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

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Primary Objective* To demonstrate the efficacy of tofacitinib in inducing remission in subjects with moderately to severely active UC.Secondary Objectives* To evaluate the safety and tolerability of tofacitinib in subjects with moderately to...

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

Summary

ID

NL-OMON41381

Source
ToetsingOnline

Brief title
A3921095 (9002/007), OCTAVE Induction 2

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: Induction Therapy, Tofacitinib, Ulcerative Colitis

Outcome measures

Primary outcome

* The proportion of subjects in remission at Week 8. 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 Endpoint

* The proportion of subjects achieving mucosal healing at Week 8. Mucosal healing is defined by Mayo endoscopic subscore of 0 or 1.

Safety Endpoints

* Incidence and severity of adverse events.

* Incidence of serious infections (see Section 7.2.10 for definition).

* 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 in inducing remission in subjects

with moderately to severely active UC.

Secondary Objectives
* To evaluate the safety and tolerability of tofacitinib in subjects with moderately to severely active UC.
* To evaluate the efficacy of tofacitinib in achieving mucosal healing in subjects with moderately to severely active UC.
* To evaluate the effect of tofacitinib induction therapy on clinical outcomes in subjects with moderately to severely active UC.
* To evaluate the tofacitinib pharmacokinetic (PK) exposure during induction therapy in subjects with moderately to severely active UC.
* To evaluate the effect of induction treatment of tofacitinib on quality-of-life in subjects with moderately to severely active UC.

Study design

This is a Phase 3, randomized, double blind, placebo controlled, parallel group, multi center study in subjects with moderately to severely active ulcerative colitis. This study consists of a screening period up to three weeks, and a 9 week double-blind treatment period with the final complete evaluation at Week 8 followed by a 4 week safety follow up for subjects who are not participants in a maintenance study (A3921096) or an open label study (A3921139).

Approximately 545 subjects in total will be enrolled into the study. After the screening period, subjects who meet the inclusion and exclusion criteria at the baseline visit will be randomly assigned to receive one of two treatments of tofacitinib 10 mg BID or matched placebo BID at a 1:1 allocation ratio. Subjects will be stratified based on the status of prior treatment with anti TNF therapy, steroid use at baseline and geographic region. Subjects will receive double-blind treatment for 9 weeks.

Subjects who complete the double blind treatment and achieve clinical response at Week 8 are eligible to enter a double blind maintenance study (A3921096). Clinical response is defined by a decrease from baseline in Mayo score of at least 3 points and at least 30 percent, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1.

Subjects who complete the double blind treatment and do not achieve clinical response are eligible to enter an open label study (A3921139).

Subjects who are early withdrawals from the study or who are not transferred into the maintenance study or open label study will have a 4 week safety follow up after the last dose of study medication.

Intervention

Subjects will be randomized at a 1:1 ratio to one of the two treatment groups:
* Tofacitinib 10 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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Pfizer

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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

1. Subject must be at least 18 years of age. 2. Males and females with a diagnosis (endoscopic or radiographic and histological) of UC *4 months prior to entry into the study. A biopsy report supporting the diagnosis must be available in the source documents. 3. Subjects with moderately to severely active UC as defined by a total Mayo score of *6, with a rectal bleeding score of *1 and an endoscopic subscore of *2 on the Mayo score determined within 10 days of baseline visit (Visit 2). 4. Subjects must have failed or be intolerant (discontinued the medication due to an adverse event as determined by the investigator) of at least one of the following treatments for UC: * Oral or intravenous corticosteroids. * Azathioprine or 6 mercaptopurine (6 MP). * Anti-TNF-alpha therapy: infliximab or adalimumab. 5. Subjects currently receiving the following treatment for UC are eligible providing they have been and are anticipated to be on stable dose for designated period of time: * Oral 5 ASA or sulfasalazine stable dose for at least 4 weeks prior to baseline and during the study period. * Oral corticosteroids (prednisone equivalent up to 25 mg/day; budesonide up to 9 mg/day) stable dose for at least 2 weeks prior to baseline and during the study period. * Chronic treatment for ulcerative colitis with antibiotics (eg, metronidazole, rifaximin) stable dose for at least 2 weeks prior to baseline and during the study period. 6. No evidence of active or latent or inadequately treated infection with Mycobacterium tuberculosis (TB) prior to randomization as defined by all of the following: * A negative QuantiFERON® TB Gold (QFT-G) In Tube test documented within 3 months prior to or during screening. If initial and repeat QFT-G tests are indeterminate, a negative Mantoux/Purified Protein Derivative (PPD) tuberculin skin test (with a result of <5 mm of induration) documented within 3 months prior to or during screening is required. [Subjects with a history of Bacille Calmette Guérin (BCG) vaccination must have a negative QFT-G test]. * A chest radiograph, taken within the 3 months prior or during screening, without changes suggestive of active TB infection as determined by a qualified radiologist. * No history of either untreated or inadequately treated latent or active TB infection. * If a subject has previously received an adequate course of therapy for either latent (9 months of isoniazid in a locale where rates of primary multi drug TB resistance are <5% or an acceptable alternative regimen) or active (acceptable multi drug regimen) TB infection, neither a QFT G test nor a PPD test is needed, but a chest radiograph must still be obtained if not performed within 3 months prior to a given Screening visit. Documentation of adequate treatment for TB will be obtained prior to first dose of study drug. * A subject who is currently being treated for active TB infection is to

