An Exploratory Study to Compare the Efficacy and Safety of Micafungin as a Pre-emptive Treatment of Invasive Candidiasis versus Placebo in High Risk Surgical Subjects with Intra-abdominal Infections - A Multicentre, Randomized, Double-Blind Study

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Primary Objectives:To assess the incidence and the time to confirmed IFI in subjects treated pre-emptively with micafungin versus placebo.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Fungal infectious disorders
Study type	Interventional

Summary

ID

NL-OMON34416

Source
ToetsingOnline

Brief title
INTENSE

Condition

- Fungal infectious disorders

Synonym
Invasive Candidiasis caused by intra-abdominal infections; fungal infections that entered your body

Research involving
Human

Sponsors and support

Primary sponsor: Astellas Pharma B.V.
Source(s) of monetary or material Support: Industrie (Astellas Pharma Europe B.V.)

Intervention

Keyword: Efficacy and Safety, High Risk Surgical Subjects, Intra-abdominal Infections, Micafungin

Outcome measures

Primary outcome

Primary parameters:

- The incidence of an invasive fungal infection

- The time to develop an invasive fungal infection.

Secondary outcome

Secondary objectives:

To assess the efficacy, organ dysfunction, safety and tolerability, survival

and health economic variables in subjects treated pre-emptively with Micafungin

versus placebo.

Study description

Background summary

Over the last couple of decades, Candida infections have emerged as a major cause of morbidity and mortality in hospitalized patients. It is estimated that invasive candidiasis (IC) affects around 2% of the general intensive care unit (ICU) patient population.

Despite introduction of new anti-fungal drugs and advances in the supportive management of critically ill patients, candidemia remains associated with

attributable mortality. Even though establishing attributable mortality of candidal infections is difficult, there is a general consensus that these infections are associated with substantial health care costs

Patients undergoing surgery (especially gastrointestinal) are considered to be at particularly high risk of developing IC due to their underlying severity of illness, impaired integrity of gastrointestinal mucosa and frequency of treatment with broad-spectrum antibiotics and parenteral nutrition. As a commensal of the digestive tract, Candida may leak into the peritoneal cavity after perforation of a hollow viscus or surgical section of the intestinal wall. peritoneal cavity after perforation of a hollow viscus or surgical section of the intestinal wall. While in most cases it will be cleared quickly from the peritoneum, in some patients peritoneal seeding will result in the development of an intra-abdominal Candida infection, with a risk of dissemination to the bloodstream and to extra-abdominal tissues and organs

It has been demonstrated that early introduction of anti-fungal therapy is essential for the control of infection and favorable clinical outcomes. Observational studies have shown that delayed introduction of anti-fungal treatment in candidemia is associated with worse outcomes: when anti-fungal therapy was initiated within 24 hours of drawing the first positive blood culture, the mortality was 15 to 19%, compared with 33% where initiated after 24 hours.

Current established microbiological diagnostic tools are often insensitive and cause a delay. Therefore it is interesting to search for different strategies in selected groups of patients. A limited number of bigger and smaller clinical trials with Fluconazole proved that there was a benefit with regards to pre-emptive treatment. Therefore there is a need for further research in this area, aimed at establishing the benefit of early anti-fungal treatment in homogeneous but not overly pre-selected patient populations and for the different anti-fungal drug classes.

Micafungin exerts its pharmalogical action by inhibiting the enzyme 1,3-β-D-glucan synthase, an essential component of the fungal cell wall. Micafungin shows broad spectrum fungicidal activity against Candida spp., including those with reduced fluconazole susceptibility and intrinsic resistance to fluconazole and amphotericin B.

In this research the efficacy and safety of a pre-emptive treatment with Micafungin will be compared to placebo in high risk surgery patients with intra-abdominal infections.

Study objective

Primary Objectives:
To assess the incidence and the time to confirmed IFI in subjects treated

pre-emptively with micafungin versus placebo.

Study design

An exploratory, multicenter, randomized, double-blind study. Phase II.

Intervention

The subjects will be entered into the study for 4 months. All participants will start with the pre-emptive treatment (Mycamine or placebo) for their condition for at least 1 day and a maximum of 6 weeks.

The subject will receive the study medicine every day during the treatment period until his or her condition has improved or until it is confirmed that he or she has a fungal infection.

The study is divided into the below mentioned visits:

- Baseline visit (after surgery but before start of the treatment)
- Treatment period (at least 1 day and maximum 6 weeks).
- End of Treatment visit
- End of Study visit (28 days after the treatment period)
- Long term follow-up visit (90 days after the treatment period).

