A dose-ascending, parallel group, randomised, double-blind, placebo-controlled pilot phase followed by a parallel group, randomised, double-blind, placebo-controlled phase to compare the effect of intravenous MR30507/09, MR30365/07 and fentanyl on respiratory responses, and an assessment of naloxone reversal and naltrexone blockade on MR30507/09 and MR30365/07 in healthy subjects

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This study is intended to establish a dose response rate of MR30507/09 with respect to respiratory effects compared to MR30365/07, fentanyl and placebo..

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

Summary

ID

NL-OMON39546

Source
ToetsingOnline

Brief title
MR30507/09 respiratory response pilot study

Condition

- Other condition

Synonym
Respiration

Health condition

ademhaling

Research involving
Human

Sponsors and support

Primary sponsor: Mundipharma Research Limited
Source(s) of monetary or material Support: Mundipharma Research Limited;Verenigd Koninkrijk

Intervention

Keyword: MR30507/09 / MR30365/07, naloxone reversal, naltrexone blockade, respiration

Outcome measures

Primary outcome

• To determine the effect of MR30507/09 on ventilation in healthy subjects using the dynamic end-tidal forcing technique. • To obtain a dose-response relationship for the respiratory response effects of MR30507/09 and to compare this relationship with that of MR30365/07. • To assess MR30507/09 and MR30365/07 induced respiratory depression reversibility using naloxone IV injection.

Secondary outcome

• To assess the safety and tolerability of MR30507/09 and MR30365/07. • To assess the PK of MR30507/09 and MR30365/07. • To assess arterial vs venous

blood sampling in the concentration effect model.

Study description

Background summary

The characteristics of MR30507/09 as an opioid analgesic will be investigated in an extensive clinical study programme by Mundipharma Research Ltd. The initial clinical studies will be performed in healthy volunteers with low intravenous doses.

Study objective

This study is intended to establish a dose response rate of MR30507/09 with respect to respiratory effects compared to MR30365/07, fentanyl and placebo..

Study design

A dose-ascending, parallel group, randomised, double-blind, placebo-controlled pilot phase followed by a parallel group, randomised, double-blind, placebo-controlled main phase. A separate single-dose, two-part, randomised, double-blind crossover phase will assess the ability of intravenous (IV) naloxone to reverse respiratory depression induced by MR30365/07 and MR30507/09 given as a 10 minute IV infusion. Subjects are not allowed to participate in more than one study phase. There will be a minimum 7-day washout between study drug doses in the naloxone phase. Subjects will be confined to the study unit from the morning of study drug administration (Day 1) until post-dose assessments are completed in each study period (24 hours post-dose). Subjects will be discharged from the study unit after clinical assessment by the investigator; this post dose observation period may be extended up to 48 hours or longer when necessary. Subjects will return to the study unit for a post-study medical 4-7 days after receiving their last dose of study drug.

Intervention

A single 10 minute infusion of study drug will be administered to each subject. Each dose of study drug will be given to subjects in a semi-supine position. Pilot phase: Each subject in each cohort will receive a single infusion of MR30507/09 (µg/kg) or placebo.In each cohort 4 subjects will be dosed (ug/kg). MR30507/09Cohort 1 MR30507/090.2 ug/kg (n=3) placebo (n=1) Cohort 2 MR30507/090.5 ug/kg (n=3) placebo (n=1) Cohort 3 MR30507/091.0 ug/kg (n=3) placebo (n=1) Cohort 4 MR30507/092.0 (n=3) placebo (n=1) Cohort 5 MR30507/094.0 ug/kg (n=3) placebo (n=1) Cohort 6 MR30507/096.0 ug/kg (n=3) placebo (n=1) Possibility to add extra dose groups if needed until irregular breathing

