A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP, MULTI-CENTRE STUDY TO INVESTIGATE THE SAFETY AND EFFICACY OF CP-690,550 FOR MAINTENANCE THERAPY IN SUBJECTS WITH MODERATE TO SEVERE CROHN'S DISEASE

Published: 27-12-2011
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Primary objectiveThe primary objective of the study is to estimate the effects of tofacitinib in maintaining a clinical response or being in remission in subjects with moderate to severe Crohn*s disease previously achieving clinical response or...

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

Summary

ID

NL-OMON41338

Source
ToetsingOnline

Brief title
A3921084 - Crohn's Disease (9002/0096)

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's disease, inflammatory bowel disease (IBD)

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Ministerie van OC&W,Farmaceutical industry

Intervention

Keyword: Crohn's disease, Phase 2b, placebo-controlled, Tofacitinib

Outcome measures

Primary outcome

The proportion of subjects maintaining clinical response-100, as defined by a decrease in CDAI score at least 100 points from A3921083 baseline, or being in clinical remission, as defined by a CDAI score less than 150, at Week 26.

Secondary outcome

•The proportion of subjects maintaining clinical response-100 or being in clinical remission at Weeks 4, 8, 12, 20 and 26 from the A3921083 Baseline.

•The proportion of subjects maintaining at least a clinical response-100 at Weeks 4, 8, 12, 20 and 26.

•The proportion of subjects in clinical remission at Weeks 4, 8, 12, 20 and 26.

•The proportion of subjects in clinical remission at Weeks 4, 8, 12, 20, and 26 among subjects in clinical remission at baseline of maintenance study.

•The proportion of subjects in sustained clinical remission in the maintenance phase. Sustained clinical remission is defined as being in clinical remission at both Weeks 20 and 26.

•The proportion of subjects achieving sustained clinical response in the maintenance phase. Sustained clinical response is defined as having at least a

clinical response-100 at both Weeks 20 and 26 from the A3921083 Baseline.

• CDAI scores over time and CDAI scores change from Baseline.

• The time to relapse. Relapse is defined as increase in CDAI of >100 points

from the maintenance phase baseline and a CDAI score of >220

points.

•The proportion of subjects achieving a steroid-free clinical remission at Week

26 of the maintenance phase among subjects on steroids at baseline.

• Serum CRP and fecal calprotectin over time and change from baseline in CRP

and fecal calprotectin.

• Plasma concentrations of tofacitinib .

Study description

Background summary

Tofacitinib is being developed for the treatment of adult patients with moderate-to-severe Crohn*s disease. Crohn*s disease is a chronic relapsing, transmural inflammatory disease that can affect the entire gastrointestinal tract and is most commonly located in the ileum and colon (40%) or just involves the small bowel (30%) or the colon (25%). Although the cause remains unknown, the most likely pathogenesis of Crohn*s disease is defective immunoregulation in genetically susceptible patients, leading to an upregulation of macrophages and Th1 lymphocytes and the production of an excess of cytokines, interleukins and chemokines, all of which can lead to enhanced inflammation, impaired wound healing and tissue damage. Increasing evidence suggests that upregulation of some cytokines that use the common gamma-chain in their signal transduction pathways may play a role in the pathogenesis of inflammatory bowel disease.
At present, no current pharmacological therapy provides a cure for Crohn*s disease and the treatment goal is to induce and then maintain remission. Despite available treatment options, there is still a large unmet medical need with many patients failing to achieve clinical remission or experiencing apparent loss of initial efficacy with continued use. Surgery also is not curative and often followed by disease recurrence. Thus, there is need for a novel therapy that will surpass the efficacy of currently used agents, but will

have less toxicity and a more convenient route of administration.
Tofacitinib is a potent, selective inhibitor of the JAK family of kinases, thereby blocking signaling through the common gamma chain-containing receptors for several cytokines that are integral to lymphocyte activation, proliferation and function: inhibition of this signaling pathway by tofacitinib may thus result in modulation of multiple aspects of the immune response and thereby offers a novel therapeutic approach for the treatment of Crohn*s disease.
The primary objective of this study is to estimate the effects of tofacitinib in maintaining a clinical response or being in remission in subjects with moderate to severe Crohn*s disease previously achieving clinical response or remission in induction Study A3921083. Please see chapter 1 of the protocol (introduction) for more details.

Study objective

Primary objective
The primary objective of the study is to estimate the effects of tofacitinib in maintaining a clinical response or being in remission in subjects with moderate to severe Crohn*s disease previously achieving clinical response or remission in induction Study A3921083.

Secondary objectives
- To evaluate the safety and tolerability of tofacitinib as a maintenance therapy in subjects with active Crohn*s disease.
- To estimate the effect of tofacitinib as a maintenance therapy on clinical remission, sustained remission and sustained response rates in subjects with Crohn*s disease.
- To evaluate the pharmacokinetics of tofacitinib as a maintenance therapy in subjects with moderate to severe Crohn*s disease.
- To evaluate the effect of tofacitinib as a maintenance therapy on quality of life in subjects with moderate to severe Crohn*s disease.
- To evaluate the effect of tofacitinib as a maintenance therapy on CRP and fecal calprotectin.

