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

Published: 22-12-2011
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Primary objective: The primary objective of the study is to evaluate the dose-response of tofacitinib in inducing clinical remission in subjects with moderate to severe Crohn*s disease and to select effective doses. Secondary objectives: -To...

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

Summary

ID

NL-OMON39768

Source
ToetsingOnline

Brief title
A3921083 - Crohn's Disease (9002/0083)

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: Farmaceutical industry

Intervention

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

Outcome measures

Primary outcome

The proportion of subjects in clinical remission at week 8 as defined by a

Crohn*s disease activity index (CDAI) score of less than 150 points.

Secondary outcome

-The proportions of subjects in clinical remission (CDAI<150) at Week 2 and 4.

-The proportion of subjects achieving clinical response-70 at Week 2, 4, and 8

as defined by a decrease in CDAI score of at least 70 points from baseline.

-The proportion of subjects achieving clinical response-100 at Week 2, 4, and 8

as defined by a decrease in CDAI score of at least 100 points from baseline.

-The proportion of subjects achieving either clinical response-100 or clinical

remission (CDAI<150) at Week 2, 4, and 8.

-CDAI scores over time.

-Serum CRP and fecal calprotectin levels over time.

-Plasma tofacitinib concentration over time.

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 characterize the dose-response relationship of tofacitinib in inducing clinical remission in subjects with moderate to severe Crohn*s disease and to select effective doses. Please see chapter 1 of the protocol (introduction) for more details.

Study objective

Primary objective:
The primary objective of the study is to evaluate the dose-response of tofacitinib in inducing clinical remission in subjects with moderate to severe Crohn*s disease and to select effective doses.

Secondary objectives:
-To evaluate the safety and tolerability of tofacitinib induction therapy in subjects with moderate to severe Crohn*s disease.
-To evaluate the dose-response of tofacitinib in inducing clinical response in subjects with moderate to severe Crohn*s disease.

-To characterize the pharmacokinetics of tofacitinib in subjects with moderate to severe Crohn*s disease. -To evaluate the effect of tofacitinib on quality of life in subjects with moderate to severe Crohn*s disease.
-To evaluate the effect of tofacitinib on CRP and fecal calprotectin.

Study design

This is a phase 2b, randomized, double-blind, placebo controlled, parallel group, doseranging, multi-centre study in subjects with moderate to severe active Crohn*s disease. This study consists of a screening period of 1 to 3 week duration and an 8-week double-blind treatment period, followed by a 4-week safety follow-up for subjects who do not continue in a 26-week maintenance study (Study A3921084). Approximately 275 subjects will be enrolled into the study. After the screening period, subjects who meet inclusion and exclusion criteria at the baseline visit will be randomly assigned to receive one of three treatments (tofacitinib 5 mg BID, 10 mg BID or placebo BID) with an allocation ratio of 1:1:1. Subjects will be stratified by whether or not they have previous exposure to anti-TNFα therapy. Subjects will receive double-blind treatment for 8 weeks. Subjects who complete the 8-week double-blind treatment and achieve clinical response-100 (defined by a decrease in CDAI score of at least 100 points from baseline) and/or are in clinical remission (CDAI < 150) are eligible to enter a 26-week maintenance study (Study A3921084). Subjects who withdraw early from the study and discontinue from the double-blind phase early will be asked to complete EOT/Early Withdrawal study procedures at Week 8. These early withdrawal subjects, along with subjects who complete the double-blind treatment period but are not eligible or are not willing to participate in Study A3921084, will be asked to complete EOS/Follow-up visit at Week 12, approximately 4 weeks after the last dose of study drug. Subject to IRB/EC approval, this trial will include an additional optional research component involving collection of biological samples for de-identified genetic analysis. The Molecular Profiling Supplement to this protocol provides a description of this additional research. Subjects may participate in the pharmacogenomics component of the research after signing an additional informed consent form.

Intervention

Subjects will be randomly assigned to receive one of three treatments (tofacitinib 5 mg BID, 10 mg BID or placebo BID) with an allocation ratio of 1:1:1. Subjects will be stratified by whether or not they have previous exposure to anti-TNFα therapy. Subjects will receive double-blind treatment for 8 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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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

•Male or female subjects between the ages of 18 and 65 years at screening. •Subjects with documented 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

• Diagnosis of indeterminate colitis, ulcerative colitis (UC), or clinical findings suggestive of UC. • Subjects diagnosed with Crohn's disease but without previous exposure to treatment (i.e., treatment-naïve). • Subjects receiving the following treatment for Crohn's disease: - Azathioprine, 6-mercaptopurine or methotrexate within 2 weeks prior to baseline. - Anti-TNFα therapy within 8 weeks prior to baseline. - Interferon therapy within 8 weeks prior to baseline. - Cyclosporine, mycophenolate, or tacrolimus within 4 weeks prior to baseline. - Intravenous corticosteroids within 2 weeks prior to baseline.

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):	27-05-2014
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-Tofacitinib
Generic name:	CP-690,550-10

Ethics review

Approved WMO Date:	22-12-2011
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:	28-01-2013
Application type:	Amendment

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:	13-03-2014
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)

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	EUCTR2011-001733-16-NL
ClinicalTrials.gov	NCT01393626
CCMO	NL38413.091.11