A PHASE 2A, MULTICENTER, SINGLE ARM, OPEN-LABEL, TWO-STAGE, STUDY TO EVALUATE THE EFFICACY, SAFETY,TOLERABILITY AND PHARMACOKINETICS OF PF-06480605 IN SUBJECTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS

Published: 16-08-2016
Last updated: 15-04-2024

Primary Objectives* To evaluate the safety and tolerability of PF-06480605 in subjects with moderate to severe UC.* To evaluate the efficacy of PF-06480605 in induction of endoscopic improvement (as assessed by Mayo endoscopic subscore) at Week 14…

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

Summary

ID

NL-OMON47159

Source
ToetsingOnline

Brief title
9002/0442

Condition

- Gastrointestinal inflammatory conditions

Synonym
inflammation of the intestine, inflammatory bowel disease (IBD)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Open label, Phase 2A, Ulcerative colitis

Outcome measures

Primary outcome

Primary Endpoints

* Safety and tolerability of PF-06480605: TEAEs, withdrawal due to AEs, and

SAEs will be reported.

* Endoscopic improvement at Week 14 (defined as a Mayo endoscopic subscore of 0

or 1, and without friability).

Secondary outcome

Secondary Endpoints

* Remission at Week 14 (defined as a total Mayo score *2 with no individual

subscore

>1).

* Endoscopic remission at Week 14 (defined as a Mayo endoscopic subscore of 0).

* PF-06480605 plasma concentrations.

* Incidence of development of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs).

* Change from baseline in fecal calprotectin.

* Change from baseline in hsCRP.

* Change from baseline in serum total sTL1A.

Exploratory Endpoints

* Remission at Week 14 (defined as a Mayo endoscopic subscore of 0 or 1, without friability, with stool frequency subscore of 0, and rectal bleeding subscore of 0).

* Symptomatic remission at Week 14 (defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point, and both rectal bleeding and stool frequency subscore of 0).

* Deep remission at Week 14 (defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point and 0 on both endoscopic and rectal bleeding subscores).

* Clinical response at Week 14 (defined as a decrease from baseline in total Mayo score by at least 3 points and at least 30%, with a decrease in rectal

bleeding subscore of at least

1 point or an absolute subscore of 0 or 1).

* Change from baseline in partial Mayo score.

* Change from baseline in exploratory tissue biomarkers (Exploratory tissue biomarkers include, but may not be limited to, transcriptomic [RNA], protein analysis, microbiome, immunohistochemistry [IHC], and histology).

* Change from baseline in exploratory blood biomarkers (Exploratory blood biomarkers include, but may not be limited to, transcriptomic [RNA], and protein analysis).

* Change from baseline in exploratory stool biomarkers (microbiome).

* Change from baseline of UCEIS score.

* Histologic remission at Week 14 (defined as Geboes score *3.0 or Robarts Histopathology Index [RHI] *6).

* Affinity of anti-drug antibodies.

* Breadth and magnitude of T-cell response.

* Breadth and magnitude of B-cell response.

* Pooled or exploratory analyses, if conducted, utilizing the biobanked exploratory biomarker samples across PF-06480605 studies or across multiple programs will be documented in a separate protocol and/or statistical analysis plan.

Study description

Background summary

IBD is a chronic inflammatory condition of the gastrointestinal tract that affects five million people worldwide. IBD presents as one of two major forms, UC or Crohn*s Disease (CD). UC is characterized by continuous inflammation that is localized to the colon. CD is characterized by discontinuous inflammation that affects the entire gastrointestinal tract from mouth to anus and long-term debilitating sequelae, such as fistulae and intestinal strictures.

