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# A study to assess the safety and tolerability of PH46A in healthy volunteers, to measure drug levels in these subjects and to determine the effect of food on the drug's absorption

**Submission date**
11/02/2014

**Recruitment status**
No longer recruiting

**Registration date**
11/03/2014

**Overall study status**
Completed

**Last Edited**
09/02/2017

**Condition category**
Digestive System

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

## Plain English summary of protocol

Background and study aims
Inflammatory bowel disease (IBD) is a range of diseases characterised by inflammation of the large and/or small intestine, with symptoms of malaise (feeling of general discomfort), fever, bloody diarrhoea, abdominal pain, weight loss, and nausea. Crohns disease and ulcerative colitis are the two main conditions that come under the heading of IBD. Crohns disease can affect any part of the intestine, can extend through the intestinal wall and can lead to the formation of new, additional openings from the intestine to the outside. Ulcerative colitis consists of ulcers in the colon only. The purpose of this study is to assess the safety and tolerability of single and multiple oral doses of the drug (PH46A) and the effect of the fasted and fed state on the pharmacokinetics (bodily absorption, distribution, metabolism, and excretion of drugs) of PH46A in healthy volunteers.

Who can participate?
The volunteers will be non-smoking healthy males and females aged between 18 and 55, of normal weight and currently not on any other medication. Male volunteers and female volunteers of child-bearing potential who are sexually active must use two highly effective methods of contraception with their partners throughout the study and for 30 days after completion of the study (female volunteers) or 90 days after completion of the study (male volunteers). Unless they permanently sterilised, females must have a negative pregnancy test and not be breast feeding. Female volunteers may also take part if they are post-menopausal for more than one year. Male volunteers must not donate sperm during the study and for 90 days after completion of the study.

What does the study involve?
Before the drug is tested in patients with IBD, it must be tested in healthy volunteers to establish whether there are any side effects. The volunteer subjects will be given very small doses at the start, and then a new group of subjects will be given more of the drug if the first group experiences no ill effects. In first part of the study, each group (there will be up to six

groups) will consist of eight subjects. Following random allocation, six subjects will receive PH46A and two subjects will receive a placebo (dummy). The first group will receive the lowest dose level and the last group the highest dose; all subjects in a single group will receive the same dose. For each dose of drug, only two subjects will be given the drug at first and we will wait 2 days to see if there are any side effects before giving the drug to the other subjects in the group. In this way we will look at increasing doses (up to six different doses) of the drug to see if any side effects occur. We also want to know if the presence of food affects how the drug is absorbed. We will be taking blood samples from the subjects to measure how much drug gets absorbed, and for how long it stays in the body. The next part of the study will be to look to see if taking the drug every day for a week causes any side effects and how the levels in the blood change. Again, we will look at several (up to four) different doses of the drug.

What are the possible benefits and risks of participating?
Volunteers will receive no benefit from participating in this study other than the thorough medical examination they will undergo (physical examination, electrocardiogram [ECG], laboratory tests, etc) before entering the study, which may identify an unknown health issue. Volunteers will be regularly monitored for any changes in their vital signs, ECG parameters and laboratory values. Adverse events will be recorded throughout the study period. Any changes in subjects health will be recorded and volunteers will be assessed and evaluated by the investigators. These safety monitoring requirements, the low starting dose, the dose escalation scheme only following a review of the safety data, and stopping criteria will minimise the risks to the volunteers. The potential benefits to patients of a more effective and safe drug for the treatment of IBD are considered to outweigh the potential risks, although volunteers in this study will gain no benefit. The overall risk-benefit assessment from all pre-clinical information favours the conduct of the study.

Where is the study run from?
The study is run from Biokinetic Europe, Belfast, Northern Ireland, UK.

When is the study starting and how long is it expected to run for?
The study will start in February 2014 and is expected to run until August 2014.

Who is funding the study?
Trino Therapeutics, Republic of Ireland and the Wellcome Trust, UK.

Who is the main contact?
Gaia Scalabrino, Head of Product Development.

# Contact information

### Type(s)
Scientific

### Contact name
Prof Neil Frankish

### Contact details
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# Additional identifiers

### EudraCT/CTIS number
2013-003717-17

### IRAS number

### ClinicalTrials.gov number

### Secondary identifying numbers
Protocol PH_CTPR01

# Study information

### Scientific Title
A Phase I, prospective, double-blind, randomised, placebo-controlled, dose escalating study to assess the safety and tolerability of single and multiple oral doses of PH46A and the effect of the fasted and fed state on pharmacokinetics of PH46A in healthy volunteers

### Study objectives
The purpose of this study is to assess the safety and tolerability of single and multiple oral doses of PH46A and the effect of the fasted and fed state on pharmacokinetics of PH46A in healthy volunteers.

Furthermore, the aim will be to determine the single dose pharmacokinetics of at least four and a maximum of six dose levels of PH46A following oral administration as well as determining the multiple dose pharmacokinetics of four dose levels of PH46A over 7 days. The pharmacokinetic profile of PH46A will also be compared after a single dose in the fed and fasted state. As part of the study it is hoped to determine the maximum tolerated dose in these subjects. It is also hypothesised that PH46A may alter the levels of some inflammatory biomarkers, and these may be assessed from blood sample analysis.

