ISRCTN12424734 https://doi.org/10.1186/ISRCTN12424734

A study of the safety and effect of food on absorption of KCL-286 in healthy men

Submission date
19/06/2018

Recruitment status
No longer recruiting

Registration date
18/07/2018

Overall study status
Completed

Last Edited
01/08/2025

Condition category
Nervous System Diseases

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

Plain English summary of protocol

Background and study aims
There are currently no effective treatments for spinal cord injuries (SCIs), which can result in loss of feeling and control of the body below the level of the spinal cord injury. We have discovered KCL-286, which stimulates nerve regrowth in studies in rats. This study is the first test of KCL-286 in humans and aims to investigate whether it is safe and can be tolerated in humans. If it is safe, it will be tested in men with a type of spinal cord injury in which the nerve has been pulled away from the spinal cord to see if it can improve feeling and control of the affected body parts.

Who can participate?
Healthy men aged 19-45 years who are not underweight or obese.

What does the study involve?
The study is in two parts. In the first part, the participants will receive a single dose of KCL-286 or dummy treatment, allocated at random. They will be monitored closely to see if there are any side effects. If the single dose is considered safe, some participants will be randomly allocated to two groups. One group will take KCL-286 after fasting overnight and the other group will take KCL-286 after a high-fat breakfast. This is to investigate the effect of food on how the drug is handled within the body.
In the second part of the study, the participants will take 7 doses of KCL-286 or dummy treatment over 7 or 14 days. This is to investigate whether repeated doses of the drug are safe and whether there are side effects.

What are the possible benefits and risks of participating?
[Not provided at time of registration]

Where is the study run from?
Kings College London, UK

When is the study starting and how long is it expected to run for?
January 2018 to September 2021

Who is funding the study?
The Medical Research Council

Who is the main contact?
Professor Jonathan Corcoran
jonathan.corcoran@kcl.ac.uk

Contact information

Type(s)
Public

Contact name
Prof Jonathan Corcoran

Contact details
Guy's Campus
London
United Kingdom
SE1 1UL

Additional identifiers

Clinical Trials Information System (CTIS)
2018-000076-15

Protocol serial number
CRC385

Study information

Scientific Title
A Phase I, prospective, double-blind, randomised, placebo-controlled, dose escalation study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple ascending oral doses of KCL-286 and the effects of food in healthy male participants

Acronym
KCL-286-01-Phase1

Study objectives
KCL-286 is a retinoic acid receptor beta (RARβ) agonist being developed to treat traumatic nerve injury. The primary indication is the treatment of avulsed nerve roots of the brachial plexus. The nerves in the body originate from the spinal cord as spinal nerve roots. The ventral or motor roots connect to muscles and the dorsal or sensory roots convey sensory impulses from the periphery.

Trauma to the nerve roots (typically in road traffic accidents) can result in the nerve roots being torn or avulsed from the spinal cord (SC). Such injury leads to degeneration of nerve fibres, death of nerve cells and a breakdown of connections within the SC. This is in effect a SC injury and it has a serious effect on central nervous connections and networks, with the development

of a glial scar in the SC. Disintegration of the shorter SC parts of sensory neurons with degeneration of most of the motoneuron nerve fibres and a “dying back” of these neurites within the spinal cord follows from this trauma. Within a few weeks after such injury there will be an increasing death of neurons within the spinal cord affecting both, motor and sensory, as well as autonomic nerve cells.

The functional consequence of such injury is “lower motoneuron syndrome” with flaccid muscle paralysis and eventual muscle atrophy and autonomic paralysis, including dysfunctional internal organs, as well as sensory impairments and, most disturbing, severe, almost unbearable chronic pain.

Avulsion of sensory nerve roots induces a loss of SC dorsal horn neurons and interferes with sensory connections. This interference is thought to cause the classical central pain syndrome associated with root avulsion, possibly through loss of inhibition from peripheral sensory neurons.

The nerve root traction injuries, which in the adult classically occur in motorbike accidents, affect mainly the complicated nerve formations called nerve plexa which innervate the limbs and are centrally connected to the SC through nerve ventral and dorsal roots. The brachial plexus which innervates the upper extremity is little protected from traction forces due to the loose suspension of the shoulder girdle and is easily injured when for instance a motorcyclist comes off the bike and the shoulder is impacted. The lumbosacral plexus innervating the lower extremity is more protected in the bony pelvis and fewer injuries occur.

