A MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY OF ORAL CP-690,550 AS A MAINTENANCE THERAPY IN SUBJECTS WITH ULCERATIVE COLITIS

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Primary Objective• To demonstrate the efficacy of tofacitinib as maintenance therapy in subjects with UC. Secondary Objectives• To evaluate the safety and tolerability of tofacitinib as maintenance therapy in subjects with UC.• To evaluate the...

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

Summary

ID

NL-OMON39090

Source
ToetsingOnline

Brief title
A3921096 (9002/008), OCTAVE Sustain

Condition

- Gastrointestinal inflammatory conditions

Synonym
inflammatory bowel disease, Ulcerative Colitis

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: industry

Intervention

Keyword: Maintenance Therapy, tofacitinib, Ulcerative Colitis

Outcome measures

Primary outcome

• The proportion of subjects in remission at Week 52. Remission is defined by a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0.

Secondary outcome

Key Secondary Endpoints

• The proportion of subjects with mucosal healing at Week 52. Mucosal healing is defined by a Mayo endoscopic subscore of 0 or 1.

• The proportion of subjects in sustained steroid free remission among subjects in remission at baseline of Study A3921096. Sustained steroid-free remission is defined by being in remission and steroid-free at both Week 24 and Week 52. Steroid free remission is defined by being in remission (a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and a rectal bleeding subscore of 0) in addition to not requiring any treatment with corticosteroid for at least 4 weeks prior to the visit.

Safety Endpoints

• Incidence and severity of adverse events.

• Incidence of serious infections (see Section 7.2.8).

• Incidence of addition of lipid lowering agents.

• Incidence and severity of laboratory abnormalities, and change from baseline in clinical laboratory values.

• Incidence of vital sign abnormalities and changes from baseline in vital signs.

• Incidence of clinically significant changes in physical examination from baseline.

• Incidence of electrocardiogram (ECG) abnormalities.

• Summary of adjudicated cardiovascular events.

• Summary of malignancies confirmed by central laboratory pathologist over-read.

Study description

Background summary

Tofacitinib is a potent, selective inhibitor of the JAK family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays, tofacitinib, inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimers containing JAK3 and/or JAK1 with functional selectivity over JAK2 homodimer signaling. Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including IL-2, -4,-7,-9, -15 and -21. These cytokines are integral to lymphocyte activation, proliferation, and function, and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro inflammatory cytokines, such as IL 6 and IFN Gamma. At higher exposures, inhibition of erythropoietin, prolactin and other hormones could occur via inhibition of JAK2 homodimer signaling.
The broad effects of JAK1/3 inhibition on multiple cytokine pathways provides

the rationale for developing tofacitinib as treatment for several diseases in which lymphocyte activation/proliferation plays a pathogenic role. Tofacitinib is being studied as an oral treatment for UC, Crohn*s disease, as a disease-modifying anti rheumatic drug (DMARD) for the treatment of RA, as treatment for plaque psoriasis and for the prevention of renal allograft rejection.

Study objective

Primary Objective
• To demonstrate the efficacy of tofacitinib as maintenance therapy in subjects with UC.

Secondary Objectives
• To evaluate the safety and tolerability of tofacitinib as maintenance therapy in subjects with UC.
• To evaluate the efficacy of tofacitinib maintenance therapy in achieving mucosal healing in subjects with UC.
• To evaluate the tofacitinib pharmacokinetic exposure during maintenance therapy in subjects with UC.
• To evaluate the effect of tofacitinib as maintenance therapy on quality-of-life in subjects with UC.

Study design

This is a Phase 3, randomized, double blind, placebo controlled, parallel group, multi centre study in subjects with ulcerative colitis who have completed induction studies (A3921094 or A3921095) and achieved clinical response. Clinical response is defined by a decrease from induction study baseline in Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. This study consists of a 53 week double blind treatment period with a final complete evaluation at Week 52 followed by a 4 week safety follow up for subjects who do not participate in the OLE study (A3921139).
Approximately 654 subjects will be enrolled in the study. The eligibility of a subject for the study will be assessed based on study data collected at the Week 8 visit of Study A3921094 or A3921095, which will be considered and recorded as the baseline visit for Study A3921096. Subjects who achieved clinical response after completing the 8 week induction therapy in either Study A3921094 or A3921095 are eligible to be randomly assigned to receive one of three treatments: tofacitinib 10 mg BID, 5 mg BID, or the matching placebo BID with an allocation ratio of 1:1:1. Subjects will be stratified according to the treatment assignments in the induction study (A3921094 or A3921095) and the degree of clinical response (whether remission is achieved or not). Subjects enrolled into the study will receive double blind maintenance treatment for 53