The incidence rates of UC in North America have been reported as high as 19.2 per 100,000 persons/year and prevalence as high as 248/100,000. It occurs more frequently in Caucasians and affects females about 35% more often than males. Although UC can occur at any age, the incidence peaks between 15 to 25 years with a second peak between 55 to
65 years. UC is a lifelong condition with a serious effect on the quality of life. Current treatment primarily consists of 5-aminosalicylic acid (5-ASA), corticosteroids, immunosuppressive agents (azathioprine/6-mercaptopurine), or biologic agents (anti-TNF or anti-integrin antibodies). However, despite recent advances, more effective pharmacological treatment is needed to induce and maintain remission.
PF-06480605 is a fully human neutralizing antibody against TL1A, a member of the TNF family of cytokines. PF-06480605 contains three mutations in the Fc region to reduce effector function. Its mechanism of action is to neutralize the binding and subsequent signaling of TL1A to its functional receptor DR3.

PF-06480605 is currently being developed for the treatment of IBD.

Study objective

Primary Objectives

* To evaluate the safety and tolerability of PF-06480605 in subjects with moderate to severe UC.

* To evaluate the efficacy of PF-06480605 in induction of endoscopic improvement (as assessed by Mayo endoscopic subscore) at Week 14 in subjects with moderate to severe UC.
Secondary Objectives
* To evaluate the efficacy of PF-06480605 in induction of remission at Week 14 (defined as a total Mayo score *2 with no individual subscore >1) in subjects with moderate to severe UC.

* To evaluate the efficacy of PF-06480605 in induction of endoscopic remission at Week 14 (defined as a Mayo endoscopic subscore of 0) in subjects with moderate to severe UC.

* To describe the PK of PF-06480605 in subjects with moderate to severe UC.

* To evaluate the immunogenicity of PF-06480605 in subjects with moderate to severe UC.

* To evaluate disease and pathway related biomarkers (ie, hsCRP and fecal calprotectin), and serum total sTL1A.

Exploratory Objectives
* To evaluate the efficacy of PF-06480605 based on remission, clinical response, and partial Mayo score.

* To evaluate pharmacodynamic (PD) biomarkers that might inform modulation of the TL1A pathway and enable a precision medicine strategy.

* To evaluate the correlation between the Mayo endoscopic subscore and the Ulcerative Colitis Endoscopic Index Score (UCEIS).

* To evaluate the efficacy of PF-06480605 in induction of histologic remission at Week 14 in subjects with moderate to severe UC.

* To investigate the relationship between drug peptide sequence, T-cell response and ADA induction.

* To collect exploratory biomarker sample(s) for biobanking.

Study design

This is a Phase 2a, single arm, two-stage study in subjects with moderate to severe UC. Subjects will receive 500 mg of PF-06480605 intravenously (IV) every 2weeks for a total of 7 doses. At the end of the first stage (12 evaluable subjects with a Week 14 colonoscopy), an interim analysis (IA) will be

performed for an early efficacy assessment. Enrollment in the second stage will be stopped if the futility criteria are met and any ongoing subjects in the second stage will be moved to the follow-up period. Otherwise, the study will continue to enroll additional subjects in the second stage for final efficacy assessment.
The duration of participation for eligible subjects will be approximately 8 months, including a screening period of up to 6 weeks, a 12 week treatment period, and a follow-up period ending 14 weeks after the last dose of IP. Subjects with AEs may be requested to return for additional follow-up for up to 3 months after the follow-up/end of study visit.

Intervention

Subjects will receive 500 mg of PF-06480605 intravenously every 2weeks for a total of 7 doses.

Study burden and risks

1. STUDY DESIGN AND OBJECTIVES
Study B7541002 is a Phase 2A, multicenter, single arm, open-label, two-stage study
evaluating the efficacy, safety, tolerability, and pharmacokinetics of PF-06480605 in subjects
with moderate to severe ulcerative colitis. This study will enroll a total of approximately
40 subjects with ulcerative colitis who meet eligibility criteria. The objectives of this study
are to evaluate the safety, tolerability, pharmacokinetics, and efficacy (based on Mayo
endoscopic subscore) of PF-06480605.
All eligible subjects will receive 500 mg of PF-06480605 intravenously, every 2 weeks for a
total of 7 doses. At the end of the first stage (12 evaluable subjects with a Week 14
endoscopy), an interim analysis will be performed for an early efficacy assessment.
Enrollment in the second stage will be stopped if the futility criteria are met and any ongoing
subjects in the second stage will be moved to the follow-up period. Otherwise, the study will
continue to enroll additional subjects in the second stage for final efficacy assessment. An
early pharmacokinetic (PK) readout of PF-06480605 serum concentrations will be conducted
after at least 6 subjects have completed the Week 4 visit to confirm that the predicted