Plexus injuries are caused in serious road traffic accidents or violent acts. Brachial plexus injuries occur in 1.2% of polytrauma victims. About 70% of severe brachial plexus lesions have root avulsion injuries affecting over 1000 cases in the UK annually (Midha, 1997).

Attempts to manage such injuries must involve maintenance of SC nerve cells and regeneration of nerve fibres within the spinal cord, i.e. central nervous regeneration. Root avulsion has been associated with an overall poor clinical outcome. Today, most patients are not treated at all or receive non-curative palliative procedures which do not give acceptable functional return or pain alleviation.

Medullary implantation of peripheral nerve grafts or re-implantation of avulsed ventral or motor roots into the SC, if performed early after the injury, can curtail some neuronal loss and promote some regrowth of new motor or autonomic axons through SC tissue (central nerve fibre regeneration) and further into the peripheral nerves. Such SC surgery has long since been a routine procedure at centres in London and Stockholm. However, it has not been possible to reconstruct avulsed dorsal or sensory roots as these nerve fibres are prevented or inhibited from entering into the spinal cord most likely by the formation of glial scar tissue.

The outcome from medullary reconstruction of motor neurons, results only in muscle activity among proximal arm and shoulder muscles with some alleviation of pain. There is, however, not any sensory return as only ventral or motor roots are reconnected to the SC. Most likely because of absence of sensory function the muscle activity and the movements restored are abnormal and sometimes not of any benefit. There are synkinesis and antagonistic muscle contractions which disturb the use of the arm. A medication that offers the chance of restoring sensory functions after root avulsion is necessary, to improve not only sensation, but also appropriate muscle and locomotor function, and most importantly alleviate the classical and excruciating

root avulsion pain, which dominates the lives of many victims of root avulsion. Medication that improves the motor function following re-implantation of the ventral or motor roots would also be of potentially significant benefit to patients (Adams, 2007).

Evidence from the animal work is that KCL-286 inhibits the formation of the glial scar tissue and, in the absence of this barrier, allows the re-implanted nerves to grow and make connections. In addition, KCL-286 appears to facilitate the RARβ signalling that is required for retinoid mediated neurite outgrowth of neurons, thus allowing the nerves to grow back.

A full non-clinical development programme has been conducted including animal toxicology studies (with toxicokinetics) of up to 28 days in rats and dogs.

The only significant toxicity seen in rats was related to premature closure of growth plates, which is not relevant to the human target population who will be adults whose growth plates will have closed at puberty. In dogs, cutaneous findings including reddening of the ears, gums and muzzle, decreased activity, dilated pupils, skin exfoliation and rash were observed (Teelmann, 1989). The findings are consistent with the known pharmacology of retinoids and are not considered to be different from the toxicity of retinoids currently on the market for other conditions. Further details are provided in the investigator's brochure (IB).

The proposed study is a first in human study, to be undertaken in healthy male participants, it is an adaptive design to investigate the safety and pharmacokinetics of single and multiple doses of KCL-286 administered orally and to assess the effect of food on the pharmacokinetics of KCL-286. The study is being conduct in males only due to the potential teratogenic effects of retinoids and the main indication of brachial plexus injury occurs almost exclusively in males.

Ethics approval required
Old ethics approval format

Ethics approval(s)
London-Surrey Borders Research Ethics Committee, 09/05/2018, 18/LO/0460

Study design
Prospective Phase I double-blind randomised placebo-controlled dose-escalating study

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Avulsed nerve roots of the brachial plexus

Interventions
The study comprises 2 parts: Part A employs a single ascending dose (SAD) design with a separate food interaction (FI) arm for one cohort, and Part B employs a multiple ascending dose (MAD) design.

Part A SAD will have up to 8 cohorts (S1 to S8). S1 and S2 will have 4 participants (3 active and 1 placebo in each cohort). The first 2 participants in S1 and S2 will be dosed at least 24 hours apart.

If well tolerated the remaining 2 participants will be dosed together on the following day. For the subsequent cohorts there will be 8 participants; this will include sentinel dosing of the first 2 participants (1 active, 1 placebo) in each cohort with the remainder of the cohort (n=6; 5 active and 1 placebo) being dosed at least 24 hours later.

