Phase III confirmatory efficacy and safety trial of remimazolam (CNS7056) compared with propofol for intravenous anaesthesia during elective surgery

Published: 23-05-2018
Last updated: 11-04-2024

Primary ObjectiveThis is a confirmatory trial to establish non-inferior efficacy of remimazolam compared with propofol for induction and maintenance of GA for the purpose of elective surgery in patients classes III and IV based on the American…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON48984

Source
ToetsingOnline

Brief title
CNS7056-022

Condition

- Other condition

Synonym
sedation, unconsciousness

Health condition

General anesthesia

Research involving

Human

Sponsors and support

Primary sponsor: PAION UK Limited
Source(s) of monetary or material Support: PAION UK Limited;commercial Sponsor of the study

Intervention

Keyword: anaesthesia, CNS7056, remimazolam

Outcome measures

Primary outcome

The primary efficacy endpoint (PEP) is the anaesthetic effect of remimazolam and propofol assessed as percent (%) of time of Narcotrend (NCT) Index *60 during the maintenance phase of the GA defined as the time between the first skin incision and the completion of the last skin suture.

Secondary outcome

The key secondary endpoint (KSE) is haemodynamic instability defined as critical decrease(s) in mean arterial blood pressure (MAP) between start of IMP and 15 minutes after the first skin incision.

For this endpoint, each event from the following categories will be counted and summed up per patient:

* Incidence of MAP dropping below 65 mmHg for at least 1 minute duration

* Incidence of a MAP decrease of more than 20% below the calculated (mean) baseline MAP value for at least 1 minute duration

* Incidence of a MAP decrease of more than 30% below the calculated (mean) baseline MAP value for at least 1 minute duration

* Number of norepinephrine boluses (0.01 mg) required or, if an infusion is

used to maintain MAP equal to or above 65 mmHg, then each time interval of 2 minutes duration of continuous norepinephrine infusion will be counted as one event.

The baseline MAP is calculated based on all blood pressure (BP) measurements that are taken after signing the informed consent form (ICF) and before arrival at the operation room (OR) suite.

This endpoint is a safety endpoint.

Other secondary endpoints for efficacy comprise

* Percentage of time of NCT index (NCI) *60 and *27 during the maintenance phase

* Percentage of time of NCI <27 during the maintenance phase

Percentage of patients with NCI *60 and *27 during *90% of the maintenance phase

* Percentage of patients who were administered rescue sedative medication

* The occurrence of intra-operative awakening (explicit awareness)

* Time from start of IMP to first NCI *60

* Time from start of IMP to loss of palpebral reflex

* Time from start of IMP to loss of consciousness (LOC, i.e., modified observer*s assessment of alertness / sedation [MOAA/S] = 0)

* Time from stop of IMP to response to verbal command (MOAA/S *4)

* Time from stop of IMP to end of extubation

* Time from stop of IMP to orientation to time, place, person and situation

* Time from stop of IMP to Modified Aldrete Score *9

* Investigator*s overall satisfaction with IMP

Other secondary endpoints for safety comprise

* Treatment-emergent adverse events (TEAEs)

* Events of hypotension from start of IMP until end of surgery (= completion of last skin suture)

o MAP drop below 65 mmHg for at least 1 minute duration

o MAP decrease of more than 20% below the calculated (mean) baseline MAP value for at least 1 minute duration

o MAP decrease of more than 30% below the calculated (mean) baseline MAP value for at least 1 minute duration

o Number of norepinephrine boluses (0.01 mg) required or if an infusion is used to maintain MAP equal or above 65 mmHg, then each time interval of 2 minutes duration of continuous norepinephrine infusion will be counted as one event for at least 1 minute duration

Events of bradycardia

o Heart rate (HR) below 45 beats per minute (bpm) for at least 1 minute duration

o HR decrease of >20% below the calculated (mean) baseline HR value for at least 1 minute duration

o HR decrease of >30% below the calculated (mean) baseline HR value for at least 1 minute duration

o Number of glycopyrrolate injections (0.2 to 0.4 mg as needed)

* Physical examination

* Laboratory parameters of haematology, biochemistry, coagulation and urinalysis

* Vital signs including parameters measured by FloTrac

* 12-lead electrocardiograms (ECGs)

* 3-lead ECG or 5-lead ECG

* Oxygen saturation

* Pain on injection of IMP

* Concomitant medications

* Patient's cognitive function assessed by the 3D-Confusion Assessment Method-S

score

Study description

Background summary

Phase III confirmatory efficacy and safety trial of remimazolam (CNS7056) compared with propofol for intravenous anaesthesia during elective surgery. European centres with a high volume of general anaesthesias (GA) provided each year are eligible for this trial. Up to 22 European trial centres will be initially selected. Each participating centre should have the potential to recruit 50 patients or more into the trial.

Study objective

Primary Objective
This is a confirmatory trial to establish non-inferior efficacy of remimazolam compared with propofol for induction and maintenance of GA for the purpose of elective surgery in patients classes III and IV based on the American Society of Anesthesiologists (ASA) physical status.
Key Secondary Objective
This is a confirmatory trial to establish superior haemodynamic stability associated with use of remimazolam compared with propofol for the induction and maintenance of GA for the purpose of elective surgery.

Study design

A prospective single-blind, randomised, controlled, confirmatory multi-centre, parallel group trial comparing remimazolam with propofol for induction and maintenance of GA during elective surgery.

Intervention

Remimazolam (CNS7056) and the comparator propofol are the Investigational Medicinal Products (IMPs).
In total, approx. 452 patients will be randomised with the following split into 2 groups:
* 339 patients will be randomised to remimazolam

* 113 patients will be randomised to propofol
A stratified randomisation system will be used to ascertain a randomisation ratio of 3:1 in each of the 2 subgroups ASA III and ASA IV in each trial centre.

