A multi-center, randomized, double-blind study to compare the efficacy and safety of cadazolid versus vancomycin in subjects with Clostridium difficile-associated diarrhea (CDAD).;and substuy protocol:;A multi-center sub-study to validate the CDAD-DaySyms (Clostridium difficile-associated diarrhea - Daily Symptoms) PRO in sub CDAD participating in study AC-061A301 or AC-061A302.

Published: 01-07-2014
Last updated: 20-04-2024

Primary objectiveTo determine whether the clinical response after 10-day oral administration of cadazolid is non-inferior to oral vancomycin in subjects with CDAD.Secondary objectivesTo determine whether oral administration of cadazolid for 10 days...

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

Summary

ID

NL-OMON44362

Source
ToetsingOnline

Brief title
AC-061A301_Actelion

Condition

- Gastrointestinal infections

Synonym
Clostridium difficile-associated diarrhea

Research involving
Human

Sponsors and support

Primary sponsor: Actelion Pharmaceuticals
Source(s) of monetary or material Support: Pharmaceutisch industry

Intervention

Keyword: Cadazolid, CDAD, Vancomycine

Outcome measures

Primary outcome

Primary endpoint

Clinical Cure defined as:

- Resolution of Diarrhea (ROD: <= 3 UBMs per day for at least 2 consecutive

days) on study treatment, maintained for 2 days after EOT

AND

- No additional antimicrobial treatment active against CDAD or FMT between

first dose and 2 days after EOT (inclusive).

Secondary outcome

Secondary endpoints

Sustained Cure defined as: Clinical Cure AND No Recurrence

Time to ROD, defined as:

The time (h) elapsed between the first dose of study drug and the time when ROD is considered achieved. Absolute change from baseline in CDAD DaySyms Patient Reported Outcomes (PRO). CDAD DaysSyms total daily score change from baseline up to Day 12.

Study description

Background summary

Clostridium difficile-associated diarrhea (CDAD) is an infectious disease of the gastrointestinal tract. CDAD usually occurs in patients with a history of antibiotic use that allows C. difficile to grow and elaborate virulent toxins that can cause intestinal inflammation and diarrhea.
CDAD incidence has been increasing in recent years and disease severity and mortality has also been increasing.
Several factors, including the 027/BI/NAP1 hypervirulent strain and the recurrence rate, have contributed to the overall morbidity and mortality of CDAD and have resulted in the re-emergence of C. difficile as a major global health problem. New drug therapy that reduces recurrence rates, or improves outcomes for patients infected with the hypervirulent strain or those with severe disease, remains a significant unmet medical need.

Study objective

Primary objective
To determine whether the clinical response after 10-day oral administration of cadazolid is non-inferior to oral vancomycin in subjects with CDAD.

Secondary objectives
To determine whether oral administration of cadazolid for 10 days is superior to oral vancomycin in the sustained clinical response of subjects with CDAD.
To determine whether the resolution of diarrhea (ROD) is more rapid with oral administration of cadazolid compared to vancomycin.
To determine whether CDAD symptoms, as reported by the subject, show larger improvements from baseline with oral administration of cadazolid compared to vancomycin.

Meta-analysis objective
To determine whether oral administration of cadazolid for 10 days is superior to oral vancomycin in the sustained clinical response of subjects with CDAD due to hypervirulent strains.

Safety objective
To determine safety and tolerability of an oral administration of cadazolid compared to vancomycin. Exploratory objectives are described in the core protocol.

Study design

This is a prospective, multi-center, double-blind, double-dummy, randomized, parallel group, group sequential, active controlled, Phase 3 study.

Screening Period starts with the signature of the informed consent form (ICF) and ends with subject randomization (within 24 hours of the signature of the ICF).

Treatment Period starts immediately after randomization with the first dose of study drug and ends on the day of the last dose of study drug (EOT) 10 days later.
Follow-up Period starts after the last dose of study drug and ends approximately 30 days after the last dose of study drug (Visit 5).

Re-treatment extension with cadazolid: Subjects who experience a recurrence and provide consent may enter a re-treatment extension with cadazolid consisting of a 10-day treatment of cadazolid followed by an approximately 30-day follow-up period.

Subject participation in the study will be up to 44 days; up to 88 days for subjects participating in the re-treatment extension with cadazolid.

Intervention

Investigational drug Cadazolid 250 mg or matching placebo granules for oral suspension twice daily with or without food.
Comparator Oral vancomycin 125 mg or matching placebo capsules 4 times daily with or without food.

Study burden and risks

CORESTUDY [AND RETREATMENT EXTENSION]

The study medication and procedures have risks and discomforts. In any clinical research study there is the chance of experiencing side effects to the study medication. Also with any anti-bacterial medication, overgrowth of bacteria that are not killed could lead to treatment failure. It is possible that complications and side effects of cadazolid, which are still unknown at this time, may occur.
The most common side effects reported for adults treated with the same

cadazolid dose, or a higher dose, were: headache, dizziness, confusion, gas, indigestion, itching.