Part A FI will include 8 participants (all on active treatment – no sentinel participants) who will be randomised in a two-way crossover study. One of the treatment periods will be fasted and the other will be administered after a high-fat breakfast. There will be at least 7 days or 5 half-lives (whichever is longer) between treatment periods.

Part B MAD will have 4 cohorts (M1 to M4) of 8 participants (6 active and 2 placebo). There will be up to 4 dose levels which will be administered either daily for 7 days or every other day to cover 7 doses. There will be sentinel dosing of 2 participants (1 active and 1 placebo) in each cohort with the remaining participants in each cohort being dosed after the sentinel participants have received at least 4 doses.

Safety and interim plasma pharmacokinetic data will be reviewed at the Safety Data Review Meetings during Part A and Part B prior to the commencement of the next dose cohort in each part. The starting dose to be used and whether it will be administer daily or on alternate days in Part B will be based on the safety, pharmacokinetic and pharmacodynamics data from Part A (SAD and FI).

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
KCL-286

Primary outcome(s)
1. Incidence and severity of adverse events up to 48 hours after the last dose
2. Incidence of serious adverse events up to 48 hours after the last dose
3. Change from baseline in vital signs (Heart rate, blood pressure, oral temperature and respiratory rate) measured pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36 and 48 h after the dose
4. Depression assessed using PHQ-9 questionnaire at 48 h post-dose
5. Anxiety assessed using GAD-7 questionnaire at 48 h post-dose
5. Change from baseline in laboratory data, including haematology tests (haemoglobin, hematocrit, white blood cells and platelets) and blood chemistry (alanine aminotransferase [ALT], albumin, alkaline phosphatase, aspartase aminotransferase, blood urea nitrogen [BUN], calcium, chloride, creatinine, glucose, glycosylated haemoglobin [Hb1Ac], potassium, sodium, thyroid stimulating hormone [TSD], thyroxine, total bilirubin, lipids, urea and electrolytes, creatinine and liver function tests [LFTs]) 1 day pre-dose and 24 h post-dose
6. Change from baseline in 12-lead ECGs performed after resting for approximately 10 minutes in the semi-recumbent position pre-dose and at 0.5, 1, 2, 4, 8, 12, 24 and 48 h post-dose

Key secondary outcome(s))
1. Plasma and urine concentration-time profiles assessed using blood samples taken pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36 and 48 h after the dose and urine collected pre-dose and throughout the study up to 48 h post-dose

2. Plasma and urine pharmacokinetic parameters, including but not limited to Cmax, Tmax, AUC, half-life, fraction eliminated unchanged in urine and renal clearance, as data permit, using blood samples taken pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36 and 48 h after the dose and urine collected pre-dose and throughout the study up to 48 h post-dose

Completion date
30/09/2021

Eligibility

Key inclusion criteria
1. Healthy males
2. Aged 19 to 45 years at screening
3. Able to understand and willing to follow the requirements for the study and provide written informed consent
4. Willing to avoid direct sunlight, use sun cream and cover arms and legs and to wear sunglasses and sunhat when outside during treatment and until final visit
5. Non-smokers from at least 3 months before receiving the first dose of study drug and for the duration of the study
6. Participants who are sexually active must agree to use barrier contraception with a spermicide from the time of the first dose until 3 months after the last dose (participants whose female partners are trying to become pregnant will be excluded)
7. Body mass index (BMI) ≥18 and ≤30 kg/m2
8. Body weight ≥55 kg at screening

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Male

Total final enrolment
109

Key exclusion criteria
1. Current or recent (within 3 months of screening) use of sunbeds
2. Current or recent (less than 5 years) history of drug or alcohol abuse or a positive drugs of abuse test
3. Current or past history of psychiatric conditions or suicidal ideation
4. History or presence of any clinically relevant allergy
5. Consumption of prescription or over-the-counter medications (including vitamins, herbal and

mineral supplements) within 14 days prior to study drug administration until (with the exception of occasional paracetamol) the end of the study

Date of first enrolment
01/07/2018

Date of final enrolment
31/03/2020

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Richmond Pharmacology Ltd
1a Newcomen Street
London
United Kingdom
SE1 1YR

Sponsor information

Organisation
King's College London

ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		15/07/2023	18/07/2023	Yes	No
Results article		20/08/2024	01/08/2025	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes