

CLINICAL STUDY REPORT

PRILOCC

Does subarachnoid administration of hyperbaric prilocaine produce an improved recovery from anaesthesia when compared with hyperbaric bupivacaine when used to facilitate cervical cerclage in pregnant women at risk of pre-term loss?

A randomised controlled superiority Phase IV trial.

Sponsor Protocol Code:	PRILOCC
EudraCT Number:	2019-001548-23
ClinicalTrials.gov Identifier:	NCT04394533
ISRCTN number:	14374515
REC Number:	20/LO/0231
Investigational Drugs (IMPs):	Prilocaine
Indication:	Prilocaine for Cervical Cerclage
Development Phase:	Phase IV
Study Begin (FPFV):	27/08/2021
Study End (LPLV):	10/04/2025
Report Version & Issue Date:	v1.0
Sponsor Name and Address:	Guy's and St Thomas' NHS Foundation Trust R&D Department
Sponsor contact details:	Anne Marie Murtagh Address: Floor 16, Tower Wing, Guy's Hospital, Great Maze Pond, London, SE1 9RT Telephone: 020 7188 5732 Email: QM.KHPCTO@kcl.ac.uk
Chief Investigator:	Dr Neel Desai

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:

Signed by:
Neel Desai
15BCE865B6C04F8...

Sep 4, 2026 | 23:32 BST

Printed name

Signature

Date

Dr Neel Desai

Neel Desai

CONTENTS

Contents

1. Ethics	5
2. Data Monitoring.....	5
3. Sponsors, Chief Investigator and Trial Sites.....	6
4. Co-Investigator(s), Statistician, Laboratories, Database Management	6
5. Study Synopsis	7
6. Glossary of terms	11
7. Publication (reference)	12
8. Study period (years).....	12
9. Phase of development	13
10. Objectives	13
11. Background and Context.....	14
12. Methodology.....	16
13. Number of patients (planned and analysed)	18
14. Diagnosis and main criteria for inclusion.....	19
15. Test product, dose and mode of administration	19
16. Duration of treatment	20
17. Reference therapy, dose and mode of administration.....	20
18. Criteria for evaluation: Endpoints.....	20
19. Statistical Methods	21
20. Changes in the Trial Plan	22
21. Summary – Conclusions	22
22. Conclusion.....	26
23. Date of Report.....	26

APPENDICES

i) Summary of treatment-emergent AEs in the per protocol population..... 27

ii) Summary of treatment-emergent ARs in the per protocol population 29

iii) Summary of treatment-emergent SAEs in the per protocol population..... 31

iii) Summary of treatment-emergent SARs in the per protocol population..... 34

1. Ethics

Independent Ethics Committee or Institutional Review Board

The study protocol and amendments were reviewed and approved by a National Research Ethics Service (London Central).

Ethical conduct of the study

The trial was conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (1996) as amended, the principles of Good Clinical Practice (GCP) and in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, the Research Governance Framework for Health and Social Care, the Data Protection Act 1998 and other regulatory requirements as appropriate. The trial protocol and substantial amendments were reviewed by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA)

Subject information and consent

All women assessed in the prematurity clinic and scheduled for cervical cerclage had their medical history checked as per standard, were counselled on their options for anaesthesia, introduced to the study and provided with the Patient Information Sheet (PIS).

On the morning of surgery, the eligibility of all patients presenting for cervical cerclage was confirmed against the protocol criteria. Once deemed eligible, the patients were given a further explanation of the study's objectives and the practical implications of participation. Informed written consent (ICF) was gained from those wishing to participate prior to any procedures being undertaken.

2. Data Monitoring

The investigators permitted trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor, Regulators and REC direct access to all source data or documents with any relevance to the study.

Monitoring of this trial was undertaken to ensure compliance with Good Clinical Practice and scientific integrity and was managed and oversight retained, by the KHP-CTO Quality Team.

3. Sponsors, Chief Investigator and Trial Sites

<i>Sponsors or Co-Sponsors</i>	Guy's and St Thomas' NHS Foundation Trust R&D Department Sponsor Contact: Anne Marie Murtagh, King's Health Partners Clinical Trials Office Address: Floor 16, Tower Wing, Guy's Hospital, Great Maze Pond, London, SE1 9RT Telephone: 020 7188 5732 Email: QM.KHPCTO@kcl.ac.uk
<i>Chief Investigator</i>	Name: Dr Neel Desai Address: Anaesthetics Department, 1st Floor Lambeth Wing, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH Telephone: 0207 188 0644 Email: neel.desai4@nhs.net
<i>Trial Sites</i>	Guys & St Thomas' NHS Foundation Trust Westminster Bridge Road London SE1 7EH Kings College Hospital NHS Foundation Trust Denmark Hill London SE5 9RS Musgrove Park Hospital Somerset NHS Foundation Trust Taunton Somerset TA1 5DA

