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A phase I study into the safety, tolerability, pharmacokinetics and immunogenicity of PolyCAb in healthy subjects

Submission date
25/01/2016

Recruitment status
No longer recruiting

Registration date
04/02/2016

Overall study status
Completed

Last Edited
21/07/2021

Condition category
Infections and Infestations

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

Plain English summary of protocol

Background and study aims
Clostridium difficile infection (CDI) is a common type of bacterial infection that affects the digestive system. These infections have increased dramatically since the late 1990s, and have become a major problem in hospitals and care homes, as it most commonly affects people who have been treated with antibiotics or whose immune system (natural defences) are lowered because of aging or disease. The symptoms can range from mild to severe, and generally include fever (high temperature), diarrhoea (sometimes accompanied by vomiting) and painful abdominal cramps. This is because the bacteria releases harmful toxins, which cause damage to the walls of the intestines. In particularly vulnerable patients, such as the very young or old, these toxins can enter the blood steam causing damage to other parts of the body such as the heart. MicroPharm Limited has developed a new product called PolyCAb to treat severe CDI by improving the currently available antibiotic treatments. PolyCAb is made up of antibodies (specialised proteins which bind to and neutralise harmful substances, such as bacteria or viruses). The inactivated bacteria are then removed from the body by the liver and kidneys, helping the patient to recover. The aim of this study is to test how safe and well tolerated different doses of PolyCAb are in healthy adults, in order to find the most effective dose.

Who can participate?
Healthy adults of either sex.

What does the study involve?
The study consists of two separate phases. In the first phase, seven participants receive a single intravenous injection (injection into a vein) containing PolyCAb and three participants receive an injection containing a placebo (dummy). In the second phase, a further six participants receive the same dose of PolyCAb, which is repeated on day four and seven. A further two participants in this group receive the placebo treatment three times. In both groups, the treatment times are staggered so that the safety of the drug can be reviewed as the study progresses. All participants are closely monitored immediately after the drug is given and at regular intervals for the next 28 days so that any undesirable reactions, such as rashes or itching as well as changes to vital signs (i.e. heart rate, breathing rate, temperature) can be recorded. Participants

also have blood samples taken to find out how long PolyCAb remains in the body before it is naturally removed.

What are the possible benefits and risks of participating?
There are no direct benefits involved with taking part in the study. There is a possibility that participants may have a kind of allergic reaction to the PolyCAb which could lead to rashes, stiffness and fever (serum sickness), however this will be closely monitored.

Where is the study run from?
Simbec Research Limited (UK)

When is the study starting and how long is it expected to run for?
December 2015 to December 2017

Who is funding the study?
MicroPharm Limited (UK)

Who is the main contact?
1. Dr Geoffrey Shellswell (scientific)
2. Mr Ian Cameron (scientific)

Contact information

Type(s)
Scientific

Contact name
Dr Geoffrey Shellswell

ORCID ID
https://orcid.org/0000-0001-8716-9332

Contact details
MicroPharm Ltd
Station Road Industrial Estate
Newcastle Emlyn
United Kingdom
SA38 9BY

Type(s)
Scientific

Contact name
Mr Ian Cameron

ORCID ID
https://orcid.org/0000-0002-5632-1044

Contact details
MicroPharm Ltd
Station Road Industrial Estate

Newcastle Emlyn
United Kingdom
SA38 9BY

Additional identifiers

Clinical Trials Information System (CTIS)
2014-002623-96

Protocol serial number
RD/673/25477

Study information

Scientific Title
A phase I double-blind, randomised, placebo-controlled study to assess the safety, tolerability, pharmacokinetics and immunogenicity of PolyCAb in healthy subjects following single doses and one cohort of multiple dosing

Study objectives
Primary objective:
To evaluate the safety and tolerability of a single dose and one multiple dose level of PolyCAb in healthy male or female (non-child bearing potential) subjects.

