Multicenter, randomized, double-blind, placebo-controlled study to evaluate the effect of ITF2357 on mucosal healing in patients with moderate-to-severe active Crohn*s Disease.

Published: 03-08-2007
Last updated: 08-05-2024

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Ethical review	Approved WMO
Status	Pending
Health condition type	Gastrointestinal inflammatory conditions
Study type	Interventional

Summary

ID

NL-OMON31172

Source
ToetsingOnline

Brief title
ITF2357 in moderate to severe active Crohn's disease

Condition

- Gastrointestinal inflammatory conditions

Synonym
chronic intestinal inflammation, Crohn's disease

Research involving
Human

Sponsors and support

Primary sponsor: Italfarmaco S.p.a.
Source(s) of monetary or material Support: Italfarmaco S.p.a.

Intervention

Keyword: Crohn's disease, ITF2357, mucosal healing

Outcome measures

Primary outcome

Rate of complete mucosal healing at week 8.

Secondary outcome

1. to evaluate the effect of ITF2357 on endoscopic disease activity assessed

using both the Crohn*s Disease Endoscopic Index of Severity (CDEIS) and the

Simple Endoscopic Score of Crohn*s Disease (SES-CD)

2. to evaluate the effect of ITF2357 on clinical disease activity, assessed

using the Crohn*s Disease Activity Index (CDAI)

3. to assess safety and tolerability of ITF2357

4. to assess pharmacokinetic properties of ITF2357

Study description

Background summary

ITF2357 is an orally active, synthetic inhibitor of histone deacetylase (HDAC) enzyme, which has been demonstrated to selectively inhibit the in-vitro production of pro-inflammatory cytokines and to exhibit in-vivo anti-inflammatory effects, both in animals and in humans.
A previous study completed in CD patients provided preliminary evidence that short-term (8 weeks) treatment with oral ITF2357 can induce disease improvement in a substantial proportion of patients. The dose of 50 mg b.i.d. appeared to be the most promising one, as it was able to induce a clinical benefit, with

more than 40 % of the patients achieving remission after 8-weeks.

Study objective

Primary objective of the study is to determine the ability of ITF2357, administered orally at the dose of 50 mg b.i.d. for 8 consecutive weeks, to induce complete healing of mucosal ulcerations of ileum and/or colon, assessed by endoscopy,
Secondary objectives are:
1. to evaluate the effect of ITF2357 on endoscopic disease activity assessed using both the Crohn*s Disease Endoscopic Index of Severity (CDEIS) and the Simple Endoscopic Score of Crohn*s Disease (SES-CD)
2. to evaluate the effect of ITF2357 on clinical disease activity, assessed using the Crohn*s Disease Activity Index (CDAI)
3. to assess safety and tolerability of ITF2357
4. to assess pharmacokinetic properties of ITF2357

Study design

Multicentre, randomized (1:1), double-blind, placebo-controlled study; sequential design with interim analysis after completion of 40 subjects.

Intervention

Oral ITF2357 50 mg b.i.d. or matching placebo for 8 consecutive weeks.

Study burden and risks

Based on the known mechanism of action of ITF2357, the results of pre-clinical studies in animals and on the previous clinical trial conducted in patients with Crohn*s disease, it can be expected that ITF2357 offers a clinical benefit associated with healing of intestinal mucosa to those patients affected by Crohn*s disease who do not respond to standard therapies.
Up to now ITF 2357 has been administered to 243 subjects, including healthy volunteers and patients The side effects most notified of ITF2357 are mild to moderate platelets count reductions, non specific gastrointestinal symptoms including nausea, vomiting and diarrhea, mild upper respiratory tract infections, isolated cases of palpitation and tachycardia. In addition a slight increase in creatinine levels, possibly suggesting an effect on renal function, was observed in some Crohn*s patients receiving ITF2357.
The effects on platelets observed in Crohn*s disease and psoriasis patients were more evident at the 100 mg twice daily, conversely, at doses such as 50 mg given once or twice daily the decrease in platelet counts were well confined within the range of normality.
More pronounced effects on blood cells and reduced gastro-intestinal tolerability were seen on patients with hematological malignancies treated with

higher doses of ITF23547. Recently, some important alterations in the ECG, which can possibly cause severe arrhythmias, were seen in two patients with blood tumors treated with high doses of ITF2357. In addition one patient with a severe and rare type of lymphoma had a fatal liver failure while in treatment with ITF 2357 and ITF2357 could have contributed to the occurrence of this event.

Contacts

Public
Italfarmaco S.p.a.

Via dei Lavoratori, 54
20092 Cinisello Balsamo
Italie
Scientific
Italfarmaco S.p.a.

Via dei Lavoratori, 54
20092 Cinisello Balsamo
Italie

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Age: ><=18 years
- Diagnosis of CD, (re)-established by endoscopy and/or X-ray and/or surgery in the last 36 months
- CD in active phase since at least 2 weeks before screening

- CDAI between 220 and 450
- CDEIS > 8
- ulcerations greater than aphthous ulcers in at least 1 of the bowel segments from the ileum to the rectum
- If any on-going treatment with corticosteroids (prednisone, prednisolone or budesonide), at a dose equivalent to or less than 30 mg/day prednisone, or 9 mg of budesonide, in use for at least one month and at a stable dose for at least two weeks before patient enrolment
- If any on-going treatment with immunosuppressant (azathioprine, 6-mercaptopurine, methotrexate), in use for at least 3 months before patient enrolment
- If any on-going treatment with 5-aminosalicilates, in use for at least 4 weeks before patient enrolment, at a dose ><= 2 g
- Females of childbearing potential with negative pregnancy tests
- Signed written informed consent to participate in this trial

Exclusion criteria

- Treatment in the previous 2 months with anti-TNFa antibodies
- Primary failure to previous treatment with anti-TNFa antibodies-
- Current bowel obstruction or any condition that may predispose to its development (or intestinal perforation or significant GI hemorrhage
- Expected surgery for the duration of the study
- Any ostomy or extensive bowel resection
- Positive serological anti-HCV and HBV and anti-HIV testing
- Other on-going clinical relevant viral infections (e.g. herpes zoster, Epstein-Barr, CMV), systemic fungal infections or history of recurrent serious bacterial infections
- Signs and symptoms of severe, progressive or uncontrolled renal, hepatic, haematologic, endocrine, pulmonary, cardiac, neurologic or cerebral disease
- QTc interval > 450 msec at pre-treatment evaluation
- Serum magnesium and potassium below the LLN at pre-treatment evaluation
- Platelet counts below 200 x 109/L at pre-treatment evaluation
- Unavoidable concomitant treatment with any drug known for potential risk of causing Torsades de Pointes (see list in Appendix F)
- History of cancer with less than 5 years documentation of a disease-free state
- History of tuberculosis

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:	Pending
Start date (anticipated):	01-07-2007
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ITF2357
Generic name:	ITF2357

Ethics review

Approved WMO

Date:	03-08-2007
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2007-000189-19-NL
CCMO	NL18119.018.07