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

<i>Co-Investigator(s)</i>	Name: Professor Andrew Shennan (Co-Investigator) Address: Women's Health Directorate Offices, 10th Floor North Wing, St. Thomas' Hospital, Westminster Bridge Road, London SE1 7EH Telephone: 020 7188 7905 Email: andrew.shennan@kcl.ac.uk Name: Dr Katrina Henderson (Co-Investigator) Address: Anaesthetics Department, 1st Floor Lambeth Wing, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH Telephone: 07743213741 Email: katrinahenderson@nhs.net
----------------------------------	--

Statistician	Name: Mr Paul Seed (Statistician) Address: Women's Health Directorate Offices, 10th Floor North Wing, St. Thomas' Hospital, Westminster Bridge Road, London SE1 7EH Telephone: 0207 188 3639 Email: paul.seed@kcl.ac.uk
Laboratories	N/A
Database Management	Castor CDMS

5. Study Synopsis

Title of clinical trial	Does subarachnoid administration of hyperbaric prilocaine produce an improved recovery from anaesthesia when compared with hyperbaric bupivacaine when used to facilitate cervical cerclage in pregnant women at risk of pre-term loss? A randomised controlled superiority Phase IV trial.
Protocol Short Title/Acronym	PRILOcaine for Cervical Cerclage Trial (PRILOCC Trial)
Study Phase	Phase IV
Sponsor name	Guy's and St Thomas' NHS Foundation Trust R&D Department
Chief Investigator	Dr Neel Desai
EudraCT number	2019-001548-23
REC number	20/LO/0231

Clinical Study Report

PRILOCC IRAS: 225703

IRAS project ID:	225703
Medical condition or disease under investigation	Cervical cerclage for risk of pre-term pregnancy loss
Purpose of clinical trial	To determine if a difference exists between the time required for regression of motor block between two commonly used and equipotent doses of subarachnoid hyperbaric prilocaine 2% and bupivacaine 0.5%.
Primary objective	To determine if subarachnoid hyperbaric 2% prilocaine produces a clinically meaningful reduction in time taken for regression of lower limb motor block when compared to hyperbaric 0.5% bupivacaine.
Secondary objective (s)	To compare the intraoperative characteristics of the subarachnoid block and quality of intraoperative anaesthesia in the two groups. To compare the recovery profiles in the two groups. To compare the incidence of complications in the two groups. To compare the satisfaction of the participants in each group.
Trial Design (e.g. randomised, double-blind, treatment arms, and duration of study)	Prospective, parallel group, double-blind, randomised, controlled, superiority trial.
Endpoints	Primary endpoint: The time taken in minutes from initiation of subarachnoid block (SAB) until regression of motor block as assessed using the Bromage score of I. Secondary endpoints: • Mean time in minutes until achievement of loss of cold sensation to ethyl chloride spray at the tenth thoracic dermatomal level (T10) • Mean time in minutes until achievement of complete motor block, assessed as Bromage score = IV.

Clinical Study Report

PRILOCC IRAS: 225703

	• Uppermost (cephalad) dermatomal level of sensory block as measured by loss of cold sensation to ethyl chloride spray at 20 minutes (mean). • Mean degree of motor block as assessed on the Bromage scale at 20 minutes. • Administration of hypnotic agent (proportion of cases). • Administration of analgesic agent (proportion of cases). • Mean pain score on the NRS of maximal discomfort experienced during the procedure • Mean time in minutes from SAB to ambulation • Mean time in minutes from SAB to micturition • Mean time in minutes from SAB to discharge • Proportion of cases experiencing hypotension > 10% SBP drop from baseline). • Proportion of cases experiencing bradycardia (< 45 bpm) • Proportion of cases experiencing nausea or vomiting • Proportion of cases requiring urethral catheterisation • Proportion of cases experiencing TNS • Proportion of cases experiencing backache • Proportion of cases experiencing headache • Mean level of patient satisfaction as assessed by a Numerical Rating Score (NRS, 0-10).
Planned number of subjects	135
Study population (inclusion/exclusion)	Inclusion Criteria • Healthy (ASA score 2 or 3) pregnant women presenting for cervical cerclage under SAB. • Age > 18 years

	Exclusion Criteria • Inability to read or understand the patient information sheet (PIS) • Age < 18 years • Unable or unwilling to consent to participation • Emergency cerclage where bulging membranes are present • Serious co-morbidities (ASA score 4 or above) • Any contraindication to SAB, e.g. local or generalised infection, active central nervous system disease, coagulation disorders or anti-coagulant medication • Any history of allergic reaction to any of the medications in the protocol • Concomitant use of class III anti-arrhythmics (sulfonamides, antimalarials, sodium nitroprussate, nitroglycerin, other local anaesthetics) • Any contraindication to the use of bupivacaine or prilocaine as listed in the SmPCs.
Treatment per study arm (IMP, dosage and route of administration)	<u>Hyperbaric (heavy) 2% Prilocaine</u> <i>Dose: 40 mg (2 ml)</i> <i>Supplement: Fentanyl 15 mcg</i> <i>Route: Intrathecal (SAB)</i>
Results (Efficacy & Safety)	<i>We enrolled 135 women and excluded one due to incomplete data, leaving 67 patients in each group. The mean (SD) time to achieve a Bromage score of I for the prilocaine group was 88 (51) mins compared to 129 (63) mins for the bupivacaine group (mean difference (95% CI) of 40 mins (21–60; $p < 0.001$)). Prilocaine was also superior to bupivacaine with respect to time to regression of sensory block (mean difference 55 mins (43–67; $p < 0.001$)); first micturition (mean difference 75 mins (46–104; $p < 0.001$)); first ambulation (mean difference 59 mins (34–83; $p < 0.001$)); and meeting hospital discharge</i>

