking and sedation measured only at -3, 15, 30 and 60 minutes post-dose.

13. Number of patients (planned and analysed)

13.1 Planned: 12

13.2 Analysed: 4

Screened: 5

# patients screened/re-screened	5
# patients randomised	0
# patients receiving treatment	4
# patients withdrew prior to receiving treatment	1
# patients withdrew after receiving treatment	0
# patients completed	4

Table: The reasons for patient withdrawal from the study

Patient	Reason for withdrawal
006SR	No longer interested in participating in the study

14. Diagnosis and main criteria for inclusion

Inclusion Criteria

Each subject was selected according to the following inclusion criteria:

1. Diamorphine-injecting subjects who had been in treatment for a minimum of one month;
2. Male or female;
3. ≥ 18 years;
4. Capable of providing voluntary written informed consent;
5. A non-custodial stable residence and telephone number;
6. Venous access had to be suitable for intravenous drug administration and/or cannula insertion.

7. Oxygen saturation reading of ≥92%;
8. Forced expiratory volume in 1 second ratio, predicted % (FEV_1%) of >50% (spirometry);
9. Absence of acute respiratory illness for 6 weeks prior to screening or any study day.

Exclusion Criteria

Subjects who meet any of the following criteria were excluded from the study:

1. Dependent use of cocaine or amphetamines requiring specific treatment. This was assessed at Pre-Study Screen.
2. Active significant medical condition (e.g. hepatic failure or severe hepatic disease) as determined by clinical assessment, medical history and as advised by their treating clinician. This was assessed by the clinical investigator at Pre-Study Screen, for example:
   i. Severe hepatic insufficiency (liver function tests conducted within the last 6 months prior to screening): Patients with clinical features of hepatic failure (e.g. encephalopathy, ascites, jaundice, prolonged bleeding, hypoalbuminaemia and secondary oedema – consistent with Child-Pugh Classification B or C). Patients with liver disease (e.g. HCV, HBV infection) without features of hepatic failure are potentially eligible.
   ii. Severe respiratory insufficiency or the inability to reliably perform physiological tests of respiratory function (spirometry).
   iii. Pre-existing renal or cardiac issues that the study physician or treating clinician considers inappropriate for the purposes of this trial.
3. In cases where subjects are able to perform spirometry, a FEV_1% of ≤50% as confirmed by spirometry at Pre-Study Screen.
4. Oxygen saturation reading of <92% as confirmed by finger pulse oximetry at Pre-Study Screen.
5. Acute illnesses that make participation inappropriate, as assessed by the study physician. Presence of acute respiratory illness within 6 weeks prior to screening or any of the study sessions. This was assessed during screening and on each study day. If acute illness is present, subject was asked to return 6 weeks post-acute illness. Acute diarrhoeal conditions caused by antibiotic-induced pseudomembranous colitis or by poisoning was assessed by the study physician. Assessment at Pre-Study Screen and on each Study Visit.
6. Subjects suffering from acute alcoholism or delirium tremens. This was assessed at Pre-Study Screen.
7. Subjects who have suffered from head injury or have been with diagnosed phaeochromocytoma. These was assessed at Pre-Study Screen.
8. Risk of paralytic ileus or biliary colic assessed by the study physician. This was assessed at Pre-Study Screen.
9. A benzodiazepine prescription that is above the standard therapeutic dose range (e.g. if oral Diazepam above 30mg/daily; BNF, 2016). This was examined by medical notes at the Pre-Study Screen. A drug test on each Study Visit was performed to assess whether there is any presence of benzodiazepines that the participant is not prescribed. Concomitant medication check will also be conducted at Pre-Study Screen.
10. Subjects prescribed other contraindicated drugs: monoamine oxidase inhibitors (or within 2 weeks of their discontinuation), 4-quinolone antibacterials, phenothiazines, tricyclic antidepressants, anxiolytics (see above), hypnotics, cisapride, domperidone and metoclopramide, cimetidine and selegiline. This was assessed at Pre-Study Screen.

