A Double Blinded, Placebo Controlled, Crossover Infusion Study of Respiratory Pharmacodynamics of ENA-001 in Conjunction with Propofol, Hypoxia, and Hypercapnia

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Primary Objectives:* To determine the safety and tolerability of ENA-001 in healthy subjects after low and high doses of ENA-001 under hypoxic and hypercapnic conditions in conjunction with low and high doses of propofol.* To determine the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory disorders NEC
Study type	Interventional

Summary

ID

NL-OMON50050

Source
ToetsingOnline

Brief title
Crossover Study of the PD of ENA-001 and hypoxia

Condition

- Respiratory disorders NEC

Synonym
Breathing problems, Respiratory impairment

Research involving
Human

Sponsors and support

Primary sponsor: Enalare Therapeutics Inc.
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: ENA-001, Hypoxia, Pharmacodynamics, Propofol

Outcome measures

Primary outcome

Tolerability / safety endpoints

Safety will be evaluated based on reported adverse events, physical examinations, vital signs, 12-lead ECGs, clinical laboratory test results and Columbia-Suicide Severity Rating Scale (C-SSRS) responses.

Other parameters may be collected or derived with equipment used by the study center but will not be captured in the CRF. Values will be listed with descriptive statistics.

Pharmacodynamic endpoints

Included will be Hypoxic sensitivity (*Ventilation/*Saturation), tidal volume (VT), respiratory rate (breaths/min), minute ventilation (VE), end-tidal CO2 (mmHg), and transcutaneous hemoglobin saturation (SpO2 in %), arterial blood gases, BIS, and hemodynamic parameters from arterial line monitoring.

Secondary outcome

Pharmacodynamic endpoints

Included will be Hypoxic sensitivity (*Ventilation/*Saturation), tidal volume (VT), respiratory rate (breaths/min), minute ventilation (VE), end-tidal CO2

(mmHg), and transcutaneous hemoglobin saturation (SpO2 in %), arterial blood gases, BIS, and hemodynamic parameters from arterial line monitoring.

Blood Pressure and cardiac output will be recorded using arterial lines connected to continuous monitors and mean obtained at pre-specified time points. Time point specific and summarized results will be listed with descriptive statistics.

Pharmacokinetic endpoints

PK parameters will include, but will not be limited to, Cmax, Css, AUC; AUCinf, and Tmax, and if possible, t* for ENA-001, and potentially propofol.

PK/PD endpoints

EC50 and Emax for ENA-001 effects on ventilatory measurements as determined by PK/PD models may be determined.

Study description

Background summary

Interference with normal respiratory control is a common iatrogenic event in the peri-procedural setting. Interference with ventilatory control can be the result of a procedure (e.g., colonoscopy; surgery), drug treatment (e.g., anesthetic, benzodiazepine, opioid), disease (e.g., central/sleep apnea) or combinations of these factors. In the post-procedural setting, it is not possible to predict the onset, duration, or severity of deleterious respiratory events due to a number of contributing factors, including differing drug sensitivity and pharmacokinetics, occult pulmonary and central nervous system (CNS) dysfunction, environmental activity level, and concomitant medications.

Respiration is controlled largely in the brainstem with input from the cortex and peripheral nerves. Chemoreceptors exist in both the brainstem and

peripheral nerves that are sensitive to oxygen tension, carbon dioxide tension, pH, and other chemical stimuli. The primary peripheral sensors for hypoxia are the type I glomus cells in the carotid body at the bifurcation of the internal and external carotid arteries. Activation of several ion channels (e.g., BK, TASK-1, and TASK-3) in the glomus cells/carotid body leads to stimulation of the respiratory control arc (carotid body through carotid sinus nerve to brainstem nucleus tractus solitarius (NTS). The NTS integrates signals from the peripheral sensors (e.g., carotid and aortic body chemoreceptors, and airway mechanoreceptors) providing feedback loop control of central respiratory drive.