	<i>criteria (median difference 90 mins (41–136; $p = 0.001$)).</i>
Conclusions	<i>Intrathecal prilocaine for cervical cerclage results in a faster recovery of motor and sensory function, with similar efficacy to bupivacaine, as well as a shorter time to ambulation and meeting discharge criteria.</i>
Version and date of protocol amendments	Version 1.0: 24 January 2020 Version 1.1: 31 August 2021 Version 1.2: 25 May 2022 Version 1.3: 10 May 2024
Global start of trial date / First patient first visit (FPFV)	27th August 2021
Global end of trial date / Last patient last visit (LPLV).	10th April 2025
Completion date for primary data analysis	29 th January 2026

6. Glossary of terms

AAGBI	Association of Anaesthetists of Great Britain and Ireland
AE	Adverse event
AR	Adverse reaction
ASA	American Society of Anesthesiologists
BP	Blood pressure
BPM	Beats per minute
CRF	Case report form
CSF	Cerebrospinal fluid
ECG	Electrocardiogram
eCRF	electronic case report form
GCP	Good clinical practice
GDPR	General Data Protection Regulation
GSTT	Guy's & St. Thomas' Hospital
HR	Heart rate

ICF	Informed consent form
IME	Important medical events
IMP	Investigative medicinal product
IV	Intravenous
KHP-CTO	King's Health Partners Clinical Trials Office
MHRA	Medicines and Healthcare products Regulatory Agency
NRS	Numerical rating score
PIS	Patient information sheet
RCT	Randomised controlled trial
REC	Research ethics committee
SAB	Subarachnoid block
SAE	Serious adverse event
SAR	Serious adverse reaction
SBP	Systolic blood pressure
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TNS	Transient neurological symptoms
UAR	Unexpected adverse reaction

7. Publication (reference)

Not published as of yet but has been provisionally accepted by Anaesthesia for publication
https://associationofanaesthetists-publications.onlinelibrary.wiley.com/hub/journal/13652044/homepage/productinformation.html?gad_campaignid=22801236706&gad_source=1&gbraid=0AAAAADoE1amsJKGuEVPmaCcpR9k-DV_d4&gclid=Cj0KCQjw94bTBhDQARIsAN3vv0y5PLCYjHOSQuv__pX4osSPnpQUal8mOAWDoqZvyi6U1OXEDaQ091waArrtEALw_wcB&utm_campaign=R3MR425&utm_content=Medicine&utm_medium=cpc&utm_source=google).

8. Study period (years)

Study Period – 4 years

FPFV 27-08-2021

LPLV 10-04-2025

End of trial is defined as database lock.

Patient recruitment was completed on 09th April 2025

There were four paused periods of recruitment:

1. 19th July 2022 – 31st July 2022 inc. – IT System Server failure
2. 19th Dec 2022 – 28th Dec 2022 inc. – Festive Season break
3. 26th Sep 2023 – 12th Oct 2023 inc. – EPIC launch
4. 19th April 2024 – 5th Sep 2024 inc. – Change of CI/PI SA01

9. Phase of development

Phase IV

10. Objectives

Primary Objective:

This study aimed to determine if a difference exists between the time required for regression of motor block between two commonly used and equipotent doses of subarachnoid hyperbaric prilocaine and bupivacaine.

- The hypothesis was that SAB with hyperbaric 2% prilocaine would result in a clinically significant reduction in time taken for regression of motor blockade, as determined by achieving a Bromage score* of I, when compared to an equipotent dose of hyperbaric bupivacaine when used to facilitate cervical cerclage in pregnant women.
- The null hypothesis was that no clinically significant difference existed while the alternative hypothesis was that such a difference truly existed.

Secondary Objectives:

- Compared the intraoperative characteristics of the subarachnoid block and quality of intraoperative anaesthesia in the two groups.
- Compared the recovery profiles in the two groups
- Compared the incidence of complications in the two groups
- Compared the satisfaction of the participants in each group

11. Background and Context

Background:

Cervical incompetence is defined as the inability to sustain a pregnancy to full term. It is characterized by recurrent second-trimester pregnancy losses. Cervical cerclage is a procedure that is commonly carried out in order to prevent pre-term loss in at-risk pregnancies.