Secondary objective:
To determine the pharmacokinetic parameters of PolyCAb when administered in this way.

Exploratory objective:
To examine the immunogenicity of PolyCAb.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Wales Research Ethics Committee 2, 18/11/2015, ref: 14/WA/1168

Study design
Single-centre double-blind phase I placebo-controlled study

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Severe Clostridium difficile Infection (CDI)

Interventions

Interventions as of 30/09/2016:
The study is in two cohorts. Cohort 1 (single doses) will be conducted in up to 10 subjects (1 sub-cohort of 2 subjects and one sub-cohort of 8 subjects), and cohort 2 (multiple dose) will be conducted in 1 cohort of 8 subjects.

Cohort 1a:
One subject will receive a single intravenous injection of PolyCAb (500mg ovine total immunoglobulins at a concentration of 25g/l in 153mM sodium chloride buffered with 20 mM sodium citrate/citric acid pH 5.8-6.2. The drug will be administered as a 20 mL volume, over 60 minutes (min) using a syringe driver. An additional one subject will have placebo (the same buffered saline solution as above but without the ovine immunoglobulins) administered in the same way.
Cohort 1b:
Six subjects will receive a single intravenous dose of 170 mg PolyCAb at a concentration of 5 g/l in 153mM sodium chloride buffered with 20mM sodium citrate/citric acid pH 5.8-6.2containing the excipients 100mM Arginine and 0.1% Tween® 20. The drug will be administered as a 34 mL volume over 60 minutes with a syringe driver. An additional two subjects will have placebo (the same buffered saline solution with excipients but without the ovine immunoglobulins) administered in the same way. Dosing will be staggered in that there will be an initial Dose Leader group of 2 subjects (one PolyCAb, one placebo) who will receive their treatments, at least 24 hours before the others, and at least 60 min apart. The Chief Investigator must confirm whether it is safe to continue with the dosing of the remaining 6 subjects (5 PolyCAb, 1 placebo) following a review of appropriate safety data from evaluable subjects (defined as those who have had a complete administration of either PolyCAb or placebo) in the Dose Leader pair.

Cohort 2:
Enrolment of Cohort 2 will only proceed if blinded safety data and pharmacokinetic data on the persistence of the drug from a minimum of 6 subjects in Cohort 1 has been reviewed by the Sponsor and Chief Investigator and found to be satisfactory. Once this is in place, 8 subjects (in 2 sub-cohorts of 4 subjects,) will receive the same 34 mL dose of PolyCAb (6 subjects) or placebo (2 subjects) as used in Cohort 1b, but on three occasions (days 1, 4 and 7). Subjects will be assessed at intervals for any physical adverse events (local tolerability, itching, rashes, inflammation), vital signs (blood pressure, heart rate, respiratory rate and temperature) and standard laboratory safety tests (haematology, biochemistry and urinalysis). In addition, blood samples will be taken to measure the presence of ovine immunoglobulin G (pharmacokinetics of PolyCAb) and the presence of human antibodies directed against the administered ovine immunoglobulins (immunogenicity assessments).

Original interventions:
The study is in two cohorts. Cohort 1 (single ascending doses) will be conducted in up to 16 subjects (2 cohorts of 8 subjects), and cohort 2 (multiple dose) will be conducted in 1 cohort of 8 subjects.

Cohort 1:
Six subjects will receive a single intravenous injection of PolyCAb (500mg ovine total immunoglobulins at a concentration of 25g/l in 153mM sodium chloride buffered with 20 mM sodium citrate/citric acid pH 5.8-6.2. The drug will be administered as a 20 mL volume, over 60 minutes (min) using a syringe driver. An additional 2 subjects will have placebo (the same buffered saline solution as above but without the ovine immunoglobulins) administered in the same way. Dosing will be staggered in that there will be an initial Dose Leader group of 2 subjects (one PolyCAb, one placebo) who will receive their treatments 24 hours before the others, and at least 15 min apart. The Chief Investigator must confirm whether it is safe to

continue with the dosing of the remaining 6 subjects (5 PolyCAb, 1 placebo) following a review of appropriate safety data from evaluable subjects (defined as those who have had a complete administration of either PolyCAb or placebo) in the Dose Leader pair.

