A MULTI-CENTER, OPEN-LABEL STUDY OF CP-690,550 IN SUBJECTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS

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Primary Objective• To assess the safety and tolerability of long-term tofacitinib therapy in subjects with UC.Secondary Objectives• To evaluate the efficacy of long term tofacitinib therapy in subjects with UC.• To evaluate the effect of long term...

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

Summary

ID

NL-OMON47738

Source
ToetsingOnline

Brief title
A3921139 (9002/009), OCTAVE Open Label

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: Tofacitinib, Ulcerative Colitis

Outcome measures

Primary outcome

Primary Endpoints

• As this is an open label extension study, there will be no primary efficacy endpoint.

• Incidence and severity of adverse events.

Secondary outcome

Secondary Endpoints

• The proportion of subjects in remission at Month 2, Month 12, Month 24 and Month 36. Remission in this study is defined as a Mayo score smaller than or equal to 2 with no individual subscore >1, and rectal bleeding subscore of 0.

• The proportion of subjects in remission at Month 2, Month 12, Month 24, and Month 36 among the following four subgroups of subjects based on the status at baseline of Study A3921139: 1) in remission defined by a total Mayo score smaller than or equal to 2 with no individual subscore >1, and rectal bleeding subscore of 0, 2) treatment failure defined by an increase in Mayo score of at least 3 points from baseline value of the maintenance study (A3921096), 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 greater than or equal to 2), 3) all other subjects from maintenance study A3921096 neither in remission nor fulfilling the definition of treatment failure, and 4) non responders from induction studies A3921094 or A3921095.

• The proportion of subjects in partial Mayo score (PMS) remission over time.

• The proportion of subjects who achieve mucosal healing at Month 2, Month 12, Month 24 and Month 36. Mucosal healing is defined as a Mayo endoscopic subscore of 0 or 1.

• The proportion of subjects with total score in Inflammatory Bowel Disease Questionnaire (IBDQ) greater than or equal to 170 over time.

• Incidence of serious infections (defined as any infection AE that requires hospitalization or parenteral antimicrobials, or meets other criteria that require the infection to be classified as a serious adverse event (SAE)).

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

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

• Incidence of clinically significant changes in physical examinations from

baseline.

• Incidence of electrocardiogram (ECG) abnormalities during treatment.

• Summary of adjudicated cardiovascular events.

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

• Proportion of subjects with addition of lipid lowering agents.

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 tofacitinibblocks 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*. 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 tofacitinibas 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 assess the safety and tolerability of long-term tofacitinib therapy in subjects with UC.

Secondary Objectives
• To evaluate the efficacy of long term tofacitinib therapy in subjects with UC.
• To evaluate the effect of long term tofacitinib therapy on quality-of-life in subjects with UC.

Study design

This is a Phase 3, multi center, open label study in subjects who have completed or demonstrated treatment failure in the maintenance study A3921096, or who were non responders after completing 8 weeks of treatment in the induction studies A3921094 or A3921095. Approximately 725 subjects are expected to become eligible for the study. This study will continue up to first market approval (FMA) in a global major market which may occur prior to Month 36.

Subjects who completed Study A3921096 or had early withdrawal due to treatment failure as defined in the A3921096 protocol are eligible to enroll in this study, A3921139. In addition, subjects who complete 8 weeks of treatment in Study A3921094 or A3921095 and are classified as non responders are eligible to enroll in this study. The eligibility of a subject for this study will be assessed based on study data collected at Week 8/9 of Study A3921094 or A3921095 (for non responders) or the Week 52/53 visit (for completers) or early termination visit (early withdrawals due to treatment failure) of Study A3921096. The study data collected at the Week 8/9 visit for Study A3921094 or A3921095 (for non responders) or the Week 52/53 visit or early termination visit of Study A3921096 will be recorded as the baseline data for Study A3921139.