It is routinely performed as a day case procedure. The anaesthetic used to facilitate this varies widely across the UK and globally. Most centres, however, prefer to use regional anaesthesia to avoid exposing the fetus to general anaesthetic drugs but it can be difficult to achieve discharge on the same day and some units continue to use general anaesthesia due to its perceived advantages in this regard.

The major challenge of performing this as a day case procedure is achieving adequate anaesthesia for comfortable performance of the cerclage whilst providing adequate regression of motor and sensory blocks to allow ambulation and bladder control within an appropriate timescale. Spinal anaesthesia, or subarachnoid block (SAB), is commonly employed to facilitate a wide variety of pelvic and lower limb surgeries. In the United Kingdom, the commonly administered subarachnoid agents are bupivacaine, prilocaine and, until recent decades, lidocaine. The duration of action of bupivacaine makes it less well suited to day surgery as it is often difficult to reach discharge criteria within a convenient time frame. At our trust this has, on occasion, necessitated the use of an indwelling urinary catheter for seven days. An institutional audit of 40 patients receiving SAB for cerclage with either bupivacaine or prilocaine documented eight patients with bladder volumes of over 500 ml which required bladder catheterisation.

Context:

Achieving discharge on the same day as surgery after SAB is difficult, even in the most controlled of ambulatory care settings. In these situations, provision can be made to schedule the surgery as early in the day as possible in order to maximize the time for SAB regression. It becomes even more important when the resources used are shared with emergency obstetric services, as is often the case for cervical cerclage performed in UK maternity units. The consequences of delays in recovery times are much greater in these situations and the potential safety benefits are to the patients themselves, other patients waiting for the occupied resources and cost-savings to the trust.

We could only find one RCT examining efficacy of drug choice or dose (bupivacaine vs. lidocaine) in this context. Lidocaine has a short duration of action and had been used with good effect but became unpopular towards the end of the last century due to an unacceptable incidence (between 10 and 17%) of transient neurological symptoms (TNS). TNSs are defined as back pain with radiation in the buttocks, thighs, hips and calves, occurring within 24 hours. TNSs are invariably resolved within two days without long-term sequelae. A systematic review of the literature revealed that the relative risk for developing TNS after SAB with lidocaine was 4.35 (95% confidence interval, 1.98-9.54) when compared to prilocaine and bupivacaine.

Prilocaine is rapidly metabolized in kidney, liver and lung. One of its metabolites, O-toluidine, oxidises haemoglobin and can produce clinically significant methaemoglobinaemia. Methaemoglobin is altered state of haemoglobin in which the ferrous irons of haem are oxidized to the ferric state. Methaemoglobinaemia leads to cyanosis but this is only seen at doses much higher (8 mg/kg) than used for SAB (0.5 – 1 mg/kg). Other drugs that can increase the production of methaemoglobin are lidocaine, benzocaine, nitroglycerine, sodium nitroprusside, phenytoin, sulfonamides and metoclopramide.

Hyperbaric 2% prilocaine for subarachnoid injection contains 20 mg/ml of prilocaine and 60 mg/ml of dextrose. Prilocaine is approved for use in pregnancy with similar precautions to that advised for bupivacaine. Concomitant use of drugs that cause methaemoglobinaemia should be avoided. It should be avoided in patients with anaemia or congenital or acquired methaemoglobinaemia. Similar to bupivacaine it should be used with caution in renal and liver impairment. It has a low incidence of allergic reactions but it should, obviously, be avoided in patients with a known hypersensitivity to prilocaine.

SAB with prilocaine has been shown to have a faster recovery profile than bupivacaine in other surgeries. Hampl et al compared 50 mg of hyperbaric prilocaine to 12.5 mg of hyperbaric bupivacaine for short gynaecological procedures. The recorded mean times to ambulate were 165 mins and 200 mins, respectively, and to void were 253 and 299 mins, respectively ($p < 0.05$). A further randomised comparison of prilocaine (60 mg) and bupivacaine (15 mg) was performed in Germany by Rättsch and colleagues. The regression of the motor block was 135 min versus 210 min, and time for spontaneous micturition was 306 min versus 405 min, respectively (the p-values for both these comparisons were stated as < 0.05). There is a substantial amount of evidence to support the subarachnoid administration of prilocaine in a variety of day surgeries in non-pregnant populations. A review by Boublik combined the results of the eight studies in their review which had used between 40 and 60 mg of prilocaine. The duration of the block, defined as the time to ambulation, was 129 +/- 41 minutes, and the time to voiding was 241 +/- 28 minutes.

A recent retrospective study (poster presentation, presented to the Group of Obstetric Anaesthetists in London, GOAL) of anaesthetic technique for cerclage in London (UK) maternity units demonstrated a wide variation in doses of both bupivacaine (mean: 9.8 mg and range: 7.5 to 12.5 mg) and fentanyl (mean: 21 mcg and range: 15 - 40 mcg). There is one dose finding study examining prilocaine, in the context of SAB for ambulatory knee arthroscopy. Their up-down sequential allocation design and subsequent isotonic regression demonstrated an ED90 of heavy 2% prilocaine (for a T12 block) to be 38.5 mg (95% CI: 35.7 to 39.5).

