Crossover Study of the PD of ENA-001 and hypoxia.

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON24789

Source
NTR

Brief title
CHDR2119

Health condition

Respiratory impairment

Sponsors and support

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

Intervention

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 (ΔVentilation/ΔSaturation), 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 (ΔVentilation/ΔSaturation), 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, AUC; AUCinf, and Tmax, and if possible, t½ 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

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 design

Up to -42 days till EOS + 7 days

Intervention

ENA-001 (3-way crossover):
• 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

• Placebo identical to active treatment for 270 minutes

Propofol will be administered in set order (open-label) for three 70-minute periods during each ENA-001/placebo treatment session, through TCI (target-controlled infusion):
• Placebo (no infusion)
• Low dose is 600 ng/ml
• High dose is 1200 ng/ml

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.

Contacts

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Eligibility criteria

Inclusion criteria

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 ≥60 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 be within normal limits or clinically acceptable to the investigator. However, subject's liver function test results (i.e., AST, ALT) must not be elevated >2x above the normal limits at Screening and on Day -1.
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.
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 use a medically acceptable means of contraception (double barrier) from screening through at least 3 months after the last dose of study drug, abstain from heterosexual intercourse or have a sole-sexual partner that is vasectomized.
10. Subjects must be free of any clinically significant disease that would interfere with the study evaluations.
11. Subjects presenting out of range values of lab/ECG/vital signs compatible with normal variation of the normal healthy subject can be included in the study at the investigator's discretion and sponsor written approval.

Exclusion criteria

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 <5 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.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	25-08-2021
Enrollment:	12
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Plan description
Undecided

Ethics review

Positive opinion

Date:	27-08-2021
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 50050
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL9692
CCMO	NL78153.056.21
OMON	NL-OMON50050

Study results

Summary results
N.A.