An open label phase IIa trial to assess efficacy and tolerability of a once a week oral dose of 200 mg R126638 in disto-lateral toenail onychomycosis.

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The objective of this open label phase IIa trial is to evaluate the efficacy and tolerability of a once a week dose of 200 mg R126638, for a maximum of 12 weeks, for the treatment of toenail onychomycosis.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin and subcutaneous tissue disorders NEC
Study type	Interventional

Summary

ID

NL-OMON29995

Source
ToetsingOnline

Brief title
R126638 in toenail onychomycosis

Condition

- Skin and subcutaneous tissue disorders NEC

Synonym
toenail fungi, toenail infections

Research involving
Human

Sponsors and support

Primary sponsor: Barrier Therapeutics

Source(s) of monetary or material Support: Barrier Therapeutics NV.

Intervention

Keyword: IIa, onychomycosis, R126638, trial

Outcome measures

Primary outcome

Therapeutic cure i.e. mycological and clinical cure

Secondary outcome

Scoring of individual signs and symptoms

Measuring length of unaffected nail

Mycological evaluation

Study description

Background summary

R126638 is a synthetic triazole antifungal agent, with excellent potential for oral and topical treatment of fungal infections of skin, hair, nails, oral and genital mucosa. It is clear from in vitro data that R126638 is active against infections caused by dermatophytes (Trichophyton spp., Microsporum canis, Epidermophyton floccosum), yeasts (including C. albicans and Malassezia spp.) and many other fungi (Odds et al., 2004). The strong activity of R126638 is ascribed to its prominent affinity to fungal cytochrome P450, which is involved in the biosynthesis of ergosterol from lanosterol (Vanden Bossche et al., 2004). Ergosterol is a vital component of cellular membranes in fungi and its specific inhibition by R126638 results in altered fungal growth and impaired viability. In vivo experiments in mice and guinea-pigs provided further evidence for a potent antifungal activity of R126638. A superior efficacy of R126638 over itraconazole (factor 4-8) has been found in experimental models of superficial fungal infections (Odds et al., 2004).

Experiments in human liver microsomes revealed that CYP3A4 was the cytochrome P450 form which was the most sensitive to inhibition by R126638. The drug shows a much lower interaction potential with CYP 3A4 compared to ketoconazole and itraconazole and does not significantly inhibit the human cytochromes P450 1A2, 2D6, 2C9, 2A6 and 2E1 (Vanden Bossche et al., 2004).

Onychomycosis is the most frequent nail disease and represents 30% of all mycotic infections of the skin. It is often caused by dermatophyte, yeasts or moulds. Fungal nail infections are chronic and recalcitrant to treatment. Currently available topical antifungals are generally ineffective; therefore oral antimycotics have become the treatment of choice. Itraconazole and terbinafine have been developed for pulse-therapy. The disadvantage of both drugs is the use for a complete week every month for several months. Fluconazole and the new azole, R126638, might require shorter treatment durations. For fluconazole a treatment schedule of a single weekly dosing has been tested in explorative trials. Since the MIC values for fluconazole are higher than those for R126638 (Jessup et al., 2000; Odds et al., 2004), it is expected that R126638 might show a high activity in onychomycosis by similar treatment schedules.
Recent pharmacokinetic studies have shown that R126638 has a high affinity for the nail (Van de Velde et al., in prep). In volunteers who received 100 or 200 mg o.d. for 1 week nail plate kinetics indicated that the drug could be detected in the nail at the first sampling point at 2 weeks after start of therapy, indicating that R126638 penetrates the nail via the nail bed. The identification of R126638 in fingernails by a second concentration peak, reflects that penetration via the nail matrix. Itraconazole penetrates the nail in a similar way. The Cmax in toenails seen at 4 to 8 weeks amounted to 179.3±144.1 ng/g. In part of the subject a secondary peak was seen at 12 to 24 weeks. Clearance from the nails was shown to be slow since the mean residence times were 27.8±15.4 weeks for the 200 mg dose group.

R126638 will be administered p.o. as oral solution at a dose of 200 mg once a week for a maximum of 3 months. Exposure levels after administration of this single weekly oral dose of 200 mg are expected to lead to an effective treatment of onychomycosis by clearing the dermatophyte, yeast or mould infection.

The expected exposure levels are also lower than those observed at the no-toxic effect dose levels in rats and dogs. To obtain a high bioavailability, R126638 should be administered as an oral solution after overnight fasting. The plasma level after intake of a single dose of 200 mg R126638, given as an oral solution, produced a Cmax of 755 ng/ml and an AUC0-24h of 7672 ng.h/ml (Bruynseels et al., 2004). Slight clinical changes such as vomiting and soft faeces were observed in dogs from the dose of 40 mg/kg body weight onwards. Both symptoms were slight and disappeared shortly thereafter. At a dose of 40 mg/kg the Cmax amounted to 1595 ng/ml and the AUC0-24h was 26500 ng.h/ml in these dogs.
Cardiovascular safety, clinical laboratory safety and tolerability of single oral doses of 12.5 up to 1200 mg were studied in three phase I cross-over trials each with 18 volunteers (Van der Geest et al., 2000; Tritsmans et al., 2000; Leempoels et al., 2000). A fourth phase I study was a multiple dose trial with R126638 dosed for 1 week at 100 mg and 200 mg compared to placebo (Bruynseels et al., 2004). In these four phase I studies, the number of

adverse events with R126638 was limited and comparable with placebo. Furthermore, in all four phase I studies, no consistent or relevant changes in vital signs, electrocardiogram, and clinical laboratory tests were reported. From these studies it was concluded that R126638 administered as a single dose (dose ranging from 12.5 to 1200 mg) and as a multiple dose for 1 week at (dosages of 100 and 200 mg) is safe and well tolerated. (Van der Geest et al., 2000; Tritsmans et al., 2000; Leempoels et al., 2000; Bruynseels et al., 2004).