Although an ampoule of prilocaine is more expensive than bupivacaine (£7.88 vs. £1.45), if it is shown to have clinical advantages, then this cost may be balanced by efficient resource utilisation and patient satisfaction.

We aimed to examine the recovery profiles of two equipotent doses of hyperbaric prilocaine and bupivacaine. Given the evidence, the survey of practice in other centres and the commonly used doses at this institution the following regimens were compared:

40 mg of hyperbaric 2% prilocaine with 15 mcg of fentanyl (*intervention*) and

10 mg of hyperbaric 0.5% bupivacaine with 15 mcg of fentanyl (*comparator*).

12. Methodology

Trial Duration: 4 years

Trial Follow-up: 24 Hours

Table: Schedule of events

Introduction to Study 1-2 Weeks before surgery	Prematurity clinic All women assessed in the prematurity clinic and scheduled for cervical cerclage. All patients had their medical history checked as per standard and were counselled on their options for anaesthesia, introduced to the study and provided with the Patient Information Sheet (PIS).
--	--

Eligibility Screening & Recruitment Day of surgery	The Labour Ward On the morning of surgery, the eligibility of all patients presenting for cervical cerclage were confirmed against the protocol criteria. Once deemed eligible, the patient was given a further explanation of the study's objectives and the practical implications of participation. Informed written consent (ICF) were gained from those wishing to participate prior to any procedures being undertaken.
--	---

Enrolment	Subject Randomisation	
	Random allocation to groups was achieved using "Castor" randomisation software. This software uses a validated variable block randomisation model.	
Day of surgery	Baseline demographic data	
	1) Age	6) Indication for cervical cerclage
	2) Weight	7) Gestational age
	3) Height	8) Gravida
	4) ASA score	9) Parity
	5) Ethnicity	

Treatment Groups Day of surgery	Intervention Subarachnoid block (SAB) with 40 mg (2 ml) of hyperbaric 20 mg/ml	Control Subarachnoid block (SAB) with 10 mg (2 ml) of hyperbaric 5 mg/ml

	prilocaine and 15 mcg (0.3 ml) fentanyl (50 mcg/ml)	bupivacaine and 15 mcg (0.3 ml) fentanyl (50 mcg/ml)
--	---	--

Intraoperative data collection (Day of surgery in theatre)	1) Time since last solid, time since last fluid (hours) 2) Baseline blood pressure (BP) and heart rate (HR) 3) Time of SAB 4) Sensory and motor block evaluation at 0, 5, 10, 15 and 20 minutes 5) Time of start of surgery 6) Lowest BP & HR 7) Incidence vasopressor or vagolytic treatment (Y/N) 8) Need for anaesthetic, sedative or analgesic supplementation (Y/N) 9) Incidence of nausea or vomiting 10) Intraoperative fluid volume infused (ml) 11) Time of end of surgery 12) Maximum NRS pain score during procedure
--	--

Intraoperative surgical demographics (Day of surgery in theatre)	1) Grade of operating surgeon 2) HISTORY: Indication for cerclage; previous cervical procedures – LLETZ/cone; plurality (singleton/twins) 3) EXAMINATION: Last cervical length and date; length of vaginal portion of cervix – any structural abnormalities 4) TECHNIQUE: Type of disinfectant – chlorhexidine/iodine; Suture material – braided/nylon; Position of knot – anterior/posterior; number of knots; bladder mobilisation; fluid dissection (ml) 5) CATHETER: In/out pre-op; in/out post-op; indwelling indication; urine colour 6) PROCEDURE: Duration (from speculum insertion to removal); difficulty 1-10; overnight admission; complications
--	---

Postoperative data collection (Day of surgery in labour ward recovery)	1) Motor block assessment at arrival in recovery and every 15 mins until Bromage score of I reached Primary outcome: Time from SAB to Bromage score of I 2) Sensory block assessment at arrival in recovery and every 15 mins until regression to T12 reached 3) Need for postoperative analgesia – medication and doses 4) Fluid intake (intravenous and/or oral, ml) 5) Bladder volume as assessed by bladder scan every 60 minutes
--	--

	6) Incidence of need for catheterisation 7) Time of first ambulation 8) Time of first spontaneous micturition 9) Time of meeting discharge criteria
--	--

Follow up (Telephone call at 24 hours after discharge)	1) Screening questions for transient neurological symptoms (TNSs) 2) Incidence of backache 3) Incidence of headache 4) Patient satisfaction numerical rating score (NRS, 0-10)
--	---

Trial Medication:

Prilocaine (hyperbaric 2%), 20mg/ml hyperbaric solution for injection

Dosing Regimen:

Dose: 40 mg (2 ml)