be excluded. * A subject who is currently being treated for latent TB infection can only be enrolled with confirmation of current incidence rates of multi drug resistant TB infection in the locale, documentation of an adequate treatment regimen, and with prior approval by the sponsor. 7. 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, he/she is biologically capable of having children and is sexually active. 8. Women of childbearing potential must have a negative pregnancy test prior to study enrollment. 9. Subjects receiving non-prohibited concomitant medications for any reason, must be on a stable regimen, which is defined as not starting a new drug or changing dosage with 7 days or 5 half lives (whichever is longer) prior to first study dose. 10. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, daily bowel movement diary call, and other study procedures. 11. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study. For the full list of exclusion criteria refer to section 4.2 of the protocol.

Exclusion criteria

1. Presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or clinical findings suggestive of Crohn*s disease. 2. Subjects with disease limited to distal 15 cm. 3. Subjects without previous treatment for UC (ie, treatment-naïve). 4. Subjects receiving the following therapy within the designated time period or are expected to receive any of these therapies during the study period: * Azathioprine, 6-mercaptopurine, or methotrexate within 2 weeks prior to baseline. * Anti-TNF-alpha therapy (eg, infliximab, adalimumab, or certolizumab) within 8 weeks prior to baseline. * Cyclosporine, mycophenolate, mofetil/ mycophenolic acid, or tacrolimus within 4 weeks prior to baseline. * Interferon therapy within 8 weeks prior to baseline. * Intravenous corticosteroids within 2 weeks prior to baseline. * Rectally administered formulation of corticosteroids or 5-ASA within 2 weeks prior to baseline. * Anti-adhesion molecule therapy taken within 1 year (eg, natalizumab or any investigational anti-adhesion molecule therapy). * Subjects with prior treatment with lymphocyte-depleting agents/ Subjects who have received rituximab or other selective B lymphocyte depleting agents are eligible if they have not received such therapy for at least 1 year prior to baseline * Other marketed immunosuppressants or biologics with immunomodulatory properties within 3 months prior to baseline. 5. Subjects displaying clinical signs of fulminant colitis or toxic megacolon. 6. Subjects with evidence of colonic adenomas or dysplasia. However, subjects with prior history of adenomatous polyps will be eligible if the polyps have been completely removed and the subjects are free of polyps at baseline. 7. Subjects at risk for colorectal cancer must have a colonoscopy. Colonoscopy report and pathology report (if biopsies are obtained) must be available in the source document: * If the subject is *50 years of age, a colonoscopy within 10 years of the screening visit is required to exclude adenomatous polyps. Subjects whose adenomas have been completely excised at baseline will be eligible. * If the subject has extensive colitis for *8 years or disease limited to left side of colon (ie, distal to splenic flexure) for *10 years, regardless of age, a colonoscopy within 1 year of the screening visit is required to survey for

dysplasia. Subjects with dysplasia or cancer identified on biopsies will be excluded. 8. 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. 9. Subjects who have positive stool examinations for enteric pathogens, pathogenic ova or parasites, or Clostridium difficile toxin at screening. 10. Subjects with clinically significant infections currently or within 6 months of baseline (eg, those requiring hospitalization or parenteral antimicrobial therapy or opportunistic infections), a history of any infection requiring antimicrobial therapy within 2 weeks of baseline, or a history of any infection otherwise judged by the investigator to have the potential for exacerbation by participation in the study. 11. Subjects with a history of more than one episode of herpes zoster, a history of disseminated herpes zoster or disseminated herpes simplex. 12. Subjects infected with human immunodeficiency virus (HIV) or hepatitis B or C viruses (Subjects with positive HCV antibody must have further testing for HCV RNA by PCR). 13. Subjects who have been vaccinated with live or attenuated vaccine within 6 weeks of baseline or scheduled to receive these vaccines during study period or within 6 weeks after last dose of study medication. 14. Subjects with history of any lymphoproliferative disorder (such as EBV-related lymphoproliferative disorder, as reported in some subjects on other immunosuppressive drugs), history of lymphoma, leukemia, myeloproliferative disorders, multiple myeloma, or signs and symptoms suggestive of current lymphatic disease. 15. Subjects with malignancies or a history of malignancies, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin. 16. Subjects receiving prohibited concomitant medications, including moderate to potent CYP3A inducers or inhibitors in the specified time periods prior to the first dose of study drug or are expected to receive any of these medications during the study period. * For moderate to potent CYP3A inducers, within 28 days or half-lives, whichever is longer, prior to first dose of study drug. * For moderate to potent CYP3A inhibitors, within 7 days or 5 half-lives, whichever is longer, prior to first dose of study drug. 17. Subjects with a history of bowel surgery within 6 months prior to baseline. 18. Subjects with significant trauma or major surgery within 4 weeks of screening visit. 19. Subjects likely to require any type of surgery during the study period.

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):	13-06-2013
Enrollment:	33
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:	12-12-2012
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:	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

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	EUCTR2011-004579-35-NL
ClinicalTrials.gov	NCTnumberunderapplication
CCMO	NL39325.018.12