observed (e.g. 9.0 and 12.0 µg/kg) Data from each cohort will be assessed prior to commencing dosing in the next cohort. There will be a minimum of 48 hours between completion of dosing a cohort at one dose level and the start of dosing the next cohort at the next dose level. A further cohort(s) of 4 subjects may be added at a dose(s) falling between doses previously assessed, or at a higher dose(s) than previously assessed. If a higher dose(s) is to be assessed, dosing may continue until such time as irregular breathing is observed or any other safety signals are observed that meet individual stopping criteria. Dose levels will be determined based on review of safety and PD data from the pilot phase. Safety data will be reviewed on an ongoing basis by a Safety Data Review Committee (SDRC) comprising Investigator or Co-investigator and Sponsor personnel (to include Clinical Leader and/or additional medical designee, Clinical Operations representative, and Drug Safety representative). Data for a subject(s) meeting the individual stopping rules, will be reviewed by the SDRC before proceeding to dosing at the next dose level.The following stopping rules apply: • Apnoea defined as discontinuation of rhythmic breathing for > 90 seconds • pCO2 > 9 KPa • O2 saturation 85% or less • Increase in QTc of more than 60 msec above pre-dose values of each study period or QTc greater than 500 msec • Liver function tests (ALT, AST, ALP) - discontinue subject if SAE criteria reached • Investigator*s judgement of AEs/SAEs (e.g. severe nausea and vomiting, and non-related SAEs) • Serious adverse drug reaction. The following cohort stopping criteria also apply: • Severe respiratory depression, defined as in need of naloxone administration. • Serious adverse drug reaction. If two subjects in a cohort meet either of the above stopping rules, further dosing in the cohort and further dose escalation will be stopped. The SDRC may also revise the planned dose levels following a Cohort safety review. If a subject(s) meets the individual stopping rules, further subjects may continue to be dosed at the same dose level, based on SDRC review. SDRC review must take place prior to further dose escalation. If a subject(s) meets the individual stopping rules, up to two additional subjects may be randomised to expand the cohort. If two subjects in a cohort meet the cohort stopping rules, further dosing in the cohort and further dose escalation will be stopped. Safety data will be reviewed by the SDRC before proceeding to the next cohort and before proceeding to, and to select doses for, the main phase. Main phase: Subjects in each group will receive a single 10-minute infusion of MR30507/09MR30365/07, placebo or fentanyl according to a random allocation schedule. The starting dose of MR30507/09 (A, B,C and D; µg/kg) will be determined from the pilot phase. Group Dose (µg/kg) Group 1 (n=11) MR30507/09(A) (n=3); MR30365/07 0.2 (n=6); placebo (n=1); fentanyl 2.0 (n=1) Group 2 (n=11) MR30507/09 (B) (n=3); MR30365/07 0.25 (n=6); placebo (n=1); fentanyl 2.0 (n=1) Group 3 (n=11) MR30507/09(C) (n=3); MR30365/07 0.3 (n=6); placebo (n=1); fentanyl 2.0 (n=1) Group 4 (n=11) MR30507/09 (D) (n=3; MR30365/07 0.4 (n=6, if no safety stopping criteria met at 0.3 dose);placebo (n=1), fentanyl 2.0 (n=1) Group 5 (n=5) Additional group if required: MR30507/09 (dose to be determined, n=3); placebo (n=1); fentanyl 2.0 (n=1) As the main phase is double-blind, and contains multiple active treatments, an Independent Safety Data Monitoring Committee (ISDMC) will be set up before the main phase is initiated. The ISDMC will

consist of at least 3 independent persons (i.e. independent from the study and Sponsor). When cohort stopping criteria are met, the ISDMC members will be un-blinded to study treatments and doses to assist with safety data monitoring. Safety data (AE listings) will be provided to the ISDMC and ISDMC meetings scheduled depending on subject recruitment. Ad hoc committee meetings will be called depending on severity and frequency of AEs and where unblinding is necessary. The same individual and cohort stopping rules apply as for the pilot phase. If cohort stopping rules are met in the main phase, the ISDMC may advise to stop further dosing of the treatment that resulted in meeting the stopping criteria, the treatment(s) not involved in reaching the stopping criteria may continue in the next cohort(s) . Naloxone phase: Subjects will receive a single 10-minute infusion of MR30507/09 or MR30365/07 in Study Period 1 according to the random allocation schedule. Subjects will receive the alternate treatment in Study Period 2. Naloxone IV injection or placebo will be administered 5 minutes after the end of MR30365/07 infusion according to the random allocation schedule. The timing of naloxone or placebo administration for MR30507/09 will be determined from the pilot phase PD data. Reversal effects will be monitored and naloxone administration repeated at 0.4 mg at 4 minute intervals, as necessary up to a maximum of 4 doses. Reversal will be deemed to have been effective when ventilation levels return to baseline (+/- 10%). All treatments will be administered in a semi-supine position and will be followed by the appropriate measurements and safety assessments. The same individual and cohort stopping rules apply as for the pilot phase. Naloxone administration in this phase will not be considered an SAE as it is a scheduled study procedure.