weeks.
Subjects will be required to remain on stable doses of their concomitant medications for UC during the study treatment period, with the exception of corticosteroids. Tapering steroids will be commenced from Week 0, when the subject enters into the study. For subjects receiving corticosteroids, the daily dose of prednisone or equivalent should be decreased at a rate of 5 mg per week until the dose reaches 20 mg/day, then by 2.5 to 5.0 mg per week to 10 mg/day, and then by 2.5 mg per week until the dose reaches 0 mg. For subjects receiving budesonide, the daily dose of budesonide should be decreased at a rate of 3 mg every three weeks until the dose reaches 0 mg.
At the end of the double blind treatment period, subjects who complete the study will have an opportunity to enter the open label Study A3921139.
Subjects who withdraw early due to treatment failure will have an opportunity to enter the open label study A3921139. Treatment failure is defined by an increase in Mayo score of at least 3 points from the baseline of the maintenance study, accompanied by an increase in rectal bleeding subscore by at least 1 point, and an increase of endoscopic subscore of at least 1 point yielding an absolute endoscopic subscore of at least 2 after a minimum treatment of 8 weeks in the study. Centrally read endoscopic subscores will be used to determine treatment failure.
Subjects who do not participate in the OLE (eg, withdraw early from the study not due to treatment failure and subjects who complete the double blind treatment period but do not participate into the open label study) will conclude this study and have a 4 week safety follow up after the last dose of study drug. These subjects will be given the Post Treatment UC HCRU questionnaires to be completed every 4 weeks and sent back to the site on a monthly basis until the anniversary of the study (Week 52).
During the double blind treatment period, subjects who demonstrate loss of response based on partial Mayo scores could have an unscheduled endoscopy performed to assess for treatment failure. Further unscheduled endoscopy is not required unless clinically warranted in the opinion of the investigator.

Intervention

Subjects will be equally randomized to one of the three treatment groups:
• Tofacitinib 10 mg BID orally.
• Tofacitinib 5 mg BID orally.
• Placebo BID orally.

Study burden and risks

Based on the totality of the non-clinical and clinical data generated thus far, potentially important safety risks that have been observed with the oral use of tofacitinib in humans include infections, neutropenia, anemia, increases in serum creatinine, increases in lipids (increase in total, high density lipoprotein [HDL], and low density lipoprotein [LDL] cholesterol), and

increases in transaminases. Additional safety risks that may be associated with the use of tofacitinib include an increased risk for lymphoproliferative disorders/lymphoma (observed risk in renal transplant population treated with additional immunosuppressive co medications; potential risk in other populations) or other cancers and effects on pregnancy and fetus.

Complete information on tofacitinib safety information for the oral use of tofacitinib can be found in the current version of the tofacitinib Investigator*s Brochure.

Contacts

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Scientific
Pfizer

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Subjects who met study entry criteria and completed 9-week induction treatment from

Study A3921094 or A3921095.;2. Subjects who achieved clinical response in Study A3921094 or A3921095.
- Clinical response is defined by a decrease from the induction study baseline (A3921094 or A3921095) Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1. For eligibility assessment, clinical response will be determined based on the central-read endoscopy performed at Week 8 of Study A3921094 or A3921095 and the central-read endoscopy performed at Week 0 of Study A3921094 or A3921095.;3. Women of childbearing potential must test negative for pregnancy prior to study enrollment.
- Female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 4 weeks after the last dose of assigned treatment. A subject is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children and is sexually active.;4. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, bowel movement diary calls, and other study procedures.;5. Evidence of a personally signed and dated informed consent document(s) indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

Exclusion criteria

1. Subjects who had major protocol violation (as determined by the Sponsor) in Study A3921094 or A3921095.;2. Presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical findings suggestive of Crohn*s disease.;3. Subjects who have had surgery for UC or in the opinion of the investigator, are likely to require surgery for UC during the study period.;4. Subjects who are expected to receive any of prohibited concomitant medications, including medications that are either moderate to potent CYP3A inducers or inhibitors, during the study period as specified in Appendix 2 of the protocol.;5. Subjects who are expected to receive live or attenuated virus vaccination during study period and for 6 weeks after last dose of study drug.;6. Women who are pregnant or breastfeeding, or planning to become pregnant during the study period.;7. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities which may affect subject safety or interpretation of study results (ie, baseline QTcF >450 ms, complete LBBB, acute or indeterminate age myocardial infarction, 2nd-3rd degree AV block, or serious bradyarrhythmias or tachyarrhythmias; see Appendix 4 of the protocol.;8. Subjects who, in the opinion of the investigator or Pfizer, will be uncooperative or unable to comply with study procedures.;9. Subjects who are investigational site staff members or relatives of those site staff members or subjects who are Pfizer employees directly involved in the conduct of the trial.;10. Any other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.;11. Subjects who are participating in or interested in participating in other investigational studies during study A3921096.

Study design

Design

Study phase:	3
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):	15-08-2013
Enrollment:	47
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tofacitinib

Ethics review

Approved WMO Date:	12-03-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-11-2012

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-01-2016
Application type:	Amendment
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	EUCTR2011-004580-79-NL
ClinicalTrials.gov	NCTnumberunderapplication
CCMO	NL39327.018.12