Study burden and risks

The doctor will perform the following tests during the study:

After surgery before study medication intake:
• Medical History including any medications
• Pregnancy Test (if applicable)
• Physical Exam including a measurement height and weight
• Blood pressure, respiratory rate and temperature
• Blood sample for monitoring kidney and liver function
• Blood sample for PCR and Beta-D-Glucan analysis
• The doctor will investigate if the subject has, or is showing signs of, a fungal infection
by taking swabs from parts of the body and blood and maybe a scan to make a part of the inside of the body visible
• The subject will be asked by the doctor about his/her general condition and complaints. If these
complaints warrant further investigation, additional tests will be done

During the treatment period:
• Physical Exam (at least twice a week)
• Blood pressure, respiratory rate and temperature (at least twice a week)

• Blood test for monitoring kidney and liver function (at least twice a week)
• Blood sample for PCR and Beta-D-Glucan analysis (at least twice a week)
• The doctor will investigate if the subject has, or is showing signs of, a fungal infection
by taking swabs from parts of the body (at least twice a week) and blood (at least once a week)
and maybe a scan to make a part of the inside of the body visible
• The subject will be asked by the doctor about his/her general condition and complaints. If these
complaints warrant further investigation, additional tests will be done

28 days after the last dose of study medication:
• Physical Exam
• Blood pressure, respiratory rate and temperature
• Blood test for monitoring kidney and liver function
• The doctor may take a scan to make a part of the inside of the body visible
• The subject will be asked by the doctor about his/her general condition and complaints. If these
complaints warrant further investigation, additional tests will be done
• The subject will be asked to complete a questionnaire twice, once asking how he/she felt before
going to the intensive care unit and again asking how he/she felt at the end of the study.

90 days after the last dose of study medication:
• The subject will be asked by the doctor about his/her general condition and complaints. If these
complaints warrant further investigation, additional tests will be done

The study medication will be administered intravenously.

The risks for the subjects are the side effects of the study medication.

Side effect reported by subjects using Mycamin® are specified below:
Abnormal blood tests (decreased white blood cells [leucopenia; neutropenia]); decreased red blood cells
(anaemia), decreased potassium in the blood (hypokalaemia); decreased magnesium in the
blood (hypomagnesaemia); decreased calcium in the blood (hypocalcaemia), headache,
inflammation of the vein wall (at injection-site), feeling sick; being sick; diarrhoea;
abdominal pain, abnormal liver function tests (increased alkaline phosphatase; increased
aspartate aminotransferase, increased alanine aminotransferase), increased bile pigment in the

blood (hyperbilirubinaemia), rash, fever, rigors (shivering).

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

The subject will be eligible for the study if all of the following apply:
1. >= 18 years of age.
2. Localized or generalized intra-abdominal infection requiring surgery and ICU stay.
3. If CAI, at least 72 hours (but not more than 120 hours) of ICU stay, counted from the end of surgery, and a further expected duration of ICU stay of >= 48 hours.
4. If NAI, duration of ICU stay <= 48 hours, counted from the end of surgery, and a further expected duration of ICU stay of >= 48 hours.
5. Female subject of childbearing potential must have a negative urine or serum pregnancy test prior to randomization and must agree to maintain highly effective birth control during

the study. A highly effective method of birth control is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner.
6. The subject has been fully informed and has given written informed consent to participate in the study. Witnessed informed consent is accepted in case the subject is capable of making the decision but not capable of signing the document. Subjects who lack the capacity to give consent may be included in the study with a relative/legal representative written agreement for the subject to participate according to the local law of the country. If during the course of the study drug treatment the subject condition changes and is capable of providing consent, then this will be obtained.

Exclusion criteria

Subjects will be excluded from participation if any of the following apply:
1. Acute pancreatitis.
2. Neutropenia (ANC <1,000/mm3) at the time of randomization.
3. Infected intra-peritoneal dialysis.
4. Patients undergoing solid organ transplantation.
5. Documented invasive candidiasis at the time of randomization.
6. Expected survival < 48 hours.
7. Any systemically active anti-fungal within 14 days prior to administration of the study drug.
8. Allergy, hypersensitivity, or any serious reaction to an echinocandin anti-fungal or any of the study drug excipients.
9. Currently receiving and/or has taken an investigational drug within 28 days prior to randomization.
10. Pregnant woman or breast-feeding mother.
11. *Do Not Resuscitate* order.
12. Severe liver insufficiency, advanced liver fibrosis, cirrhosis or hepatitis.
13. The subject, in the opinion of the investigator, may find it difficult to adhere to the provisions of treatment and observation specified in the protocol.
14. Any concomitant medical condition that could interfere with the study conduct and protocol procedures or contraindicate subject*s participation in the study.

Study design

Design

Study phase:	2
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):	03-01-2011
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Mycamine
Generic name:	Micafungin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-03-2010
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-08-2010
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-09-2010
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	18-02-2011
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2008-006409-18-NL
ClinicalTrials.gov	NCT01122368
CCMO	NL33282.056.10