Study objective

The objective of this open label phase IIa trial is to evaluate the efficacy and tolerability of a once a week dose of 200 mg R126638, for a maximum of 12 weeks, for the treatment of toenail onychomycosis.

Study design

Open label phase IIa trial

Intervention

Blood sampling: On maximum 7 of the 8 visits. This for a safety evaluation.
ECG recording: Three times, once pre-treatment and twice post-treatment. This for a safety evaluation with special attention for the QT/QTc interval.

Study burden and risks

The number of adverse events reported in clinical trials with R126638 was very limited and relatedness with the product considered absent or doubtful. Adverse experiences reported in association with the use of R126638 are expected to be similar with those reported for other azoles:
1) headache
2) gastro-intestinal disturbances (nausea, diarrhoea)
3) skin reactions (such as itch, erythema)
4) reversible changes in liver enzymes.

Contacts

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Scientific

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male and female subjects of 18 to 70 years old including extremes.
2. Clinical diagnosis of disto-lateral onychomycosis of the toenails.
3. Diagnosis confirmed by microscopic examination and culture
4. If the subject is of childbearing potential, she must have a negative urine pregnancy test at inclusion and agree to use effective forms of birth control (double barrier method) during the duration of the clinical trial or until the first menses after 60 days following the last dose of study medication, whichever is longer. She must be on a stable regimen, for at least one month, of oral contraceptives, contraceptive implant or depot injection, contraceptive patch, IUD, condom and spermicidal agent or diaphragm and spermicidal agent.
5. Availability of a signed informed consent prior to beginning protocol-specific procedures, indicating an understanding of the purpose of this trial and a willingness to adhere to the treatment regimen and trial procedures described in this protocol.
6. The subject is in good health and free of any disease or physical condition which, in the investigator*s opinion, might impair evaluation of onychomycosis of the toenail(s).

Exclusion criteria

1. More than 50% involvement of the most severely affected toenail.
2. An involvement of the nail matrix.
3. Lateral onychomycosis involving > 50% of the length of the most severely affected toenail.
4. Extensive hyperkeratosis (>3mm nail thickness) on the most severely affected toenail.

5. An involvement nail of the little toes only
6. Psoriasis or diabetics.
7. History of significant sensitivity, or significant allergy to azoles or related drugs or any ingredient in the study medication.
8. Severe coexisting hepatic, renal, or bone marrow disease, hyperlipidemia, chronic pancreatitis, or a history indicating adrenal cortex dysfunction or any other serious disease (including cancer and subjects known to be HIV positive).
9. History of heart-failure, myocardial infarction within the past six months, cardiac arrhythmia, or under treatment for heart disorders.
10. Clinical significant abnormal ECG-intervals or morphology of the ECG, QT or QTc>450 ms.
11. Use of any local or systemic anti-mycotic therapy two weeks (local) or three months (systemic) before treatment.
12. Current use of prohibited medication. CYP3A4 metabolized substrates such as triazolam, oral midazolam, alprazolam, buspirone, Ca-channel blockers such as dihydropyridines and verapamil, tiralazad, fentanyl, alfentanyl, coumarins; CYP3A4 metabolized HMG-CoA reductase inhibitors such as lovastatin, simvastatin, atorvastatin, pravastatin; potent enzyme inducers of CYP3A4, e.g. phenytoin phenobarbital, carbamazepine, isoniazid, rifampin, rifabutin; potent inhibitors of CYP3A4, e.g. ritonavir, indinavir and saquinavir; drugs known to prolong QT-interval such as class Ia and III antiarrythmics, sotalol, terenadine, astemizole, cisapride, levacetylmethadol (levomethadyl), misolastine, azolastine, antimalarials such as chloroquine, quinidine and halofantrine, macrolides, quinolones, antipsychotics; systemic immunosuppressants e.g. cyclosporine and tacrolimus, rapamycin (sirolimus), methotrexate, 6-mercaptopurine; systemic corticosteroids.
13. Out of range laboratory values that the investigators considers as pathologic.
14. History or suspicion of alcohol abuse or drug abuse, or psychological or other emotional problems which, in the investigator*s opinion, are likely to invalidate informed consent, or limit the ability of the subject to comply with the protocol requirements.
15. Breasting-feeding women and pregnant women.
16. Participation in an investigational study within 30 days prior to study entry.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-10-2006
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pramiconazole
Generic name:	Pramiconazole

Ethics review

Approved WMO Date:	11-07-2006
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-08-2006
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-09-2006
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2005-004611-30-NL
CCMO	NL13110.060.06