A phase II, two-part, multiple-dose, dose-finding, single-blind study to investigate the safety and efficacy of ABP-700 for procedural sedation in adult patients undergoing colonoscopy

Published: 04-04-2016
Last updated: 16-04-2024

Trial objectives* To assess the dose-response relationship, efficacy and safety of ABP-700 for procedural sedation in adult patients undergoing colonoscopy.* To quantify the pharmacodynamic effect of ABP-700 including time to procedure start,...

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

Summary

ID

NL-OMON45846

Source
ToetsingOnline

Brief title
MDCO-ABP-15-01

Condition

- Other condition

Synonym
not applicable

Health condition

sedatie

Research involving
Human

Sponsors and support

Primary sponsor: Medicines Company
Source(s) of monetary or material Support: The Medicines Company

Intervention

Keyword: ABP-700, Colonoscopy, Pharmacodynamics, Sedation

Outcome measures

Primary outcome

Efficacy endpoints:

* Number of successfully completed procedures by assigned ABP-700 infusion

dose. Success defined as patients who meet the following 2 criteria:

- Procedure completion

- No significant respiratory depression as assessed by oxygen saturation

decrease to less than 90% and no need for assisted positive pressure

ventilation (manual or mechanical)

* Number of successfully completed procedures (as above) by assigned ABP-700

infusion dose with and without bolus ABP-700 adjustment

* Number of successfully completed procedures by assigned ABP-700 infusion dose

with and without bolus ABP-700 adjustment that require or do not require rescue

sedative medication.

* Time to procedure start

* Depth and duration of sedation

* Number of supplemental ABP-700 bolus doses required

Recovery from sedation and discharge conditions as assessed by the Modified

Aldrete score (APRS)

Safety endpoints:

* Quantification of hemodynamics to include frequency of adverse events and change from baseline for heart rate, blood pressure and ECG parameters (e.g. QTc)
* Frequency of MOAA/S <3 (deep sedation events)
* Frequency of respiratory depression (< 8 breaths per minute), arterial desaturation (SpO2 < 90%), apnea (> 30s) and patients who require maneuvers to open or maintain the airway (e.g. chin lift, jaw thrust) and any mechanical or hand assisted ventilatory support'
* Frequency of injection site reactions
* Frequency of (S)AEs
* Frequency of clinically relevant laboratory findings (hematology, biochemistry)

Exploratory endpoints:

* Patient satisfaction with the procedure
* Proceduralist satisfaction (endoscopist and anesthesiologist)
* Procedural recall as measured by the Modified Brice questionnaire

Time to full cognitive recovery as measured by PQRS (cognitive domain only)

Secondary outcome

N.A.

Study description

Background summary

Phase I testing of ABP-700 alone and with remifentanil co-infusions in healthy subjects have shown the ability to produce consistent dose dependent sedation effects with conditions favorable for procedural care including minimal involuntary muscle movement, stable hemodynamics and little respiratory depression. When ABP-700 is given as a single-stage 30-minute continuous infusion, a delay (> 10 minutes) was observed in the attainment of arterial steady state plasma concentrations and stable clinical effect. Subsequent testing showed that a dual stage *step down* infusion methodology quickly achieved and maintained plasma concentrations required to produce a desired clinical effect while also minimizing the peak plasma concentrations produced during bolus administration. With these dual stage infusions, steady state arterial plasma concentrations were attained in 3-4 minutes and thereafter maintained steady state concentrations of approximately ± 10-15% of the target plasma concentration over the course of a 30-minute infusion. This study aims to test various dual stage infusion regimens which are intended to produce a range of clinical sedation effects in order to determine their ability to support procedural care when the procedural stimulation profile is generally uniform and of low-moderate intensity.
To confirm the dose- and presumed effect-site concentration of ABP-700 versus effects and adverse reaction in patients stimulated by invasive procedures, this study will be performed in subjects undergoing routine colonoscopy with ABP-700 dosages that replicate the range of presumed effector-site concentrations of the phase I studies. Patients undergoing colonoscopy are expected to demonstrate variability of tolerance to discomfort and variability of response. Therefore the study will include administration of additional MDCO-700 given as bolus doses when needed to ensure patient comfort and the opportunity for completion of colonoscopy

Study objective

Trial objectives
* To assess the dose-response relationship, efficacy and safety of ABP-700 for procedural sedation in adult patients undergoing colonoscopy.
* To quantify the pharmacodynamic effect of ABP-700 including time to procedure start, sedation depth, patient recovery and readiness for discharge
* To quantify the cardio-respiratory effects of sedation doses of ABP-700

Exploratory objectives
* To determine endoscopist and anesthesiologist satisfaction with the procedure
* To determine patient satisfaction with the procedure
* To determine patient procedural recall.