Study design

This is a Phase 2b, randomized, double-blind, placebocontrolled, parallel group, dose-ranging, multi-centre study in subjects with Crohn*s disease who completed the double-blind induction treatment in Study A3921083 and achieved clinical response-100 and/or clinical remission (CDAI<150) at Week 8. This trial will include a 26-week double-blind treatment period and a 4-week follow-up period.

The subject eligibility for Study A3921084 will be assessed based on study data collected at the Week 8 visit of Study A3921083. Subjects who achieve clinical response-100 and/or clinical remission (CDAI<150) after completion of the

8-week induction therapy in Study A3921083 and who fulfill all other inclusion/exclusion criteria will be randomly assigned to receive one of three treatments, tofacitinib 10 mg BID, 5 mg BID, or placebo BID with an allocation ratio of 1:1:1. Subjects will be stratified according to the treatment assignments and the degree of clinical response (remission or not) during Study A3921083.

Intervention

Subjects will be randomly assigned to receive one of three treatments, tofacitinib 10 mg BID, 5 mg BID, or placebo BID with an allocation ratio of 1:1:1. Subjects will be stratified according to the treatment assignments and the degree of clinical response (remission or not) during Study A3921083. Subjects will receive double-blind treatment for 26 weeks. The study drug and placebo are in the form of tablets and patients will be asked to orally take 2 tablets twice a day. Please see section E4 of this ABR form for the procedures to which the subjects will be subjected.

Study burden and risks

The unmet medical need in patients with Crohn*s disease, expected efficacy of tofacitinib in this indication and the safety profile of the compound which has emerged from the phase 2/3 programs in RA and other indications, imply that tofacitinib has a novel anti-inflammatory mechanism of action which is anticipated to be possibly effective in treating Crohn*s disease. The benefits to the subjects participating in this study will be a potential control of the disease activity by improving symptoms (stool frequency, abdominal pain) and general well-being. All subjects may also benefit from gaining knowledge about their health status through study tests and physician assessments, as well as having close monitoring of their inflammatory bowel disease.

The risks associated with tofacitinib are similar to the risks associated with the use of other immunosuppressive agents, including a potential increased risk for infections. Decreases in white blood cell counts, particularly neutrophils, and decreases in haemoglobin have been observed. These effects were usually mild to moderate and returned to normal after discontinuation of therapy. In previous studies with tofacitinib , increases in levels of LDL and HDL cholesterol were also reported, with the ratios of total / HDL cholesterol unchanged. The long-term implications of these changes for cardiovascular risk are currently unknown. Also seen in previous studies were slight increases in measured serum creatinine and serum transaminases. This effect generally returned to normal after discontinuation of therapy. Infections, anemia and neutropenia are all consistent with the pharmacology of tofacitinib as a potent inhibitor of JAK3 with cross-over to JAK1 and moderate selectivity for JAK2. Hypothetical safety risks that may be associated with the use of tofacitinib include an increased risk of lymphoma and lymphoproliferative disorders,

malignancy and teratogenicity.

The available data on the potential and identified risks of tofacitinib are thus considered to not preclude clinical studies in Crohn*s disease patients and the risks are minimized through appropriate pre-enrolment screening and close safety monitoring. Therefore, the overall risk-benefit assessment for this study is considered to be favourable.

Contacts

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Scientific
Pfizer

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

•Subjects who met study entry criteria, and who completed Week 8 visit of Induction Study A3921083.
•Subjects who achieve clinical response-100 (reduction in CDAI by 100 points) and/or clinical

remission (CDAI<150) in Study A3921083.
•Women of childbearing potential must test negative for pregnancy prior to study enrolment.;Inclusion criteria of the A3921083 induction study:
•Male or female subjects between the ages of 18 and 65 years at screening.
•Subjects with clinical diagnosis of Crohn's disease for at least 6 months prior to screening.
•Subjects with active moderate to severe ileal, ileocolic, or colonic CD defined by a baseline score of Crohn's Disease Activity Index (CDAI) of 220 to 450 at baseline.

Exclusion criteria

•Subjects who had major protocol violation (as determined by the Sponsor) in the A3921083 study.
•Fecal culture/toxin assay indicating presence of pathogenic infection, unless the subject has completed a full course of treatment or, if treatment is ongoing, be clinically improved in the judgement of the investigator.
•Presence of active (draining) fistulae, intrabdominal or perineal collection or abscess (MRI imaging is not required for entry to this study unless clinically indicated).

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):	29-10-2014
Enrollment:	15

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-Tofacitinib
Generic name:	-

Ethics review

Approved WMO Date:	27-12-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-11-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-01-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-06-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-04-2015

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-06-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2011-001754-28-NL
ClinicalTrials.gov	NCT01393899
CCMO	NL38428.091.11