A phase Ib study to investigate the safety and pharmacokinetics of BR-003 in patients undergoing spinal fusion surgery

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This study has been transitioned to CTIS with ID 2024-516338-37-00 check the CTIS register for the current data. This study aims to assess the Pharmacokinetic (PK)-parameters and safety of treatment with BR-003 in humans. BR-003 is a pliable, ring-…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Nervous system, skull and spine therapeutic procedures
Study type	Interventional

Summary

ID

NL-OMON53887

Source
ToetsingOnline

Brief title
STX-102

Condition

- Nervous system, skull and spine therapeutic procedures

Synonym
postoperative pain after back surgery, postoperative pain after spine surgery

Research involving
Human

Sponsors and support

Primary sponsor: SentryX

Source(s) of monetary or material Support: SentryX (sponsor)

Intervention

Keyword: pharmacokinetics, postoperative pain, safety, spine surgery

Outcome measures

Primary outcome

Primary objective:

- Assess systemic safety by confirming that the Cmax of BR-003 when

co-implanted with a pedicle screw onto the spine, stays below the known toxic

levels of 2000ng/mL

Secondary outcome

Secondary objectives:

- To investigate additional pharmacokinetic parameters (Tmax, AUC, T1/2)

- Assess the safety of BR-003

• Incidence, classification and grading of Adverse Events

• Clinical laboratory results (blood chemistry)

• ECG data

• Wound healing

• Vital signs, neurological assessment

• Radiological assessment

Study description

Background summary

Instrumented spine surgeries are among the most painful medical procedures overall. During surgery, instruments and surgical implants unavoidably damage

the bone of the spinal column and surrounding soft tissues. The outer bone layer, the periosteum, is exceptionally rich in pain receptors, especially in the spine. For several days after spine surgery, patients experience debilitating pain that cannot be sufficiently suppressed by currently available analgesics. Inadequately controlled pain impedes postoperative recovery, extends hospital stays and increases healthcare expenditures. Furthermore, acute postoperative pain is a significant predictive factor for the development of chronic pain conditions. For these reasons, pain management is widely regarded as an integral aspect of recovery after spine surgery.

Currently, systemic opioids are the mainstay of postoperative pain treatment. Although they are the strongest painkillers available, opioids fail to provide sufficient pain relief in up to 80% of surgical patients. Opioids are highly addictive and have many debilitating side-effects impeding recovery after surgery. Chronic opioid use is prevalent, especially after spine surgery, and represents a substantial public health burden. There is a large unmet clinical need for improved non-opioid pain treatments.
Local anaesthetics have long been recognized as promising alternatives. Rather than exerting their effects in the entire body, they are injected at specific sites to block pain signals locally. Local anesthetics have well-established safety and efficacy profiles and are widely used to treat acute postsurgical pain in a variety of procedures. However, even for bupivacaine, the longest-acting agent in this drug class, its limited duration of action is a major limiting factor. Because repeated administrations near the spinal periosteum are challenging, uncomfortable, and undesirable due to an associated risk of infection, local anaesthetics have limited added value in major procedures like spine surgery. Solutions are needed that locally block pain for the first three days after surgery, after which the most intense pain begins to subside . If opioids can be replaced in this critical early phase, the pain thereafter becomes manageable with conventional oral non-opioid analgesics. So far, extended-release formulations have not been able to demonstrate clinical superiority over their generic counterparts. These novel injectables still work for up to 24 hours, at best, and are not kept in place near the surgical site.
To bridge the first three days and unlock their full potential, further improved non-opioid local pain treatments are needed.

Study objective

This study has been transitioned to CTIS with ID 2024-516338-37-00 check the CTIS register for the current data.

This study aims to assess the Pharmacokinetic (PK)-parameters and safety of treatment with BR-003 in humans. BR-003 is a pliable, ring-shaped, biocompatible hydrogel that contains bupivacaine, a well-known and approved local anaesthetic. Attached to the shanks of pedicle screws, BR-003 is co-implanted locally without affecting existing surgical workflows. After placement, BR-003 provides a targeted, sustained release of bupivacaine for at

least three days before dissolving within approximately 36 weeks (based on a sheep study).

Primary objective:
- Assess systemic safety by confirming that the Cmax of BR-003, when co-implanted with pedicle screws onto the spine, stays below the known toxic levels of 2000 ng/mL

Secondary objectives:
- To investigate additional pharmacokinetic parameters (Tmax, AUC, T1/2)
- Assess the safety of BR-003
• Incidence, classification and grading of Adverse Events
• Clinical laboratory results (blood chemistry)
• ECG data
• Wound healing
• Vital signs, neurological assessment
• Radiological assessment

Study design

The study will consist of 2 cohorts with 12 patients in total. The study is divided into two parts; the main study period, covering the first 42 days after the day of surgery, and the follow-up period, starting after the 42 day main study period until 12 months after the day of surgery.

In cohort I, six patients that will undergo a 1-level fusion will be included, with 4 pedicle screws and 4 BR-003s with a dose of 36 mg per BR-003. They will receive a cumulative dose of 144 mg bupivacaine base. Data from the main study period of cohort I will be assessed by an independent DSMB and only when considered safe, cohort II can start.

In cohort II, the cumulative dose will be increased to 216 mg bupivacaine base. Six patients planned for 2-level fusions will receive a cumulative dose of 216 mg (6 BR-003s).

In both cohorts patients will be hospitalized from the day of surgery (standard of care) until day 4 after the surgery. Thereafter the patient will visit the hospital on day 9, 14 en 42. The follow-up period of this study consists of two telephonic contacts at month 3 and 6 after
surgery, and a hospital visits at month 12 after the surgery. The day 9 visit can also take place at the patients home. More details about the visits and assessments can be found in the section *Study assessment schedule*.

Intervention

BR-003 (36mg bupivacaine base) is a medicinal product presented as an

Implantation Matrix (IM) providing sustained release of bupivacaine to manage postoperative pain, to be administered during spinal fusion surgery, co-implanted with a pedicle screw.

Study burden and risks

All enrolled patients will undergo elective spine surgery for a degenerative condition. These surgical procedures carry a certain risk profile that is discussed beforehand by the treating physician/spine surgeon. Details on the additional burden and risks for participating in this phase Ib trial can be found below. In the preoperative phase patients routinely undergo screening to ensure safety during the surgical procedure. During this mandatory visit all activities pertaining to the '*screening* part of the current study can be completed, thereby minimising the burden on patients in terms of time investment or discomfort. During and after surgery, patients will receive standard of care pain treatment/management and will receive additional monitoring for vital functions but also for items related to patient (dis)comfort and perceived changes in well-being in relation to the reason for the surgery. These monitoring activities will also be used to complete most of the activities related to the current study, again minimising patient burden and discomfort. For the assessments required for the current study that cannot be completed during routine examinations, the patient burden and associated risks is considered low and acceptable. The additional assessments are: multiple ECG recordings, frequent blood sampling for PK, 3 blood chemistry samples, wearing an accelerometer on one leg from surgery until day 14, completing a questionnaire about pain management once and completing three times two questionnaires on health related quality of life and the extent to which a person*s functional level is restricted by disability.

The risks associated with participating in the current study are mainly related to the systemic and local effects of exposure to bupivacaine. For the expected systemic effects of bupivacaine, the applicant has extensively studied the effects of implanting BR-003 in a large animal model and found the systemic levels of bupivacaine to be in orders of magnitude lower than the toxic threshold. The applicant therefore suggests the risks of adverse events caused by systemic bupivacaine, including cardiotoxic or neurotoxic effects, to be very low. The local effects of sustained high levels of bupivacaine in the surgical wound has also been studied previously by the applicant in the same large animal model. Potential adverse events may include wound healing disturbances and compromised ingrowth at the interface of bone and implant. The applicant has found a very low incidence of primary wound healing disturbances and no secondary wound healing disturbances.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
1. Males and females aged between 18 years and 80 years (inclusive)
2. Planned for open or percutaneous posterior spinal stabilisation with 4 (for cohort I) or 6 (for cohort II) pedicle screws with a diameter of 5 to 7.5 mm (inclusive) with or without concomitant posterolateral fusion, vertebral augmentation, intervertebral body fusion devices, osteotomies, and posterior decompression. Only primary instrumented spinal surgery cases can be included.
3. Willing and able to comply with the protocol for the duration of the study

4. Give written informed consent prior to any study-related procedure not part of the standard
practice, with the understanding that the consent may be withdrawn by the subject at any time
without prejudice to his/her (post-)surgery care
5. Females are eligible only if not currently pregnant, nursing, or planning to become pregnant
during the study or within 9 months after study drug administration. Female subjects must be surgically sterile, at least 2 years menopausal, or using an acceptable method of birth control.
WOCBP, must have a documented negative pregnancy test within 24 hours before surgery.

Exclusion criteria

1. Concomitant anterior/lateral procedures (e.g. anteriorly placed vertebral cage, anterior plating,
ALIF/XLIF)
2. Use of ilium screws or use of (additional) pedicle screws, with a size < 5 mm or > 7.5 mm.
3. Indication for surgery being:
a. Active or previous (para)spinal infection
b. Metastatic, malignant or benign tumours of the spine
c. Fracture/other traumatic injury
4. Known high risk of intra-/postoperative surgical complications (e.g. patients having previously
undergone more than 2 non-instrumented spinal surgeries at the index level)
5. Planned use of a surgical drain
6. Planned use of an epidural catheter
7. Use of local amino-amide or amino-ester anaesthetics within 5 days prior to the scheduled
surgery (10 days in case of slow release products), peri-op and post op for the first two weeks after the surgery.
8. Has a pre-existing concurrent acute or chronic painful physical/restrictive condition expected to
require analgesic treatment in the postoperative period for pain that is not strictly related to the
surgical indication and which may confound the postoperative assessments.
9. Has a medical condition such that, in the opinion of the Investigator, participating in the study
would pose a health risk to the subject or confound the postoperative assessments. Conditions
may include, but are not limited to, the following:
a. History of allergic reactions to bupivacaine or excipients or BR-003, or if the

investigational product is otherwise contra-indicated
b. ASA-classification >3, as assessed during the most recent pre-operative screening.
c. Clinically significant renal or hepatic abnormalities (defined as an AST or ALT > 3x
Upper limit of normal (ULN), creatinine > 2x ULN)
d. History of clinically significant cardiac abnormality such as myocardial infarction within
6 months prior to study participation, NYHA class III or IV, or clinically significant
abnormalities on ECG
e. History of coronary artery bypass graft surgery within 12 months prior to study
participation
10. Uncontrolled anxiety, schizophrenia, or other psychiatric disorder that, in the opinion of the
Investigator, could interfere with study assessments or compliance
11. A body mass index (BMI) > 39 kg/m2 or patients with a weight below 50 kg
12. History of, suspected, or known addiction to or abuse of illicit drug(s), prescription medicine(s),
or alcohol
13. As per subject history and/or medical records, has active infection or is currently undergoing
treatment for Hepatitis B, Hepatitis C, or human immunodeficiency virus (HIV)
14. Participation in another interventional study

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-05-2023
Enrollment:	6

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BR-003
Generic name:	Bupivacaine implantation matrix

Ethics review

Approved WMO Date:	07-12-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-01-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-516338-37-00
EudraCT	EUCTR2022-001069-11-NL
CCMO	NL81348.056.22