Cohort 2:
Enrolment of Cohort 2 will only proceed if blinded safety data and pharmacokinetic data on the persistence of the drug from a minimum of 6 subjects in Cohort 1 has been reviewed by the Sponsor and Chief Investigator and found to be satisfactory. Once this is in place, 8 subjects (in 2 sub-cohorts of 4 subjects,) will receive the same 20 mL dose of PolyCAb (6 subjects) or placebo (2 subjects) as used in Cohort 1, but on three occasions (days 1, 4 and 7).
Subjects will be assessed at intervals for any physical adverse events (local tolerability, itching, rashes, inflammation), vital signs (blood pressure, heart rate, respiratory rate and temperature) and standard laboratory safety tests (haematology, biochemistry and urinalysis). In addition, blood samples will be taken to measure the presence of ovine immunoglobulin G (pharmacokinetics of PolyCAb) and the presence of human antibodies directed against the administered ovine immunoglobulins (immunogenicity assessments).

Intervention Type
Biological/Vaccine

Phase
Phase I

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

Primary outcome(s)
Cohort 1:
1. Adverse Events (AEs) and concomitant medication check are monitored continuously throughout the study
2. 12 lead ECGs pre-dose, day 1 (at 2, 4, 8 and 12 hours), and days 2, 8, 15, 22, 29
3. Vital signs (compared with pre-dose values) including supine blood pressure, heart rate, respiratory rate and temperature are measured pre-dose, day 1 (at 2, 4, 8 and 12 hours), and days 2, 8, 15, 22, 29
4. Local tolerability assessment (degree of erythema with or without induration, vesicles, bullae, pustules, erosion or ulceration at the injection site) is measured pre- and immediately post-dose, day 1 (at 15 min, 30 min, 1, 2, 8 and 12 hours), and days 2, 3, 6, 8, 15, 22, 29
5. Laboratory safety tests on haematology (haemoglobin, haematocrit, mean cell volume, mean cell haemoglobin concentration, red blood cells, while blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets), biochemistry (total protein, albumin, total bilirubin, alanine transaminase, aspartate transaminase, gamma glutamyl transferase, glucose, sodium, potassium, bicarbonate, creatinine and urea) and urinalysis (protein, glucose, specific gravity, ketones, urobilinogen, bilirubin, pH and blood) are measured on days 1, 3, 8, 15, 22 and 29

Cohort 2:
1. 12 lead ECGs are completed on days 1, 4 and 7 (pre-dose, 2h, 4h, 8h, 12h), and days 2 5, 8, 15, 22 and 29
2. Vital signs (as above) are measured on days, 1, 4 and 7 (pre-dose, 2h, 4h, 8h, 12h), and days 2, 5, 8, 10, 12, 15, 22 and 29
3. Local tolerability (as above) are measured on days 1, 4 and 7 (pre- and immediately post-dose,

15 min, 30 min, 1h, 2h, 8h, 12h), and days 2, 5, 8, 10, 12, 15, 22 and 29
4. Laboratory safety tests (as above) are measured on days 1, 2, 5, 8, 15, 22 and 29

Key secondary outcome(s))
Cohort 1:
1. Drug concentration measurements for pharmacokinetic determinations, determined by measuring (by immunoassay) the presence of ovine immunoglobulins in the subjects' serum are measured pre-dose, immediately on completion of drug or placebo infusion, 15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h, 7 d, 14 d, 28 d.
2. Immunogenicity –Immunoassay to determine the development of human antibodies directed against ovine immunoglobulins are measured pre-dose, and on days 8, 15, 22, and 29