* To evaluate cognition and memory function of the patient

Study design

This is a phase II two-part, multiple dose, dose-finding, single-blind study in adult patients undergoing elective colonoscopy for screening or diagnostic purposes. This study is designed to test various ABP-700 infusion regimens for rational selection of one or more dosage regimen(s) to be used for future clinical development of ABP-700 in procedural sedation. It is also intended to quantify pharmacodynamic effects, readiness for discharge, cognitive and memory function, both patient and provider satisfaction, and cardio-respiratory effects related to these dosing regimens

Intervention

Patients will provide written Informed Consent prior to undergoing any protocol related assessments or procedures, which may occur up to 14 days prior to or on the day of the scheduled colonoscopy. The anticipated duration of the colonoscopy is generally not expected to exceed 30 minutes.
After establishing eligibility during screening, and confirmed continued eligibility on the day of procedure, patients will be randomized in a 1:1:1 ratio to one of three ABP-700 infusion regimens (Part 1). ABP-700 regimens are fixed two-stage infusions. All patients will receive a concomitant remifentanil infusion beginning 5 minutes prior to the initiation of the ABP-700. Both the ABP-700 and the remifentanil infusions will continue until procedure completion. Supplemental oxygen will be delivered at a rate of 2L/minute via nasal cannula. Patients will be dosed according to their assigned regimen.
Following the initiation of ABP-700 but prior to the start of the procedure (sedation initiation phase), patients will be evaluated for a minimum of 5 up to a maximum of 10 minutes. During this sedation initiation phase, patients should be calm, cooperative and without hemodynamic or tolerability issues that, in the opinion of the anesthesiologist or endoscopist, compromise the ability to start the procedure or patient safety. Once the provider has established that the procedure may begin, the procedure start time will be recorded. The start of the procedure is defined as the time of the digital rectal examination (DRE) or colonoscope insertion whichever comes first. During the sedation initiation phase, no other medications except the ongoing infusions of ABP-700 and remifentanil should be given. Dose adjustments should not be made during this time.
If at the end of the maximum10-minute sedation initiation period, the patient is without hemodynamic or tolerability issues, the procedure should begin. If a decision is made not to proceed with the assigned regimen, the reason(s) will be recorded and rescue midazolam may be administered in order to achieve adequate sedation and start the procedure. ABP-700 infusion will continue unless the decision to give rescue midazolam is due to safety or tolerability issues. If ABP-700 is discontinued, the patient will also immediately receive

rescue midazolam. The procedure will then be completed using institutional Standard of Care. The day of procedure and follow-up assessments will be completed in these treatment failure patients.
ABP-700 will be maintained according to the assigned dosing regimen for the duration of the procedure. After the start of the procedure, up to 2 supplemental ABP-700 bolus doses of 50 µg/kg are allowed at the discretion of the anesthesia provider to maintain conditions acceptable for procedure completion. These supplemental bolus doses can occur no more frequently than every 5 minutes with no more than 2 boluses allowed. If adequate sedation conditions cannot be maintained using supplemental ABP-700 doses, the anesthesiologist can administer alternative rescue midazolam as needed.
BIS and MOAA/S scores will be recorded beginning at least 1 minute prior to the start of remifentanil co-administration and will continue until the patient is considered fully recovered.
After the procedure has ended and the infusions have stopped, a patient is considered fully recovered once he/she has both a BIS > 70 and 3 consecutive MOAA/S scores of 5, each scored 1 minute apart. Within 15 minutes after full recovery, the patient, the anesthesiologist and the endoscopist will complete patient and clinical satisfaction instruments to determine satisfaction with the procedure.
Patients will subsequently be transferred to a recovery area for further evaluations until they are determined ready for discharge. Procedural recall will be measured by the Modified Brice questionnaire. Patient recovery will be assessed using the Modified Aldrete (APRS) recovery scoring system. Cognitive recovery will be measured using the cognitive domain of the Post-operative Quality Recovery Scale (PQRS).
Patients will be contacted by phone after 5-7 days for a follow-up.