Supplement: Fentanyl 15 mcg

Route: intrathecal (SAB)

Number of participants (planned and analysed)

13. Number of participants (planned and analysed)

13.1 Planned 135

13.2 Analysed 133

Table 1: Number of patients screened, randomised, and withdrew for each arm

Arm	PRILOCAINE	BUPIVICAINE
# patients screened	441	441
# participants randomised/treated/study arm	68	67
# participants completed/study arm	66	67
# participants that did not complete the study arm	2	0

Table 2: The reasons for participant withdrawal from the study for each study arm

Prilocaine Arm

Participant No.	Reason for withdrawal
110041	Anaesthetist took clinical decision to use Hyperbaric (heavy) 0.5% Bupivacaine instead of the randomised drug. After discussion with the anaesthetist delivering the drug, the CI and R&D Lead decided to withdraw patient.
110067	Patient withdrawn as procedure was abandoned.

Bupivacaine Arm	
Participant No.	Reason for withdrawal
	No withdrawals

Table 3: Planned and Actual Number of Participants Enrolled per Country

<i>Trial country</i>	<i>Planned number of participants</i>	<i>Actual number of participants enrolled</i>
<i>United Kingdom</i>	<i>135</i>	<i>135</i>

14. Diagnosis and main criteria for inclusion

Healthy (ASA score 2 or 3) pregnant women presenting for cervical cerclage under SAB.

Age > 18 years

15. Test product, dose and mode of administration**Baseline therapy**

Dose: Hyperbaric Prilocaine 2% 40 mg (2 ml)

15mcg Fentanyl added to syringe along with the trial medication and administered into the subarachnoid space.

IMP**Table: Dose of IMP administered to each study participant**

All participants that randomised to the Prilocaine group received 40mg (2mls) of the IMP with the exception of two participants:

110075 – Received 60mg (3mls)

110091 – Received 60mg (3mls)

16. Duration of treatment

A single intrathecal (SAB) dose.

Data collection from the patient would end after a telephone conversation at 24 hours after discharge from hospital.

17. Reference therapy, dose and mode of administration

Hyperbaric (heavy) 0.5% Bupivacaine

Dose: 10 mg (2 ml)

Supplement: Fentanyl 15 mcg

Route: Intrathecal (SAB)

18. Criteria for evaluation: Endpoints

18.1 Efficacy

Primary endpoints:

The time taken in minutes from initiation of subarachnoid block (SAB) until regression of motor block as assessed using the Bromage score of I.

Secondary Efficacy Parameters:

Compared the intraoperative characteristics of the subarachnoid block and quality of intraoperative anaesthesia in the two groups. This was assessed using the following outcomes:

- sensory and motor block evaluation;
- incidence of vasopressor or vagolytic treatment;
- need for anaesthetic, sedative or analgesic supplementation;
- maximum NRS pain score during procedure.

Compared the recovery profiles in the two groups. This was assessed using the following outcomes:

- time from SAB to ambulation;
- time from SAB to micturition;
- time from SAB to discharge.

Compared the incidence of complications in the two groups. This was assessed using the following

outcomes:

- incidence of hypotension (> 10% SBP drop from baseline);
- incidence of bradycardia (< 45 bpm);
- incidence of nausea or vomiting;
- incidence of need for catheterisation;
- incidence of TNS;
- incidence of backache;
- incidence of headache.

Compare the satisfaction of the participants in each group. This was assessed using the following outcome:

- patient satisfaction Numerical Rating Score (NRS, 0-10).

18.2 Safety

Safety Parameters:

The recommended maximum single dose of subarachnoid 0.5% heavy bupivacaine is 20 mg (4 ml). The recommended maximum single dose of subarachnoid 2% heavy prilocaine is 80 mg (4 ml). The doses in this study were 10 mg 0.5% heavy bupivacaine OR 40 mg 2% heavy prilocaine, equating to 2 ml of either drug, which was therefore well within recognised safe limits.

Other risks were related to the technique of the procedure. Postoperatively and at 24-hour follow-up, the patient was assessed for any potential adverse events related to the technique or the IMPs.

Specific Safety Endpoints:

The trial could have been prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Ethics Committee/regulatory authority concerned.

If the trial had been prematurely discontinued, active participants would have been informed and no further participant data would have been collected. The Competent Authority and Research Ethics Committee would have been informed within 15 days of the early termination of the trial.

19. Statistical Methods

The primary outcome is the time from initiation of SAB until a Bromage score* of I. After checking for normality by standard diagnostic plots, a comparison between the groups will be made using multiple regression with a dummy variable for treatment arm. A correction will be made for unequal variance using the robust standard errors. Adjustment will be made for maternal BMI and height, as these are known to be related to anaesthetic effect.

No power calculation has been carried out for the secondary outcomes, and no priority is made between them. Continuous measures, including the patient satisfaction score, will be analysed as described above for the primary outcome. Binary measures will be expressed as percentages, and compared by means of risk ratios, using binary regression with a log link, adjusted for BMI and height,

as described above.

