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Danavorexton in healthy volunteers receiving an opioid

Submission date
13/04/2022

Recruitment status
No longer recruiting

Registration date
20/04/2022

Overall study status
Completed

Last Edited
24/06/2025

Condition category
Respiratory

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Danavorexton is a new compound that is central to the control of arousal and wakefulness. Clinical studies with sleep-deprived healthy volunteers and patients with sleep disorders have demonstrated that danavorexton administered into a vein was well-tolerated and improved wakefulness. The aim of this study is to assess the safety, tolerability, pharmacokinetics (how the body affects the drug), and pharmacodynamics (how the drug affects the body) of danavorexton in healthy volunteers undergoing opioid-induced respiratory depression (OIRD), and to assess the effect of danavorexton on OIRD. The information obtained from the present study may become beneficial to patients who have OIRD in the future.

Who can participate?
Healthy male volunteers aged 18 to 55 years

What does the study involve?
Participants will receive single low and high dose danavorexton or placebo (dummy drug) on two separate occasions.

What are the possible benefits and risks of participating?
The most common nonserious side effects (occurring in more than 5% of subjects) reported in clinical trials with danavorexton include the following: nausea or feeling like vomiting, increased blood pressure, and an increased need to urinate. These side effects were categorized as mild or moderate, and no serious side effects occurred in any participant. Participants may also experience side effects from remifentanil which will be used to induce OIRD. Some side effects of remifentanil include: blurred vision, chest pain, confusion, dizziness or feeling lightheaded when getting up, irregular breathing (too fast or too slow), irregular heartbeat, chest pain, muscle stiffness, sweating or unusual tiredness. There are no direct benefits from participating.

Where is the study run from?
Leiden University Medical Center (Netherlands)

When is the study starting and how long is it expected to run for?
March 2021 to May 2022

Who is funding the study?
Takeda (USA)

Who is the main contact?
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Contact information

Type(s)
Principal Investigator

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Additional identifiers

EudraCT/CTIS number
2021-003869-35

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
TAK-925-1021

Study information

Scientific Title
A randomized, double-blind, placebo-controlled, two-way crossover, Phase I study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of danavorexton in healthy subjects undergoing opioid-induced respiratory depression

Acronym
TAK-925-1021

Study objectives
The purpose of this study is to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of danavorexton in healthy subjects undergoing opioid-induced respiratory depression (OIRD) as well as to assess the effect of danavorexton on OIRD.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 26/01/2022, Stichting BEBO (Dr. Nassaulaan 10, 9401 HK Assen, Netherlands; +31 (0) 592 40 58 71; info@stbebo.nl), ref: not applicable

Study design
Single-center randomized double-blind placebo-controlled crossover trial

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Other

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Opioid-induced respiratory depression

Interventions
Participants will receive sequentially single intravenous (IV) low- and high-dose danavorexton or placebo on two separate occasions. On study days 1 and 3, participants will stay at the hospital for several hours after each infusion has completed and will be monitored to ensure they are stable post-opioid and TAK-925 infusions. They can then be discharged home. After day 3 there is a virtual follow up on day 9 but no further planned in-person visits. Dosages cannot be disclosed as per sponsor requirements. Randomization is performed by a designee of the sponsor prior to the start of the study.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Danavorexton

Primary outcome measure
Safety and tolerability will be assessed by the number of subjects with at least one treatment-emergent adverse event (TEAE) at any timepoint during the study

Secondary outcome measures
Plasma concentrations of danavorexton are measured using high-performance liquid chromatography tandem mass spectrometry (HPLC-MS-MS) at 15 different timepoints after infusion until 9 hours after the start of the infusion. The following PK parameters of danavorexton will be estimated:
1. Observed plasma concentration at the end of infusion (Ceoi)
2. Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUClast)
3. Area under the plasma concentration-time curve from time 0 to infinity (AUC∞)