ENA-001 is intended to be a first in class, fast acting, and short-duration intravenous agent acting partially through the BK(Ca2+) (Maxi K channels) in the carotid body to stimulate respiration and increase minute ventilation by primarily increasing tidal volume and secondarily through minor increases in the respiratory rate. ENA-001 is being developed as an intravenous therapeutic agent for short to intermediate term use to stimulate ventilation for treatment of respiratory depression in post-operative patients while not acting through antagonism of mu-opioid receptors and not being a CNS stimulant.

Two common uses for short acting anesthetics in the hospital are: sedation facilitating diagnostic or therapeutic procedures (e.g., cardioversion, colonoscopy); and surgical interventions under general anesthesia. This study is designed to further evaluate the potential of ENA-001 on ventilation during anesthetics. Among short acting anesthetic agents, propofol is used widely by both anesthesiologists and proceduralists. Accompanying the benefits of propofol during procedures are undesired ventilatory effects with reduced respiratory drive and diminished neuromuscular tone in the upper airways.

Previous studies with this compound (Roozekrans, 2014), confirmed the stimulatory effects on respiratory function under hypercapnic ventilatory conditions and with co-administration of an opioid. This study aims to evaluate the ventilatory response after ENA-001 administration under hypercapnic and hypoxic ventilatory conditions and with co-administration of propofol. This design will lead to knowledge regarding the ventilatory response after propofol administration under different ventilatory conditions.

Study objective

Primary Objectives:
* To determine the safety and tolerability of ENA-001 in healthy subjects after low and high doses of ENA-001 under hypoxic and hypercapnic conditions in conjunction with low and high doses of propofol.
* To determine the ventilatory response (minute ventilation) of low and high doses of ENA-001 under hypoxic and hypercapnic conditions in conjunction with low and high doses of propofol. The hypoxic response will be assessed by calculation the Hypoxic Ventilatory Sensitivity. (*Ventilation/*Saturation = Hypoxic Sensitivity in L/min per % desaturation).

Secondary Objectives:
* To determine the cardiovascular response of low and high doses of ENA-001 during hypoxic and hypercapnic conditions in conjunction with low and high doses of propofol.
* To determine the ventilatory response (minute ventilation) of low and high doses of ENA 001 after previous treatment with low and high doses of propofol under normocapnic and mild hypercapnic conditions during normoxia.
* To determine the PK parameters of ENA-001 and propofol in healthy volunteers.

Study design

Subjects will be initially screened up to 6 weeks prior to randomization. Following successful initial medical screening at CHDR, they will be scheduled for the study and receive a randomization number.
Subjects will then undergo 3 separate treatment periods. In each of these periods, low or high doses of ENA-001 or placebo will be continuously perfused throughout for a period of 270 minutes. Additionally, subjects will receive different intravenous propofol dosages or placebo in set order: placebo * propofol low dose * propofol high dose. Each treatment session of propofol or placebo is 70-minutes. During each propofol treatment session, different ventilatory conditions are applied.

Intervention

ENA-001:
A loading dose will be administered at 2.0 mg/kg/h for 10 (for low dose) or 20 minutes (for high dose) for both the low and high dose followed by continuous infusion of the following for 250-260 minutes, so that the total infusion time is 270 minutes:
* Low dose is fixed rate of 2 mg/kg/h for 10 minutes followed by 0.4 mg/kg/h for 260 minutes or
* High dose is fixed rate of 2 mg/kg/h for 20 minutes followed by 1.1 mg/kg/h for 250 minutes

Propofol will be administered over a 155-minute period per dosing session, composed of two 70-minute low/high dosing regimens separated by a 15-minute transition dose. Propofol will be infused from a 10 mg/ml preparation as follows:
* Low dose: 3-min at 239 mcg/kg/min; 6-min at 0 mcg/kg/min; 61-min at 24 mcg/kg/min
* Transition dose: 15-min at 47 mcg/kg/min
* High dose: 3-min at 239 mcg/kg/min; 6-min at 0 mcg/kg/min; 61-min at 44 mcg/kg/min

Both products are for IV injection and are prepared as a sterile product ready

for use per subject by the investigational pharmacy, according to the randomization schedule.