The following side effects were most frequently reported in adults treated with vancomycin: nausea, belly or stomach pain, low potassium, diarrhea, vomiting, gas, fever, headache, swelling of body tissue (usually in the legs), back pain, tiredness.
Kidney failure, chronic kidney disease and increased levels of creatinine have been reported with the use of vancomycin, occurring mostly in patients who receive very high doses of vancomycin given by a needle inserted into a vein (intravenously), have an underlying kidney disease, or who are on other medications associated with kidney disease. Blood tests will be done to monitor the kidney function during the study and after the study treatment is stopped. The risk of having kidney problems is higher for adults who are more than 65 years old.

More information about risks and discomforts related to the study medication and procedures.

Cadazolid
Side effects may occur at the dose of cadazolid that is given in this study.
The most common side effects reported for 62 adults with C.diff associated diarrhea treated with the same cadazolid dose or a higher dose were:
• Headache 8%
• Dizziness 5%
• Confusion 3%
• Gas 3%
• Indigestion 3%
• Itching 3%
In animals treated with cadazolid, slight and reversible increases in liver function tests were observed at doses higher than the dose that will be given in this study. In some patients treated with cadazolid, small and reversible increases in liver function tests have been observed.
In laboratory testing on cells, genotoxic effects (alteration of genetic information) were observed at doses higher than the dose of cadazolid that will be given during this study.

Vancomycin
The following side effects were most frequently reported in 260 adults treated with vancomycin for C.diff associated diarrhea:
• Nausea 17%
• Belly or stomach pain 15%
• Low potassium 13%
Other commonly reported side effects for vancomycin included:
• Diarrhea 9%
• Vomiting 9%
• Gas 8%

• Fever 9%
• Headache 7%
• Swelling of body tissue, usually in the legs 6%
• Back pain 6%
• Tiredness 5%
Kidney failure, chronic kidney disease and increased levels of creatinine have been reported with the use of vancomycin, occurring mostly in patients who receive very high doses of vancomycin given by a needle inserted into a vein (intravenously), have an underlying kidney disease, or who are on other medications associated with kidney disease. Hearing loss has been reported with vancomycin, occurring mostly in patients who receive very high doses of vancomycin given by a needle inserted into a vein (intravenously), have an underlying hearing loss, or who are on other medications associated with hearing loss.

Study Procedures
There is a slight risk of pain or bruising and infection when blood is drawn. Some subjects may experience lightheadedness or fainting during or after having their blood drawn.
For the electrocardiogram (ECG), electrodes will be placed on the body using a weak glue or tape and there is a risk of skin irritation when the electrodes are removed.

Pregnancy
Information about risks, precautions and prevention related to pregnancy
The safety of cadazolid during pregnancy is not known. Research in animals investigating whether the drug can cause abnormalities of the embryo/foetus is still ongoing.
Women cannot take part in this study if they are pregnant, or if they are nursing (breastfeeding). Women who are able to have children, must use a reliable form of birth control throughout the study and up to 30 days after stopping taking study medication.
Therefore, they can only participate in this study if they are postmenopausal, surgically or naturally sterile, or are using one of the following method of contraception:
• Diaphragm, cap or contraceptive sponge with a spermicide used in combination with condoms with or without spermicide.
• Intra-uterine devices (IUD)
• Injectable contraceptive agents, levonorgestrel implants, or transdermal contraceptive hormone patches, provided they have been used for at least one month prior to the start of study drug.
• Sterilization method such as tubal ligation or partner's vasectomy
Oral contraceptives require additional methods to be used as diarrhea could affect how well they work. In this case you must also use a diaphragm, cap or contraceptive sponge with a spermicide in combination with condoms with or without spermicide.

SUBSTUDY [PRO]

There is no risk of physical harm related to participating in this optional sub-study; however, you may feel uncomfortable sharing personal information about your symptoms of C. Diff associated diarrhea.

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

- Signed Informed Consent.
- Male or female >= 18 years of age. Females of childbearing potential must agree to use an adequate and reliable method of contraception.
- Subject with a diagnosis of mild-moderate or severe CDAD (first occurrence or first recurrence within 3 months) with: Diarrhea: a change in bowel habits with > 3 unformed

bowel
movements (UBM) within 24 hours prior to randomization,
AND
Positive C. difficile toxin test on a stool sample produced within 72 hours prior to randomization.

Exclusion criteria

- More than one previous episode of CDAD in the 3-month period prior to randomization.
- Evidence of life-threatening or fulminant CDAD.
- Likelihood of death within 72 hours from any cause.
- History of inflammatory colitides, chronic abdominal pain, or chronic diarrhea or known positive diagnostic test for enteropathogenes.
- Antimicrobial treatment active against CDAD administered for > 24 hours except for metronidazole treatment failures (MTF)
- Known hypersensitivity or contraindication to study drugs, oxazolidinones, or quinolones.
- Unable or unwilling to comply with all protocol requirements.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-09-2015
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cadazolid
Generic name:	-
Product type:	Medicine
Brand name:	Vancomycine
Generic name:	-
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-07-2014
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	13-10-2014
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	25-03-2015
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	02-04-2015
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	30-10-2015
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	23-11-2015
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

Approved WMO Date:	10-02-2016
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	15-02-2016
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	20-05-2016
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	23-05-2016
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	16-08-2016
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	23-08-2016
Application type:	Amendment
Review commission:	METC Isala Klinieken (Zwolle)

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	EUCTR2013-002528-17-NL
ClinicalTrials.gov	NCT01987895
CCMO	NL48699.075.14