11. Alcohol and other drug use on the specific study days. A drug screen (Angelscope) and breathalyser (BACtrack, Xtend®) was used to confirm additional drug/alcohol use on the study days. A positive drug screen (excluding prescribed drugs) and an excessive blood alcohol content (BAC) (based on the legal driving limit in England & Wales of 0.8g/L) will result in a re-invitation to an alternative study date. This was assessed on each Study Visit.
12. Current psychiatric diagnosis of major depression with suicidal ideation, psychosis, bipolar disorder, or any psychiatric disorder that would compromise the subject's ability to complete the study. These was assessed at Pre-Study Screen.
13. At screening and on each study day, if there is a chance that female subjects may be pregnant; subjects will undergo a pregnancy test. A positive pregnancy test will result in an exclusion from the study. In addition, mothers who are lactating, women of childbearing potential who refuse to use adequate contraception and pregnancy tests during the study, or women who are planning to become pregnant during the period of the study will also be excluded. This was assessed at Pre-Study Screen and on each Study Visit by the clinical investigator.
14. Any other factor that in the opinion of the study physician would make the subject unsafe or unsuitable for the study. This was addressed at Pre-Study Screen and on each Study Visit by clinical investigator.

NB: clinical and diagnostic assessment was conducted by the study clinical investigator/physician.

15. Test product, dose and mode of administration

Dosing Regimen/Schedule of Treatment
Diamorphine at 100% of the participant's regular maintenance dose were used for the Regular dose condition, 110% and 120% of the participant's maintenance dose were used for the 110% and 120% dose condition, respectively (see table 1). Dose was self-administered intravenously or intramuscularly. Doses were prescribed for each session separately.

Two unmasked nurses were involved in bringing the medication to the patient (the medication was stored and dispensed by Maudsley pharmacy) and were responsible for supervising the self-administration of the injectable diamorphine.

Subjects	**Location**	**Testing session**	**Diamorphine dose relative to maintenance dose (route)**	**Dose frequency***
n=12	King's CRF	1	100% (IV/IM)	1x
	King's CRF	2	110% (IV/IM)	1x
	King's CRF	3	120% (IV/IM)	1x
	King's CRF	4	100% (IV/IM)	1x

Follow-up home visits n=12	Participant's home	1	100% (IV/IM)	1x
	Participant's home	2	100% (IV/IM)	1x

Table 1: Schedule of Treatment

Investigational Medicinal Product (IMP)
Diamorphine Hydrochloride powder for solution for Injection (100mg or 500 mg, any brand allowed). A white to off-white, sterile, freeze dried powder of Diamorphine Hydrochloride BP for reconstitution for injection. Only 100mg and 500mg strengths were used, depending on the patients' maintenance dose.

IMP dispensing was conducted by SLaM pharmacy. The diamorphine supplied for the purposes of this study was a licensed product that is available in the UK. Commercial stock was used for the trial purposes. The IMP labelling complied with Eudralex Volume 4 annex 13 for the purposes of the trial.

This was a single blind trial where dose was masked only to participant. This was conducted by making up each injection with water per volume to achieve same volume for each participant. All doses of diamorphine were made up to 3ml (maximum) with water per volume so participants did not know what dose they were given.

Two nurses were required to be present in order to prepare the diamorphine injection for administration at the study site (King's CRF).

IMP for home visits were not planned to be provided by the study team. No home visits occurred in this study

16. Duration of treatment

12 weeks per set of sessions (with subjects receiving treatment as per standard of care pre-study, between visits and after the study).

17. Reference therapy, dose and mode of administration

Not applicable

18. Criteria for evaluation: Endpoints

18.1 Efficacy

Primary endpoints were:

- Blood oxygen saturation (SpO_2)
- End-tidal carbon dioxide ($ETCO_2$)
- Transcutaneous carbon dioxide ($TcCO_2$)
- Intercostal parasternal electromyography to measure neural respiratory drive

Secondary endpoints were:

- Pupil size
- Subjective drug effects (using visual analogue scale)
- Staff rating of drug effects (using visual analogue scale)

Wearable device measurements:

- Arm movements using the three-axis gyroscope, accelerometer, and magnetometer embedded in the wrist watch (Apple Watch or similar)
- Respiratory pattern using the microphone embedded in the wrist watch (Apple Watch or similar)
- Respiratory pattern using the gyroscope and accelerometer embedded within a small biosensor attached to surface of chest (Altair Medical)
- Blood oxygen sensor embedded in wrist watch (Apple Watch or similar)

All endpoints were obtained by measurements taken during the study visits.

18.2 Safety

Safety Parameters

Vital Signs

Blood pressure and heart rate were measured manually in the sitting position. These were conducted at the pre-study screening and pre- and post- dose on all study days.