Study burden and risks

Although respiratory status remains generally well preserved after both bolus dosing (ANVN-01 and ANVN-03) and infusion dosing (ANVN-02 and ANVN-01-04), both self limited episodes of respiratory depression and apnea have been reported with ABP-700. In the presence of co-infusions of remifentanil, apnea necessitating provider intervention has been reported.
Transient skeletal muscle contractions or IMM (i.e., muscle twitching and myoclonus) has also been observed with ABP-700. Low doses of fentanyl, midazolam or a combination of fentanyl and midazolam are effective at attenuating or eliminating these movements. Midazolam (0.015 mg/kg to 0.03 mg/kg) was effective in rapidly stopping (approximately 30 sec to 90 sec) any ABP-700-induced severe IMM.
IMM, ranging from mild twitching of the face, torso, and/or limbs to more extensive flexor/extensor jerking movements of the limbs (i.e., myoclonus) has been observed with ABP-700. In general, IMM was dose dependent, occurring with higher frequency and severity with higher doses. Pre-treatment with either fentanyl or midazolam or a combination of midazolam plus fentanyl decreased the frequency and severity of IMM following bolus dosing of ABP-700. Fentanyl

pre-treatment and remifentanil co-infusion decreased the frequency and severity of IMM following infusion dosing of ABP-700.
Airway patency and airway reflexes were preserved with ABP-700 and ABP-700 was not associated with clinically meaningful respiratory depression (i.e., oxygen saturation decrease or intervention required). Respiratory stability was also maintained when ABP-700 was dosed following pre-treatment with either an opiate, benzodiazepine, or combination of an opiate and benzodiazepine. Infrequent, short-lived and self-limited episodes of respiratory depression were seen with ABP-700 bolus dosing with these pre-treatments.
Apnea necessitating provider intervention (i.e., chin lift, jaw thrust, positive pressure mask ventilation) was seen with ABP-700 bolus dosing, infusion dosing, and infusion dosing in the presence of a continuous remifentanil co-infusion (0.05 *g/kg/min and 0.5 *g/kg/min).
Nausea has been reported with ABP-700 and was seen more frequently in subjects who received remifentanil either as a pre-treatment or a co-infusion. Nausea has been self-limited and a single dose of an anti-emetic (i.e., ondansetron), when treatment was required, has been effective at amelioration.
Mild injection/infusion site reactions at the site of administration have been observed with ABP-700.

Contacts

Public
Medicines Company

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patient must be male or female 18 - 75 years of age, inclusive.
2. Patient must give written informed consent before initiation of any study-related procedures
3. Patient is scheduled to undergo elective colonoscopy
4. BMI 18.0 * 29.0 kg/m2
5. ASA class I * II
6. Modified Mallampati score I * II

Exclusion criteria

1. Any ASA physical status III or worse, or history of one or more of the following:
- History or presence of significant cardiovascular disease including atrial fibrillation, or cardiovascular disease risk factors, hyperlipidemia, coronary artery disease, or any known genetic pre disposition to cardiac arrhythmia (including long QT syndrome, > 450 msec)
- History of any neurological or seizure disorder or psychiatric disease
- History or presence of significant pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic or dermatologic disease
- History of any illness that, in the opinion of the PI, might confound the results of the study or pose an additional risk to the patient by their participation in the study
2. History of any recent illness (e.g., upper respiratory infection) that does not satisfy ASA III or greater requirements but in the opinion of the PI, may pose an additional risk to the patient by their participation in the study.
3. Patients with a history of essential hypertension that are not well on controlled on medication and/or have been diagnosed with hypertension for less than 6 months and/or are not on stable therapy for at least 4 weeks prior to the study

Study design

Design

Study phase: 2

Study type:	Interventional
Masking:	Single blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-06-2016
Enrollment:	75
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ABP-700
Generic name:	ABP-700

Ethics review

Approved WMO Date:	04-04-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-04-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-10-2016

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-10-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-02-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-05-2017
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	EUCTR2015-004019-19-NL
CCMO	NL57064.056.16