The data obtained from the study will enable the design of future studies investigating efficacy of PH46A in patients with UC to be planned and developed.

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
NRES Committee East of England - Cambridge East, 30/01/2014, ref:14/EE/0023
Protocol number: PH_CTPR01, IRAS project ID:146130, REC application: 146130/541502/1/69

### Study design
Single centre double-blind randomised placebo-controlled dose escalating study on the safety of single & multiple doses of PH46A and on its pharmacokinetics in fasted and fed volunteers

## Primary study design
Interventional

## Secondary study design
Randomised controlled trial

## Study setting(s)
Hospital

## Study type(s)
Screening

## Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet: Contact Details: Alison Duffin, aduffin@biokineticeurope.com, David Bell, david@biokineticeurope.com

## Health condition(s) or problem(s) studied
Ulcerative colitis

## Interventions
This is a first-in-human Phase I double-blind, randomised, placebo-controlled, dose escalating study.

The study comprises two parts: Part A employs a single ascending dose design with a separate food effect arm, and Part B employs a multiple ascending dose design.

The study comprises two parts, Part A will look at the administration of a single dose to subjects with increasing dose levels administered to subsequent groups; and Part B will look at the administration of multiple doses of a single dose level with the dose level increased with subsequent groups. In addition, the effect of food on the amount of drug absorbed will be investigated as part of Part A. In Part A each group (there will be up to 6 groups) will consist of 8 subjects: 6 subjects will receive PH46A and 2 subjects will receive placebo. The first group will receive the lowest dose level and the last group the highest dose; all subjects in a single group will receive the same dose. At the start of dosing of each group in Part A, two subjects will receive the study medication (one to receive PH46a and one to receive placebo) 48 hours before the remaining 6 subjects receive the same dose. The decision whether to dose the remaining 6 subjects in a group will depend on the safety profile seen in the first two subjects. Also in Part A, the food effect investigation will be performed. Volunteers from one or more SAD cohorts will return to the study unit after a washout period of at least 7 days or 5 half-lives, to receive the same dose of study drug administered to that cohort during their first in-house confinement but in a fed (fatty breakfast) state. It is planned to have at least 6 evaluable subjects in the food effect arm.

The word 'multiple' refers to the number of doses an individual subject receives. In the multiple ascending dose phase each subject in a group will receive a dose on day 1, the same dose on day 2 and subsequent days up to day 7. The next group will receive a higher dose level than the first group and that dose level will be administered for 7 days. There will be up to 4 dose levels, each dose level administered to a single cohort. In total up to 48 healthy volunteers aged 18-55 will be randomised in Part B (MAD phase), i.e. 4 groups of 12 volunteers.

Part A will incorporate sentinel dosing of 2 volunteers in each cohort: 1 on active treatment and 1 on placebo. No further volunteers in each cohort will be dosed until at least 48 hours after dosing the second volunteer, provided that there are no serious or unexplained safety issues as determined by the Investigator.

Safety and 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. Part B may commence prior to completion of Part A.

Study start is defined as the first visit to the study unit on Day -1. The study duration for individual volunteers will be approximately 15 days in Part A and approximately 22 days in Part B, excluding the 30-day screening period. This is the duration from the first visit to the study unit on Day -1 to the post-study medical.

Those volunteers who participate in the food effect phase of Part A will have a second in-house confinement, following a wash-out period, which will be of the same duration as the first, i.e. 3 nights (the second period differs from the first only in that all volunteers will receive a fatty breakfast on Day 1).

The following safety assessments will be performed during the Treatment Period.
1. Safety bloods (biochemistry and haematology)
2. ECGs
3. Continuous telemetry monitoring
4. Vital signs (heart rate, blood pressure, tympanic temperature and respiration rate)
5. Physical examinations
7. Grip strength assessment
Blood samples will be collected for the pharmacokinetic analysis of PH46A

Volunteers will remain in the study unit until check-out on day 3 (SAD) or day 9 (MAD), at least 48 hours after study drug administration.

A post-study medical will be performed 7-14 days after the last study drug administration in both Parts A and B. It is anticipated that this will be performed 7 days after the last study drug administration, but this may be extended to up to 14 days if deemed necessary following review of the PK results. The following assessments will be performed at the post-study medical:
1. Physical examination
2. Vital signs (heart rate, blood pressure, tympanic temperature and respiration rate)
3. 12-lead ECG
4. Urinalysis
5. Serum pregnancy test for females of child-bearing potential
6. Blood samples for haematology and biochemistry
7. Blood sample for pharmacokinetic analysis
8. Review of AEs and concomitant medications

## Intervention Type
Drug

## Phase
Phase I

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

PH46A

### Primary outcome measure
Assessment of tolerability and safety, and pharmacokinetic analysis.

### Secondary outcome measures
A secondary outcome would be no loss of grip strength. Grip strength assessment will be performed at a pre-dose baseline on Day 1, between 1-2 hours post-dose and at 24 hours post-dose. Grip strength will be measured quantitatively using a Jamar hand dynamometer.