Other Safety Parameters

Oxygen saturation by pulse oximetry (SpO_2), expired end-tidal % carbon dioxide ($ETCO_2$%) and transcutaneous CO_2 were measured continuously throughout the study. These are standard clinical measures of respiratory drive. Neural respiratory drive (NRD) was also measured breath-by-breath using parasternal intercostal muscle electromyography (EMG_{para}). If one of these criteria exist, they were taken into consideration with other criteria and with clinical opinion. For further details, see 'cascade of intervention' below.

Criteria that can lead to immediate clinical intervention:

- Any fall in SpO_2 below 70%
- SpO_2% ≤80% for more than 1 minute

- Absence of parasternal intercostal muscle EMG activity and/or chest wall movement > 20secs (apnoea)
- Heart rate of ≤40bpm
- Unresponsive to verbal or painful stimuli

Other, non-continuously recorded criteria were brought to the attention of the clinical team alongside those listed above:

- Heart rate of >100bpm or arrhythmias
- Abnormalities in Speech, Gait or Level of Consciousness
- Any other sign that is of clinical concern to the clinical team

Standard procedures to deal with overdose, anaphylactic shock, and other emergency situations were available. Naloxone (a fast-acting antidote to opioid-related respiratory depression), oxygen (used to combat the high levels of carbon dioxide by increasing availability of blood oxygen) and resuscitation facilities were available at the CRF.

If medical intervention was required (i.e. excluding cases where subject is responsive after stimulation by painful/verbal stimuli), it would have been recorded and reported as an adverse event in the Case Report Form. Adverse events were also recorded for all causes as specified in Procedures for Recording and Reporting Adverse Events.

Cascade of Intervention

There are (at least) three levels of intervention that the study doctor may need to make if there are concerns about level of responsivity and the risk of onset of significant overdose. These could be considered as being a clinical algorithm in which the intensity of clinical action would be determined by the observed extent of impaired responsivity (and with procession to the next level if inadequate response at one level).

At the first level, where the clinician observes that the patient/participant may perhaps not be properly responsive, then the clinician may intervene with a **verbal prompt** (i.e. speaking to the patient and asking if they are OK) and, if necessary, a **physical prompt** of a tap on the shoulder or a shake of the arm, and, if a degree of impaired responsivity persists and if breathing is not evident, then the clinician may also give an **explicit instruction to the patient to take some deep breaths.**

At the second level, if the patient/participant is not properly responsive at the first level or if a painful stimulus is required to elicit a significant response, then the clinician may need to intervene more strongly with, if proper consciousness and breathing are not promptly restored, **provision of oxygen and/or a low dose of naloxone (such as 0.2mg or 0.4mg)** in order to re-establish a more normal level

of consciousness and responsivity. If no adequate response results, then a progressively higher dose of naloxone should be given, plus wider resuscitative actions as clinically indicated. At this level, the clinician should consider **summoning of the crash team**. (If intervention such as naloxone has been needed, then the specific session for the research study should be considered to have been stopped).

At the third level, if the clinician observes that a severe overdose has occurred and that the patient/participant is non-responsive or minimally-responsive, e.g. even to painful stimuli, then **the crash team should immediately be recalled** while naloxone doses are administered in progressively increasing doses (typically at 2-minute intervals) plus oxygen plus wider resuscitative actions as clinically indicated. (As above, if intervention such as naloxone has been needed, then the specific session for the research study should be considered to have been stopped).

19. Statistical Methods

Differences between baseline, minimum and successive time-points after drug administration was analysed using repeated measures ANOVA and/or ANCOVA to examine:

1. diamorphine dose condition (100% versus 110% versus 120% of the daily maintenance dose);
2. time since dosing on all measures.

In addition, post hoc analysis were conducted using Dunn's Multiple Comparison Test.

Interim analyses did not take place.

Missing, unused and spurious data were accounted for by investigators. Analysis was conducted on data that was available.

All eligible subjects were included in analysis.

Sample Size
This is a small study of n=12 where a power calculation is not required. Studies of this type have typically used sample sizes close to this number by utilising design of repeated measures with the same subjects, thereby obtaining strength from within-subject trial design. For example, sample sizes of n= 4 to 12 (Dowling et al., 2008; Lintzeris et al., 2006; Lintzeris et al., 2007; Walsh et al., 1994; White et al., 2009). Measuring variations between individuals would involve a much larger study which was beyond the scope of this trial.

20. Changes in the Trial Plan

Major amendments listed but none impacted planned data analysis.
SA1, date 02Jun2017: Enable recruitment, clarification on dosage and administration.
SA2, date: 07Mar2018. Adding IM
SA3, date: 7Jan2019: adding extra 4 sessions and two measures of respiratory function, adding new secondary objectives, extension of measuring period
SA4, date 12Aug2019: Wearable t-shirt temporarily removed from the study and study name change.SA5, date: 15Feb2021: addition of home testing sessions and updated RSI.

20.1 Protocol Deviations

On two occasions, EMGpara (NRDI; 003MA - 04/07/2018) and transcutaneous carbon dioxide (003MA - 27/01/2020) measures were not recorded and these were listed as missing data. There was no impact on analysis.

21. Summary – Conclusions

21.1 Demographic data

The following tables summarise the demographics of the study population:

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

Demographics and other clinical details for each of the participants. *Same participant, 2 years apart.

BMI=Body Mass Index; MST= Morphine sulphate; COPD= chronic obstructive pulmonary disease; FEV1%predicted= % predicted of Forced Expiratory Volume in 1 second; VC% predicted= % predicted of Vital Capacity

Pt #	Age	Ethnicity	BMI (kg/m2)	Prescribed daily dose (mg)	Study Dose at 100% (mg)	Usual route	Other opioids (mg)	Other prescribed medication	Use of illicit drugs	Comorbidities	FEV1 %pred	VC %pred	Injected
A	62	White	19.6	30	30	IV or IM	Morphine sulphate (450mg)	Zopiclone (7.5mg)	None	COPD (diagnosed), hypertension	64.4	86.0	Self
B	63	White	19.3	100	100	IM or IV	None	None	Cannabis oil	COPD (diagnosed), hypertension	77.3	91.9	Doctor
C	59	White	24.8	630 TDS	200	IM	Morphine sulphate (360mg)	Hep C antivirals	None	Hep C, COPD	65.8	84.2	Self
D*	70	White	25.1	30	30	IM/SC	Methadone (100mg)	Ramipril (5mg); rosuvastatin (5mg)	Cannabis in tea	Spondylitis; MI	77	90	Self

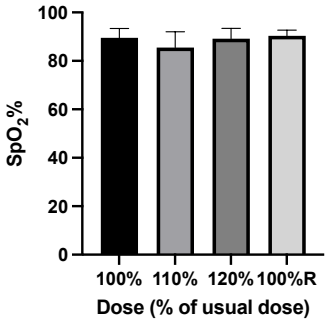
D* (re-enrolled)	72	White	22.9	60	60	IM/SC	Pregabalin (50mg)	Rosuvastatin (5mg)	Cannabis	Spondylitis; MI	92.2	119.1	Self

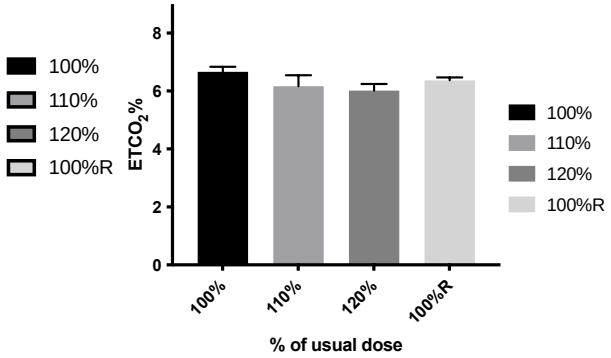
21.2 Primary outcome

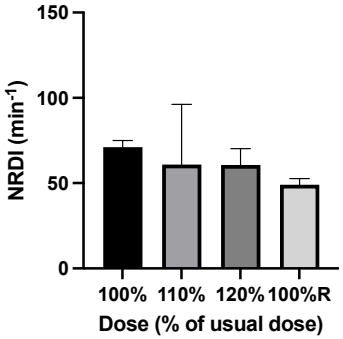
Respiratory depression criteria observed in each dose session.