Study burden and risks

The maximum trial duration for any patient will be up to 30 days. Patients will be screened within 28 days prior to the scheduled day of surgery (= Day 1). Trial follow-up procedures will be performed on Day 2.
This trial investigates the use of remimazolam as an intravenous anaesthetic to provide GA for the purpose of elective surgery in patients with ASA classes III to IV.
To provide sufficient sedation and analgesia, IMP is co-administered with remifentanil 0.2 *g/kg/min during induction of GA. During maintenance of GA, IMP is to be co-administered with remifentanil in the range of 0.2 to 0.5 *g/kg/min and the NCI is to be kept between *40 and *60. To achieve this goal, IMP can be titrated within predefined ranges. Towards the end of the surgery, IMP is to be tapered so that the NCI is *60 until completion of the last skin suture. Immediately after the completion of the last skin suture, IMP and remifentanil are to be stopped with the aim to extubate the patient as soon as possible.

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 trial, an individual must meet all of the following criteria:
* Male or female ASA III / IV patients, at least 18 years old, scheduled for an elective surgical procedure of a minimum duration of approximately 90 minutes under GA and planned to be extubated immediately post-operatively
* Total intravenous GA with the requirement for mechanical ventilation via endotracheal tube and necessary invasive BP monitoring either due to severity of illness, severity of concomitant diseases, type of surgery or decisions of the anaesthesia staff.
* Patients scheduled to stay in the hospital long enough after the surgical procedure to perform all trial follow-up procedures (~1 day)
* For female patients of childbearing potential: Negative results of 2 pregnancy tests, the first test taken at the start of Screening and the second test taken shortly before the start of the administration of the IMP as well as consent to use highly effective birth control from the last menstrual cycle prior to the start of the IMP until the end of the trial follow-up procedures. Highly effective methods of birth control include:
o Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
- Oral / intravaginal / transdermal
o Progestogen-only hormonal contraception associated with inhibition of ovulation:
- Oral / injectable / implantable
o Intrauterine device (IUD)
o Intrauterine hormone * releasing system (IUS)
o Bilateral tubal occlusion
o Vasectomised partner (provided that the partner is the sole sexual partner of the female patient of childbearing potential and that the vasectomised partner has received medical assessment of the surgical success).
o Sexual abstinence
Women who had their last menstruation at least two years ago or who underwent surgical interventions (surgical birth control, bilateral oophorectomy,

hysterectomy, etc.) are regarded as having no childbearing potential.

Exclusion criteria

- Patients scheduled for spinal anaesthesia, epidural anaesthesia (central neuroaxial anaesthesia) or regional anaesthesia. The placement of a peridural catheter with a test dose application of a local anaesthetic drug (up to 5 mL) to verify correct positioning to achieve post-operative analgesia and the regional administration of local anaesthetic for postoperative analgesia after wound closure (after the last skin suture) is accepted.
- Patients undergoing transplant surgery, cardiac surgery, or intracranial neurosurgery, patients which have to be in prone position for surgery, emergency surgery, or any surgical procedure with the need for or scheduled for post-operative ventilator support
- Patients undergoing surgical procedures that require keeping the BP at a high level, e.g. surgical procedures in beach chair position
- Patients with severe hypertension, i.e., one baseline result of systolic BP 200 mmHg or more and / or diastolic BP of 120 mmHg or more. Baseline is defined as the time after signature of ICF and before arrival in the OR suite.
- Patients with total bilirubin of *3.0 mg/dL or *3 times increase in aspartate aminotransferase or alanine aminotransferase as per reference range in laboratory tests which must be checked within the 7 days prior to start of IMP, or any other laboratory results that make the patient unsuitable for the trial.
- Patients with end-stage renal disease requiring scheduled dialysis
- Patients with known anaphylactic reactions to benzodiazepines, propofol, opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), dextran, neuromuscular blocking agents, flumazenil, naloxone, or other anaesthetic agents, or a medical condition such that these agents are contraindicated (according to local label) Patients with allergy/hypersensitivity to bovine lactose, dextran or any other excipient in the remimazolam product.
- Presence of acute alcoholic or illicit drug intoxication, shock or coma state
- Known current dependency on or regular use of central nervous system depressant drugs or alcohol
- Patients with gastroparesis or delayed gastric emptying, gastric reflux or any other increased risk for gastric aspiration
- Patients with an anticipated (small mouth opening, impaired neck movement, goitre, head and neck tumours or any other anatomical reason) or known airways difficulties, known difficulties in airway maintenance or mask ventilation.
- Patients in whom NCT may not provide results due to organic defect of the brain or forehead, or any neurologic disease interfering with the EEG monitoring
- Patients on treatment with valproate
- Any pregnant or breast-feeding patient
- Patients who participated in any clinical trial within 30 days or 5 times the half-life of the drug under investigation in any other clinical trial, whichever is longer, prior to the beginning of administration of the IMP.

Exception: Non-interventional trials as defined in the European Clinical Trials Directive 2001/20/EC: A trial where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the
patients and epidemiological methods should be used for the analysis of the collected data.
- Any patient judged to lack the ability to give informed consent or perform the trial assessments (e.g., due to dementia)
- Any patient judged by the principal investigator (PI) or subinvestigator to be inappropriate for the trial for any other reason
- Planned use of forbidden concomitant medication

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-10-2018
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Propofol
Generic name:	Propofol
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Remimazolam
Generic name:	Remimazolam

Ethics review

Approved WMO Date:	23-05-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-10-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-10-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-11-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-12-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-12-2018

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-05-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-12-2019
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
EudraCT	EUCTR2018-000174-29-NL
CCMO	NL65841.056.18