Subgroup analyses: A comparison will be made between normal weight and obese women (BMI over 30 kg.m⁻²); and between women above and below 165 cm in height, using an interaction test to check for a difference in treatment effect.

No interim analysis is planned.

20. Changes in the Trial Plan

There were no major protocol amendments or changes to planned analysis.

20.1 Protocol Deviations

There were 29 Protocol deviations in total with 6 having an impact on the analysis:

Major Deviation	Participants Affected
Allocated Drug not given and Protocol directed dose not administered	1
Missing post-op data	4
Abandoned procedure	1

21. Summary – Conclusions

21.1 Demographic data

Table 1 Baseline characteristics of the patients. Values are mean (SD) or number (proportion).

	Prilocaine	Bupivacaine
Age; years	35.2 (4.3)	34.1 (3.9)
Height; m	1.65 (0.1)	1.66 (0.1)
Height ≥ 1.65 m	34 (50.7%)	29 (43.3%)
BMI; kg.m ⁻²	27.2 (6.5)	27.9 (7.5)
BMI ≥ 30 kg.m ⁻²	17 (25.4%)	19 (28.4%)
Gravidarum; 1/2/≥3	8/9/50	9/12/46

Parity; 0/1/≥2	19/22/26	20/26/21
Gestation; weeks	16.8 (4)	17.5 (3.9)
ASA; 2/3	60/7	61/6
Duration of fasting for liquids; h	4.8 (3.3)	6.2 (4.3)
Duration of fasting for solids; h	13.9 (3.2)	13.8 (3.7)

The following tables summarise the demographics of the study population:

Figure: Gender of the safety population

Age (years)	Female (Active/Placebo)	Total
Adults (18-64 years)	68/67	135
Total	135	135

Figure: Ethnicity of the safety population

ETHNICITY	TOTAL
Asian British	7
Black British	44
Mixed	5
Not Disclosed	6
Other	7
White British	48
White Other	18
TOTAL	135

21.2 Primary outcome

For the primary outcome, lower limb motor function returned more quickly in women who had received intrathecal prilocaine compared with those who received bupivacaine. The mean (SD) time to achieving a bilateral Bromage score of I was 88 (51) mins for prilocaine and 129 (63) mins for

bupivacaine with a mean difference (95% CI) of 40 mins (21–60; $p < 0.001$). Neither BMI nor height affected the time to regression of lower limb motor blockade. Similar differences regarding the time to regression of lower limb motor blockade were demonstrated for the left leg and right leg with a mean difference (95% CI) of 38 mins (19–57; $p < 0.001$) and 36 mins (17–55; $p < 0.001$), respectively.

21.3 Safety results

Table: Listing of Adverse Events for all patients

Adverse Events	PRILOCAINE	BUPIVICAINE
Total Number of AEs per Study Arm	13	3
Participants affected by non-serious adverse events	10	1

Table: Listing of Serious Adverse Events for all participants

Serious Adverse Events	PRILOCAINE	BUPIVICAINE
Participants affected by SAEs	3	2
Total Number of SAEs per Study Arm	3	2
Total number of all cause deaths per Study Arm	0	0
Total number of deaths resulting from adverse events per Study Arm	0	0

Within the per protocol population (n= 135), a total of 16 AEs, including 5 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, 16 patients (11.85%) patients experienced at least one AE. The proportion that experienced at least one SAE was 3.7% (n=135).

Incidence of adverse drug reactions (ADRs): 0/16 AEs (0 %) were assessed as related to at least one study drug and 0/135 patients (0 %) experienced 0 ADR.

There was 1 Serious Adverse Reaction (SAR), 0 unexpected SARs and 0 SUSARs.

In the active arm, there were 0 total deaths of all causes.
In the placebo arm, there were 0 total deaths of all causes.

All SAEs/SARs, including those that resulted in death, can be found in the appendices below.

22. Conclusion

The use of hyperbaric prilocaine 2% for transvaginal cervical cerclage has clear advantages over hyperbaric bupivacaine 0.5% and similar efficacy. Faster recovery of motor and sensory function, time to ambulation and time to meeting discharge criteria are all potential benefits, improving patient flow, reducing length of stay and helping to meet the demands of a busy maternity unit.