Cohort 2:
1. Drug concentration measurements for pharmacokinetic determinations, determined by measuring (by immunoassay) the presence of ovine immunoglobulins in the subjects' serum are measured for days 1, 4 and 5 - Pre-dose, immediately upon completion of the drug/placebo infusion, 15 min, 30 min, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 12 h and 24 h. In addition, for day 7: 3 d, 5 d, 8d, 15 d, and 22d. 28 d.
2. Immunogenicity –Immunoassay to determine the development of human antibodies directed against ovine immunoglobulins are measured pre-dose, and on days 8, 15, 22, and 29

Completion date
31/03/2017

Eligibility

Key inclusion criteria
1. Healthy male and female subjects between 18 and 70 years of age. At least 2 subjects in each cohort should be > 60 years of age. (added 30/09/2016)
2. Female subjects of non-child bearing potential with negative pregnancy test at screening visit (to be confirmed prior to first dose)
3. Male subject willing to use two effective methods of contraception (unless anatomically sterile or abstaining as preferred and usual lifestyle)
4. Body Mass Index between 18.5 and 30
5. No clinically significant abnormal serum biochemistry, haematology and urine levels measured within 28 days of the first dose
6. Negative results for urinary drugs of abuse screen, determined within 28 days of the first dose (a positive alcohol test may be repeated at the discretion of the Investigator)
7. Negative HIV and hepatitis B surface antigen (Hep B) and hepatitis C virus antibody (Hep C) results
8. No clinically significant abnormalities in vital signs (blood pressure, pulse, respiration rate and oral temperature) determined within 28 days of the first dose
9. No clinically significant abnormalities in 12-lead ECG determined within 28 days of the first dose
10. Available to complete the study (including all follow-up visits)
11. Subject must satisfy a medical examiner about their fitness to participate in the study
12. Subject must provide written informed consent to participate

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Receipt of regular prescription and / or OTC medication within 28 days of the first dose that may have an impact on the safety and objectives of the study (at the Investigator's discretion)
2. Subjects with any clinically significant disease including but not limited to cardiovascular, respiratory, metabolic, immunologic, hepatic, renal, endocrinal, neurologic, skin or psychiatric disease
3. Subject with a current or past history of any psychological or psychiatric disorders
4. Evidence of gastrointestinal, renal, hepatic, central nervous system, respiratory, cardiovascular or metabolic dysfunction
5. Subjects with allergy/ hypersensitivity to any medication including marketed, unmarketed or OTC medications. Any clinically significant findings at planned site of infusion, including dark skin, tattoos or veins not suitable for venepuncture.
6. A clinically significant allergic disease (excluding non-active seasonal allergy)
7. A clinically significant history of drug or alcohol abuse in past 3 years
8. Inability to communicate well with the Investigator (i.e., language problem, poor mental development or impaired cerebral function)
9. Participation in a clinical study or receipt of treatment with any ovine antibodies or other ovine serum constituents
10. Participation in a New Chemical Entity clinical study within the previous 3 months or a marketed drug clinical study within the previous 30 days (Washout period between studies is defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study)
11. Donation of 450 mL or more blood within the previous 3 months
12. Vaccination within the previous 3 months which may have an impact on the safety or objectives of the study (at the Investigator's discretion)

To be confirmed at Baseline / Prior to First Dose:
1. Development of any exclusion criteria since the Screening Visit
2. Receipt of any medication since the Screening Visit that may have an impact on the safety and objectives of the study (at the Investigator's discretion)

Date of first enrolment
15/12/2015

Date of final enrolment
31/12/2016

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
Simbec Research Limited
Pentrebach
Merthyr Tydfil
United Kingdom
CF48 4DR

Sponsor information

Organisation
MicroPharm Limited

Funder(s)

Funder type
Industry

Funder Name
MicroPharm Limited

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		16/05/2017	21/07/2021	No	No
HRA research summary			28/06/2023	No	No