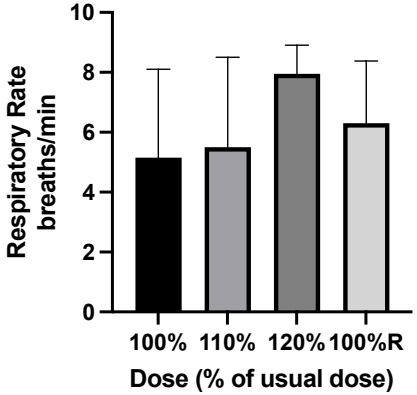
Participant	Dose session #	Dose of Diamorphine (mg)	SpO_2 mean below 96%	SpO_2 <90% >10s	Lowest SpO_2 (%)	SpO_2 dips below 80%	$ETCO_2$ breaths >6.5%	Peak $ETCO_2$ (%)	Respiratory Pauses >10s	Longest respiratory pause (secs)
A	1	30	X	X	84.3	-	X	8.9	X	33
A	2	33	X	X	85.6	-	-	7.6	X	58
A	3	36	X	X	84.9	-	X	8.8	X	57
A	4	30	X	X	84.9	-	-	7.7	X	56
B	1	100	-	-	92.0	-	X	7.9	X	32
B	2	110	X	X	84.3	-	X	9.1	X	47
B	4	100	-	X	91.9	-	-	7.8	X	32
C	1	200	-	-	93.9	-	X	8.0	X	18
C	2	220	X	-	92.0	-	X	7.9	X	16
C	3	240	X	-	93.5	-	-	7.4	X	15

C	4	200	X	-	93.0	-	-	7.8	X	15
D	1	30	X	X	87.1	-	X	8.4	X	48
D* (re-enrolled)	1	60	X	X	88.9	-	X	7.9	X	61
	Number of sessions criteria observed		10/13	8/13	n/a	0/13	8/13	n/a	13/13	n/a









21.3 Safety results

Two AEs reported. No deaths or SAEs.

Table: Listing of Adverse Events for all patients

Adverse Events	**e.g. Treatment Arm**	**e.g. Placebo**
Total Number of AEs per Study Arm	2	N/A
Subjects affected by non-serious adverse events:	1	N/A

Table: Listing of Serious Adverse Events for all patients

Serious Adverse Events	**e.g. Treatment Arm**	**e.g. Placebo**
Total Number of SAEs per Study Arm	0	N/A
Total number of all cause deaths per Study Arm	0	N/A
Total number of deaths resulting from adverse events per Study Arm	0	N/A

Within the per protocol population (n= 4), a total of 2 AEs, including "0" 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, 1 patient (25%) patients experienced two AE. The proportion that experienced at least one SAE was 0% (n=0).

Incidence of adverse drug reactions (ADRs): 0 /0 AEs (0 %) were assessed as related to at least one study drug and 0 / 0 patients (0%) experienced 0 ADR.

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

22. Conclusion

Four male participants (aged 59-72) with a total of 13 dosing sessions across all participants. Respiratory depression measures of pulse oximetry, end-tidal carbon dioxide, transcutaneous carbon dioxide and Neural Respiratory Drive Index did not differ significantly between doses, both at peak/nadir post-diamorphine administration or % change from baseline to peak/nadir. Pupil size was significantly lower in the 110% and 120% dose sessions compared to the usual 100% dose. However, none of the subjective drug responses showed a significant difference between doses. With no serious adverse events occurring and participants tolerating the unusual method of administering diamorphine, this is a safe model of opioid overdose.

23. Date of Report

This is version 1.0 of the Clinical Study Report synopsis, dated 11/JUN/2024.

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** *(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 Placebo 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** *(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					
Cardiac disorders					
Congenital, familial and genetic disorders					
Ear and labyrinth disorders					
Eye Disorders					
Gastrointestinal disorders					
General disorders and administration site conditions		1	2		2

Hepatobiliary disorders					
Immune system disorders					
Infections and infestations					
Injury, poisoning and procedural complications					
Investigations					
Metabolism and nutritional disorders					
Musculoskeletal and connective tissue disorders					
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Nervous system disorders					
Pregnancy, puerperium and perinatal conditions					
Product issues					
Psychiatric disorders					
Renal and urinary disorders					
Reproductive system and breast disorders					
Respiratory, thoracic and mediastinal disorders					
Skin and subcutaneous tissue disorders					
Social circumstances					
Surgical and medical procedures					
Vascular disorders					

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

0

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

0

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

0