Study burden and risks

Available non-clinical data on safety and efficacy of MR30507/09 demonstrates that MR30507/09 may be a potent analgesic with a similar adverse event (AE) profile to other mu-opioid receptor agonists. Therefore similar precautions apply to MR30507/09 as to other analgesics in this class. Preliminary clinical studies must be performed to evaluate the potential analgesic efficacy and adverse effects MR30507/09 may have in humans. Based on non-clinical data comparing MR30507/09 to MR30365/07 and fentanyl, it is expected that typical opioid effects will be observed after administering MR30507/09 to humans. A low starting dose (0.2µg/kg) will be selected based on non-clinical data, before dose escalating, to establish the MR30507/09 therapeutic range based on pharmacodynamic responses. Each dose level will be completed and safety and pharmacodynamic data assessed by a Safety Data Review Committee (SDRC), before dose escalation can occur. Individual subject and cohort stopping criteria also apply. In order to ensure the safety of all volunteers enrolled into the study, stringent cardiovascular assessments (12 lead ECGs) will be performed at regular intervals up to 24 hours post-dose to enable thorough assessment of QTc changes. In addition, a central ECG provider will be employed to review all ECGs. Rigorous stopping rules have been defined within this protocol and any observable cardiovascular events will be thoroughly documented and regularly reviewed by a SDRC comprising Sponsor and Investigator site personnel. The

study will be performed in the anaesthesiology department of a hospital, with all appropriate emergency procedures in place and by investigators experienced in managing respiratory depression. Naloxone injection will be available for emergency use for severe respiratory depression. Other supportive measures to assist respiration and hemodynamics will also be available e.g. maintenance of fluid and electrolyte levels (100 mL/h of 2.5% glucose infusion for up to 24 hours), oxygen, and vasopressors. Subjects will be monitored overnight in an observation ward by an on duty physician and nursing staff. Extra blankets or Bair® hugger therapy will be used, in case of low body temperature, as appropriate to prevent hypothermia. Cardiovascular emergency measures such as defibrillation, magnesium sulfate (infusion), and antiarrhythmic drugs, will also be available. The overall risk/benefit assessment is considered acceptable, under the conditions described above.

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

1. Written informed consent obtained.
2. Healthy male subjects aged 18 to 45 years inclusive.
3. Body weight ranging from 60 to 100 kg and a BMI >= 18 and <= 30
4. Healthy and free of significant abnormal findings as determined by medical history, physical examination, vital signs, laboratory tests and ECG.
5. Male subjects must be willing to use contraception with their partners throughout the study and for 30 days after completion of the study and agree to inform the Investigator if their partner becomes pregnant during this time
6. Subject is deemed suitable by the Investigator for inclusion in the study.

Exclusion criteria

1. Any history of drug or alcohol abuse, or recreational drug use within 30 days prior to study drug administration.
2. Any history of conditions that might interfere with drug absorption, distribution, metabolism or excretion.
3. Use of opioid or opioid antagonist-containing medication in the past 90 days.
4. Any history of frequent nausea or vomiting regardless of etiology.
5. Any history of seizures or symptomatic head trauma.
6. Participation in a clinical drug study during the 90 days preceding the initial dose in this study.
7. In the Investigator*s opinion a clinically significant upper or lower respiratory infection within 4 weeks prior to the screening visit.
8. History of asthma, COPD, or other bronchial or lung diseases.
9. History of regurgitation or difficulty of intubation.
10. A history of additional risk factors for Torsades de Pointes (e.g. heart failure, hypokalaemia, personal or family history of long QT syndrome, syncope, or family history of sudden death).
11. Abnormal cardiac conditions including QTc interval greater than 450 msec at screening or pre-dose.
12. Use of medication within five times the half-life or minimum 14 days for prescription medication or 7 days for over-the-counter preparations (including vitamins, herbal and/or mineral supplements), whichever is longer, before the first dose of study treatment and during the study.
13. Refusal to abstain from food 6 hours preceding and 8 hours following study drug administration and to abstain from caffeine or xanthine containing beverages entirely during each confinement.
14. Weekly alcohol intake exceeding the equivalent of 21 units/week.
15. Consumption of alcoholic beverages within 24 hours before study drug administration, and refusal to abstain from alcohol for at least 48 hours after study drug administration.
16. History of heavy smoking (more than 20 cigarettes a day) within 45 days of study drug administration and refusal to abstain from smoking while in the study unit.

17. Blood or blood products donated within 90 days prior to study drug administration or any time during the study, except as required by this protocol.
18. Abnormal result obtained from Allen*s circulation test.
19. Positive results of urine drug screen, alcohol test, HBsAg, Hepatitis C antibody, or HIV tests.
20. Known sensitivity to fentanyl, opioids, naloxone, natrexone, or related compounds.

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):	21-02-2013
Enrollment:	78
Type:	Actual

Medical products/devices used

Product type:	Medicine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Fentanyl Bipharma
Generic name:	fentanyl solution
Product type:	Medicine
Brand name:	MR30365/07
Generic name:	MR30365/07
Product type:	Medicine

Brand name:	MR30507/09
Generic name:	MR30507/09
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Naloxone 400 micrograms/ml
Generic name:	naloxone solution
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	22-11-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	04-02-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-02-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-05-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-10-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO	

Date:	18-12-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-01-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2012-002229-31-NL
CCMO	NL42507.058.12