### Overall study start date
07/02/2014

### Completion date
31/08/2014

## Eligibility

### Key inclusion criteria
1. Healthy male and female volunteers aged 18-55, as determined by medical history, physical examination, laboratory test values, vital signs and 12-lead ECGs at screening.
2. Non-smokers from at least three months before receiving the first dose of study drug and for the duration of the study.
3. Body mass index (BMI) ≥ 18 and ≤ 29 kg/m2
4. Body weight ≥ 55 kg and ≤ 100 kg at screening
5. Able to voluntarily provide written informed consent to participate in the study
6. Must understand the purposes and risks of the study and agree to follow the restrictions and schedule of procedures as defined in the protocol, as confirmed during the informed consent process.
7. Female volunteers less than one year post-menopausal must have a negative serum pregnancy test and be non-lactating.
8. Female volunteers who have been post-menopausal for more than one year and have elevated serum follicle stimulating hormone (FSH) or are treated with hormone replacement therapy (HRT) or female volunteers who have been permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy).
9. Male volunteers and female volunteers of child-bearing potential who are sexually active must use two highly effective methods of contraception with their partners throughout the study and for 30 days after completion of the study (female volunteers) or 90 days after completion of the study (male volunteers). Acceptable methods include: condom or occlusive cap (diaphragm or cervical/ vault caps) with spermicidal foam/ gel/ film/ cream/ suppository; male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate); established use of oral, injected or implanted hormonal methods of contraception and placement of an intrauterine device or intrauterine system. True abstinence is an acceptable method only where this is already established as the volunteers preferred and usual lifestyle.
10. Male volunteers must not donate sperm during the study and for 90 days after completion of the study.
11. Must be willing to consent to have data entered into The Over Volunteering Prevention System (TOPS).

12. An up to date medical history from the volunteers primary care physician to confirm that there is nothing in their medical history that would preclude their enrolment into this clinical study.

## Participant type(s)
Patient

## Age group
Adult

## Lower age limit
18 Years

## Upper age limit
55 Years

## Sex
Both

## Target number of participants
Up to 48 healthy volunteers Part A (SAD Phase plus food effect arm). Up to 48 subjects in Part B (MAD phase)

## Key exclusion criteria
1. Volunteers with history or presence of significant cardiovascular disease, pulmonary, hepatic, gallbladder or biliary tract, renal, haematological, gastrointestinal, endocrine, immunological, dermatological, neurological, psychiatric disease or current infection.
2. Laboratory values at screening or baseline which are deemed to be clinically significant, unless agreed in advance by the Sponsors Medical Representative and Principal Investigator.
3. Female volunteers who are pregnant or lactating.
4. Positive for human immunodeficiency virus (HIV), hepatitis B or hepatitis C.
5. Current or history of drug or alcohol abuse or a positive drugs of abuse or alcohol test at screening or check-in.
6. Participation in a clinical drug study during the 90 days preceding the initial dose in this study.
7. Any clinically significant illness within 30 days prior to study drug administration.
8. Donation of blood or blood products within 90 days prior to study drug administration, or at any time during the study, except as required by this protocol.
9. Volunteers who have a history or presence of any significant drug allergy.
10. Use of any prescription or over-the-counter medication (including vitamins, herbal and mineral supplements) within 14 days prior to study drug administration until the end of the study, with the exception of occasional paracetamol approved by the Investigator and Investigator approved contraceptives and HRT.
11. Strenuous exercise, as judged by the Investigator, within 72 hours prior to screening, within 72 hours prior to study drug administration and for the duration of the study until after the post-study medical.
12. Weekly alcohol intake exceeding the equivalent of 14 units per week for females or 21 units per week for males.
13. Consumption of alcoholic beverages within 24 hours prior to study drug administration and during study confinement.
14. Consumption of caffeine or xanthine-containing products within 24 hours prior to confinement and during study confinement.

15. Consumption of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade or other products containing grapefruit or Seville oranges within 7 days prior to confinement and during study confinement.
16. Volunteers who, in the opinion of the Investigator, are unsuitable for participation in the study.

### Date of first enrolment
07/02/2014

### Date of final enrolment
31/08/2014

## Locations

### Countries of recruitment
Ireland

United Kingdom

### Study participating centre
### Trino Therapeutics
Dublin
Ireland
D2

## Sponsor information

### Organisation
Trino Therapeutics (Ireland)

### Sponsor details
2.5 The Tower
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### Sponsor type
Industry

## Funder(s)

### Funder type

Charity

**Funder Name**
Trino Therapeutics Ltd.

**Funder Name**
Wellcome Trust (UK) WT100529MF

# Results and Publications

### Publication and dissemination plan
Not provided at time of registration

### Intention to publish date

### Individual participant data (IPD) sharing plan

### IPD sharing plan summary
Not provided at time of registration

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| HRA research summary | | | 28/06/2023 | No | No |