23. Date of Report

This is version 1.0 of the Clinical Study Report synopsis, dated

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

System Organ Class	Preferred Term	Number of Subjects Experiencing the AE in Active Arm	Total Number of Occurrences of the AE	Number of Subjects Experiencing the AE in Placebo Arm	Total Number of Occurrences of the AE
Gastrointestinal disorders	<i>Vomiting</i>	<i>4/68 (5.88%)</i>	<i>1 occurrence</i>	<i>0</i>	<i>0 occurrence</i>
General disorders and administration site conditions	<i>Pyrexia</i>	<i>1/68 (1.47%)</i>	<i>1 occurrence</i>	<i>0</i>	<i>0 occurrence</i>
Investigations	Magnetic resonance imaging	<i>1/68 (1.47%)</i>	<i>1 occurrence</i>	<i>0</i>	<i>0 occurrence</i>
Nervous system disorders	<i>Vasovagal syncope</i>	<i>2/68 (2.94%)</i>	<i>1 occurrence</i>	<i>1/67 (1.49%)</i>	<i>1 occurrence</i>
Surgical and medical procedures	Spinal anaesthesia	<i>1/68 (1.47%)</i>	<i>1 occurrence</i>	<i>0</i>	<i>0 occurrence</i>

ii) Summary of treatment - emergent ARs in the per protocol population
Not Applicable

Clinical Study Report

PRILOCC IRAS: 225703

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

System Organ Class	Preferred Term	Number of Subjects Experiencing the SAE in Active Arm	Total Number of Occurrences of the SAE in Active Arm	Total Number of Deaths due to the SAE in Active Arm	Number of Subjects Experiencing the SAE in Placebo Arm	Total Number of Occurrences of the SAE in Placebo Arm	Total Number of Deaths due to the SAE in Placebo Arm
Gastrointestinal disorders	<i>Abdominal pain</i>	<i>1/68 (1.47%)</i>	<i>1 occurrence</i>	<i>0</i>	<i>1/67 (1.49%)</i>	<i>1 occurrence</i>	<i>0</i>
Pregnancy, puerperium and perinatal conditions	<i>Early miscarriage</i>	<i>1/68 (1.47%)</i>	<i>1 occurrence</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>
Pregnancy, puerperium and perinatal conditions	<i>Spontaneous rupture of membranes</i>	<i>1/68 (1.47%)</i>	<i>1 occurrence</i>	<i>0</i>	<i>0</i>	<i>0</i>	<i>0</i>

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

System Organ Class	Preferred Term	Number of Subjects Experiencing the SAR in Active Arm	Total Number of Occurrences of the SAR in Active Arm	Total Number of Deaths due to the SAR in Active Arm	Number of Subjects Experiencing the SAR in Placebo Arm	Total Number of Occurrences of the SAR in Placebo Arm	Total Number of Deaths due to the SAR in Placebo Arm
Renal and urinary disorders	<i>Urinary retention</i>	0	0	0	1/67 (1.49%)	1 occurrence	0

Certificate Of Completion

Envelope Id: 18D69540-E98D-8716-83F7-B1EFB2089AB7	Status: Completed
Subject: Complete with Docusign: PRILOCC Clinical Study Report Final.pdf	
Source Envelope:	
Document Pages: 29	Signatures: 1
Certificate Pages: 4	Initials: 0
AutoNav: Enabled	Envelope Originator:
Envelopeld Stamping: Enabled	Kathryn Lobb
Time Zone: (UTC) Dublin, Edinburgh, Lisbon, London	kathryn.1.lobb@kcl.ac.uk
	IP Address: 2a02:6b6f:fc2b:

Record Tracking

Status: Original	Holder: Kathryn Lobb	Location: DocuSign
04-Sep-26 14:15	kathryn.1.lobb@kcl.ac.uk	

Signer Events

Neel Desai
neel.desai4@nhs.net
Security Level: Email, Account Authentication (None)

Signature

Signed by:

15BCE865B6C04F8...

Signature Adoption: Pre-selected Style
Using IP Address: 161.17.0.159

Timestamp

Sent: 04-Sep-26 | 14:23
Viewed: 04-Sep-26 | 23:32
Signed: 04-Sep-26 | 23:32

Electronic Record and Signature Disclosure:
Accepted: 04-Sep-26 | 23:32
ID: ecbc4ca4-5f16-4ce2-b3e2-b3c62b884367

In Person Signer Events	Signature	Timestamp
Editor Delivery Events	Status	Timestamp
Agent Delivery Events	Status	Timestamp
Intermediary Delivery Events	Status	Timestamp
Certified Delivery Events	Status	Timestamp
Carbon Copy Events	Status	Timestamp
Witness Events	Signature	Timestamp
Notary Events	Signature	Timestamp
Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	04-Sep-26 14:23
Certified Delivered	Security Checked	04-Sep-26 23:32
Signing Complete	Security Checked	04-Sep-26 23:32
Completed	Security Checked	04-Sep-26 23:32
Payment Events	Status	Timestamps
Electronic Record and Signature Disclosure		

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, KHP-CTO (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a \$0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact KHP-CTO:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:

To contact us by email send messages to: governance@kcl.ac.uk

To advise KHP-CTO of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at governance@kcl.ac.uk and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from KHP-CTO

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to governance@kcl.ac.uk and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with KHP-CTO

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

- i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;
- ii. send us an email to governance@kcl.ac.uk and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: <https://support.docusign.com/guides/signer-guide-signing-system-requirements>.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify KHP-CTO as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by KHP-CTO during the course of your relationship with KHP-CTO.