Overall study start date
25/03/2021

Completion date
20/05/2022

Eligibility

Key inclusion criteria
1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements
2. The subject reviews, and signs and dates an informed (electronic) consent form, in addition to any required privacy authorization, before the initiation of any study procedure
3. The subject is male and aged 18 to 55 years, inclusive, at the screening visit
4. The subject is a current nonsmoker who has not used tobacco- or nicotine-containing products (e.g., nicotine patch) for at least 6 months before the administration of the study drug.
5. The subject has regular sleep-wake habits (e.g., routinely spends 6.5 to 9 hours in bed nightly) and regularly goes to bed between 9:00 PM and 1:00 AM, as determined by investigator interviews
6. A male subject must meet the following birth control requirements:
6.1. For a male subject who is sterile: no restrictions are required for a vasectomized male subject, provided the subject is at least 1-year postbilateral vasectomy procedure before the first dose of the study drug. If a vasectomy procedure was performed less than 1 year before the first dose of the study drug, the male subject must follow the same restrictions as a male that has not had a vasectomy/sterilization (below). Appropriate documentation of surgical procedures should be provided.
6.2. For a male subject who is nonsterilized: if sexually active with a female partner of childbearing potential, the subject must agree to use an appropriate method of contraception, including a condom with or without spermicidal cream or jelly. These precautions will begin from the administration of the study drug until 5 half-lives plus 90 days after the administration of the study drug.
6.3. Male subjects must agree to not donate sperm from the time of study drug administration until 5 half lives plus 90 days after the administration of the study drug
7. The subject has a BMI ≥18 and ≤32 kg/m² at the screening visit
8. The subject must be judged to be in good health based on the results of safety laboratory tests (biochemistry, hematology, and urinalysis testing) performed at the screening visit and on medical history, physical examination, vital sign measurements, and 12-lead ECG performed at screening and baseline assessments.
9. The subject has no history of hypertension or use of antihypertensive medication. BP must be <140 mmHg (systolic) and <90 mmHg (diastolic); subjects will have a heart rate within the range

of 50 to 90 beats per minute at the screening visit. BP will be averaged over three readings that are done 10 minutes apart.
10. The subject agrees to refrain from taking excluded medications, vitamins, supplements or dietary products listed in the protocol during the study

Participant type(s)
Healthy volunteer

Age group
Adult

Lower age limit
18 Years

Sex
Male

Target number of participants
16

Total final enrolment
13

Key exclusion criteria
1. The subject has received treatment with another investigational drug within 3 months before screening, or the subject participated in more than four investigational drug studies within 1 year before screening
2. The subject received immunotherapy within the past year
3. The subject has facial hair that could interfere with the seal of a facemask (per investigator or site staff judgment) and is unwilling to shave it off before check-in
4. The subject has a positive test result for hepatitis B surface antigen, HCV, HIV antibody /antigen, or syphilis serum reaction test at screening. Note: subjects with positive HBV or HCV serology may be enrolled if quantitative polymerase chain reaction for HBV or HCV viral RNA is negative
5. The subject has a risk of suicide according to endorsement of Item 4 or 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at the screening visit or has made a suicide attempt in the previous 6 months
6. The subject has a positive alcohol or drug screen at screening or check-in, has a history of alcohol consumption exceeding 2 standard drinks per day on average within the 12 months before screening, or has a history of opioid abuse
7. The subject has caffeine consumption of more than 400 mg/day for 2 weeks before screening (one serving of coffee is approximately equivalent to 100 mg of caffeine).
8. The subject has a screening ECG with a QT interval with Fridericia correction method (QTcF) >450 ms

Date of first enrolment
10/03/2022

Date of final enrolment
08/05/2022

Locations

Countries of recruitment
Netherlands

Study participating centre
Leiden University Medical Center
Albinusdreef 2
Leiden
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2333ZA

Sponsor information

Organisation
Takeda (United States)

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Sponsor type
Industry

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Funder(s)

Funder type
Industry

Funder Name
Takeda Pharmaceuticals U.S.A.

Alternative Name(s)
Takeda, Takeda Pharmaceuticals U.S.A., Inc., Takeda Pharmaceutical Company Limited, Takeda Pharmaceuticals America, Inc., Takeda in the U.S., TPUSA

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
20/04/2023

Individual participant data (IPD) sharing plan
Separate data sharing agreements will be set up in case someone is requesting the data. Please contact Prof. Albert Dahan (a.dahan@lumc.nl).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		01/04/2025	24/06/2025	Yes	No