Matching placebo for ENA-001 will consist of the solution that is used as diluent for ENA-001. ENA-001 solution is colorless and its identity (prior to dilution and when mixed for injection) is similar to sterile normal saline solution or Ringer*s lactate.

Study burden and risks

Both study drugs have been administered to humans before and no severe side effects are expected at planned doses in this study, based on clinical experience with propofol and previous studies with ENA-001. Study drugs will be administered while remaining under appropriate surveillance in the LUMC anesthesiology department. To adequately monitor important safety parameters, an arterial line is placed which is itself associated with minimal risks and unpleasantness. Because the study drugs may induce nausea, all subjects will receive IV ondansetron prior to infusion of the study drugs. Aadditional antiemetics may be administered as needed for management of nausea and vomiting. During the study drug infusion, ventilatory measurements are performed. For this, the subjects will breathe through a facemask, which may cause slight discomfort. The ventilatory conditions applied (hypo- and hyperoxia, and hypercapnia) may lead to slight discomfort, but are not associated with relevant risks, especially given the fact that the measurements are performed in a safe and controlled environment.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

The subject must meet ALL the criteria listed below for entry at baseline:
1. Subjects must be willing to give written informed consent for the trial and able to adhere to dose and visit schedules.
2. Male and female, >18 to *55 years of age.
3. Subject must weigh *50 to *100 kg.
4. Subjects must have Body Mass Index [weight/height2 (kg/m2)] between 18 to 30 kg/m2 (inclusive).
5. Have no clinical or electrocardiographic signs of ischemic heart disease as determined by the Investigator with normal cardiac intervals appropriate for their gender. The Screening 12 lead ECG conduction intervals must be within gender specific normal range (e.g., QTcf female * 470 msec QTcF males * 450 msec, PR interval * 220 msec). ECGs are to be judged by the investigator or sub-investigator as per standardized procedures.
6. Subjects* clinical laboratory tests (blood hematology, blood chemistry, coagulation and urinalysis) must not include any clinically significant abnormalities.
7. Vital sign measurements must be within the following ranges during screening and on Day -1: (Individuals with values outside (or indicate lower or higher) of these ranges may be enrolled if clinically acceptable to the investigator and sponsor.
a. body temperature, >35.5*C to *37.5*C
b. systolic blood pressure, >90 to *150 mm Hg
c. diastolic blood pressure, >40 to *95 mm Hg
d. pulse rate, >40 to *100 bpm
8. Non-vasectomized men must agree to use a condom with spermicide (when marketed in the country), double-barrier contraception, abstain from heterosexual intercourse, or have a sole-sexual partner of non-childbearing potential during the trial and for 3 months after stopping the medication. Male subjects must agree not to donate sperm from the time of dosing until 90 days after dosing.

9. Women of childbearing potential (defined as all women who are not surgically sterile or postmenopausal for at least 1 year prior to informed consent) must have a negative pregnancy test prior to enrolment and must agree to the following contraception requirement from screening through at least 3 months after the last dose of study drug:
a. Be sexually inactive (abstinent)
b. Intrauterine device in place for at least three months prior to dosing with a barrier method (condom or diaphragm) and spermicide throughout the study.
c. Double barrier methods (e.g., condom and diaphragm) with spermicide for at least 14 days prior to dosing and throughout the study.
d. Surgical sterilization of the partner (vasectomy at least six months prior to dosing) with a barrier method (e.g., condom or diaphragm) and spermicide throughout the study.
e. Female subjects who claim to be sexually inactive but become sexually active during the course of the study must agree to use a double barrier method (e.g., condom and diaphragm) with spermicide from the time of the start of sexual activity through completion of the study.
In addition, female subjects of childbearing potential must be advised to remain sexually inactive or to keep the same birth control method for at least 14 days following study medication administration.
Females of non-childbearing potential must have undergone one of the following sterilization procedures at least 6 months prior to dosing:
f. Hysteroscopic sterilization and be using a barrier method (e.g., condom or diaphragm) and spermicide throughout the study.
g. Bilateral tubal ligation or bilateral salpingectomy and be using a barrier method (e.g., condom or diaphragm) and spermicide throughout the study.
h. Hysterectomy.
i. Bilateral oophorectomy.
Women with amenorrhea for at least 1 year prior to dosing and who have follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status, are considered post-menopausal and therefore of non-childbearing potential.
10. Subjects must be free of any clinically significant disease that would interfere with the study evaluations.