Eligible subjects will be assigned to either tofacitinib 5 mg BID or 10 mg BID depending on whether the subject is in remission at baseline of Study A3921139. Remission is defined by a total Mayo score smaller than or equal to 2 with no individual subscore >1, and rectal bleeding subscore of 0. Eligible subjects who are in remission at Week 52 of Study A3921096 will be assigned to receive tofacitinib 5 mg BID. For treatment assignment, the central read assessment of the Mayo endoscopic subscores will be used to determine if a subject is in remission. Subjects who complete Study A3921096 but do not meet the remission definition or who are early withdrawals due to treatment failure in Study A3921096 are eligible to receive tofacitinib 10 mg BID. Treatment failure is defined by an increase in Mayo score of at least 3 points from baseline value of the maintenance study (A3921096), 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 *2) after a minimum of 8 weeks of treatment in the maintenance study. Subjects who complete 8 weeks of treatment in the induction studies A3921094 or A3921095 and are classified as non responders are also eligible to receive tofacitinib 10 mg BID.

Tofacitinib dose can be adjusted from 5 mg BID to 10 mg BID for efficacy and from 10 mg BID to 5 mg BID for safety or tolerability (see Section 5.8 for dose adjustment guidelines). Dose adjustments should be limited to no more than 1 occurrence per subject during the study and should be implemented at a regularly scheduled study visit.

Subjects from the induction studies A3921094 or A3921095 (ie, non responders) who fail to demonstrate clinical response at Month 2 of this study will be withdrawn from the study. 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. The endoscopic subscore based on central reading will be used to assess clinical response.
All subjects, who withdraw early or who complete this open label study, will have a 4 week safety follow up evaluation after the last dose of study medication.

Subjects will be required to remain on stable doses of their concomitant medications for UC during the study period. Subjects who enter this study on corticosteroids (eg, subjects who withdraw from Study A3921096 due to treatment failure or non responders at the end of Study A3921094 or A3921095) will need to continue the steroid tapering regimen described in Study A3921096 (see Section 5.5). If a subject requires rescue therapy or undergoes surgery, the subject should be withdrawn from the study and appropriate agents should be given at the discretion of the investigator.

Intervention

Subjects will be assigned to one of two dose groups depending on their remission status at baseline of Study A3921139:
• Tofacitinib 5 mg BID (subjects in remission).
• Tofacitinib 10 mg BID (all other subjects).

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

Public
Pfizer

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US
Scientific
Pfizer

East 42nd Street 235
New York 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subjects must meet either inclusion criterion number 1 or 2, and all other following inclusion criteria to be eligible for enrollment into the study:;1. Subjects previously participated in Study A3921096 who either;• completed 52 week maintenance treatment in Study A3921096, or;• were early withdrawals from Study A3921096 and met treatment failure criteria defined by an increase in Mayo score of at least 3 points from baseline value of the maintenance study (A3921096), 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 >=2), after a minimum of 8 weeks of treatment in the maintenance study. Note, endoscopic subscores based on central reading will be used to assess treatment failure.;2. Subjects who previously participated in the induction Study A3921094 or A3921095 who;• did not demonstrate clinical response after completing 8 weeks of treatment. Clinical response is defined by a decrease from 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, and;• have an endoscopic subscore at Week 8 that is either the same or higher (worse) than the endoscopic subscore at Week 0 of Study A3921094 or A3921095. Note, endoscopic subscores based on central reading will be used to determine eligibility.;3. 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. ;4. Women of childbearing potential must have a negative pregnancy test prior to study enrollment.;5. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, bowel movement diary calls, and other study procedures.;6. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.

Exclusion criteria

Subjects presenting with any of the following will not be included in the study:;1. Subjects who had a major protocol violation in Study A3921094, A3921095 or A3921096.;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 medications, including medications that are either moderate to potent CYP3A inducers or inhibitors, during the study period as specified in 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 medication.;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 (see protocol Appendix4).;8. Subjects with evidence of colonic malignancy or any dysplasia. Subjects with completely resected adenomatous polyp(s) may be eligible upon consultation with the sponsor.;9. Subjects who, in the opinion of the investigator or Pfizer, will be uncooperative or unable to

comply with study procedures.;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 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.;12. Subjects who are or interested in participating in other investigational studies during study participation.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-08-2013
Enrollment:	47
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tofacitinib citrate (clinical trial image)
Generic name:	Tofacitinib citrate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tofacitinib citrate (proposed commercial formulation - debossed)
Generic name:	Tofacitinib citrate

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:	20-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2013
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:	11-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-05-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-03-2017

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-03-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-08-2020
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	EUCTR2011-004581-14-NL
CCMO	NL39328.018.12