Exclusion criteria

The subject will be excluded from entry if ANY of the criteria listed below are met at baseline:
1. Current diagnosis of psychiatric disease requiring daily medication, including controlled or uncontrolled schizophrenia, current or recently treated depressive disorders, or Columbia-Suicide Severity Rating Scale (C-SSRS) indicative of suicidal ideation or behavior at screening and day -1.
2. Past history of the anxiety disorder including panic attack, depression, obsessive compulsive disorder, phobias restricting normal daily function,

social anxiety, and paranoia.
3. History of alcohol abuse (more than an average of 2-drinks per day) within the past 2 years.
4. History of drug abuse within the past 2 years.
5. History of regular smoking within the past year (>5 per week means exclusion).
6. Failure to take or test positive of the drug of abuse tests at screening or check-in.
7. Positive for HIV, or Hepatitis B or C at screening.
8. Blood donation or blood loss within 60 days of screening or plasma donation within 7 days of screening.
9. Subjects with a history of bleeding disorders or coagulopathies.
10. History of dyspnea, asthma, tuberculosis, chronic obstructive pulmonary disease, sleep apnea or any other ventilatory / lung disease.
11. Treatment with another investigational drug within 3 months prior to screening or having participated in more than four investigational drug studies within 1 year prior to screening.
12. History of moderate to severe motion sickness.
13. Subjects who are unwilling to remove excessive facial hair preventing sealing of the occlusive face mask.
14. Subjects who, in the opinion of the investigator, will not be able to participate optimally in the study.
15. Any surgical or medical condition which might significantly alter the distribution, metabolism or excretion of any drug. The investigator should be guided by evidence of any of the following, and be discussed with the sponsor prior to enrollment into the trial:
a. history of pancreatic injury or pancreatitis;
b. history or presence of liver disease or liver injury;
c. history or presence of impaired renal function as indicated by clinically significant elevation in creatinine, BUN/urea, urinary albumin, or clinically significant urinary cellular constituents ; or
d. history of urinary obstruction or difficulty in voiding.
16. Subject who has a history of any infectious disease within 4 weeks prior to drug administration that in the opinion of the investigator, affects the subject*s ability to participate in the trial.
17. Subjects who are part of the study staff personnel or family members of the study staff personnel.
18. Subjects who have demonstrated allergic reactions (e.g., food, drug, atopic reactions or asthmatic episodes) which, in the opinion of the investigator and sponsor, interfere with their ability to participate in the trial.
19. Subjects who have a history of malignancy and are in remission >2 years.
20. Personal or family history of malignant hyperthermia.
21. Personal or family history of arrhythmias or ECG conductance abnormalities.
22. Subjects with a history of daily consumption of caffeine greater than 6 servings (40 mL each) from beverages (e.g., coffee, tea, soft drinks) and food stuffs (e.g., chocolate, ice cream, cookies) (45 gm each) in the month prior to screening.

23. Subjects with history of known difficult airway access, gastroesophageal reflex disease, gastric motility disorders, or delayed gastric emptying, or any condition that may lead to delayed gastric emptying such as diabetes.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-09-2021
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ENA-001
Generic name:	NA
Product type:	Medicine
Brand name:	N.A.
Generic name:	Propofol
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	30-06-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-08-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-10-2021
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

ID: 24789
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2021-003013-19-NL
CCMO	NL78153.056.21
OMON	NL-OMON24789