exposures of PF-06480605 in ulcerative colitis patients are consistent with expected values,
based on the healthy subject PK data. The study will include an additional research
component involving collection of biological samples for de-identified exploratory
biomarker and immunogenicity analysis.
The current non-clinical toxicology package supports a 12 week treatment period. To
mitigate the need for a placebo arm, endoscopic improvement, a more objective endpoint,
with lower placebo rates than clinical disease activity scores, was selected as the primary
endpoint. All endoscopies will be read by a Central Reader who will be blinded to study
treatment. An induction period (12 weeks of dosing with primary endpoint at Week 14)
greater than the traditional 8 weeks was chosen to increase the likelihood of achieving
endoscopic improvement.
The duration of participation for eligible subjects will be approximately 8 months, including
a screening period of up to 6 weeks, a 12 week treatment period, and a follow-up period
ending 14 weeks after the first dose of PF-06480605.

2. POTENTIAL BENEFITS
Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal
tract affecting five million people worldwide. IBD presents as one of two major forms,
ulcerative colitis (UC) or Crohn*s disease (CD). UC is characterized by continuous
inflammation that is localized to the colon. Medical therapy is available for the treatment of
UC, but surgical resection of the entire colon provides a definitive cure.
Although the exact causes of CD and UC remain unclear, inhibition of pro-inflammatory
cytokines and adhesion molecules have proven to deliver some therapeutic benefit. The first
biologic therapy approved for UC was infliximab, a chimeric IgG1 antibody against TNF-a.
In the ACT1 and ACT2 trials, infliximab treatment of refractory moderate to severe UC
patients demonstrated up to a 29% placebo-corrected clinical remission rate at Week 8. By
Week 54 this rate had dropped to 18% (Rutgeerts et al, 2005). Patients that are

intolerant to
or eventually lose response to infliximab can be switched to other anti-TNF-* therapies, such
as adalimumab or golimumab. In the ULTRA 1 and ULTRA 2 trials, adalimumab treatment
of refractory moderate to severe UC Patients demonstrated up to a 10% placebo-corrected
clinical remission rate by Week 8 (Reinisch et al, 2011). At Week 52 this rate was reported
as 9% (Sandborn et al, 2012). The PURSUIT studies showed that golimumab treatment of
UC patients with moderate to severe disease activity resulted in 12% placebo-corrected
clinical remission at Week 6 (Sandborn et al, 2014a). Similarly, at Week 52, golimumab had
12% placebo-corrected clinical remission (Sandborn et al, 2014b). The anti-*4*7-integrin
antibody, vedolizumab, represents another class of drugs that has been approved for
treatment of UC. In the GEMINI 1 trial, vedolizumab treatment of refractory moderate to
severe UC patients demonstrated a placebo-corrected clinical remission rate of 11.5% at
Week 6. However, at Week 54, the placebo-corrected clinical remission rate was a high as
29.1% (Feagan et al, 2013).
It is clear that new therapies remain a need for UC patients since the majority of patients with
moderate to severe disease do not achieve or maintain remission. Surgical resection of the
colon can present long-term complications and should be used as a last-resort treatment for
UC patients. Taken together, more robust therapies remain an unmet medical need for UC
patients.
PF-06480605 is a fully human neutralizing antibody against Tumor Necrosis Factor-like
Ligand 1A (TL1A), a member of the tumor necrosis factor (TNF) family of cytokines.
PF-06480605 contains three mutations in the Fc region to reduce effector function. Its
mechanism of action is to neutralize the binding and subsequent signalizing of TL1A to its
functional receptor Death Receptor 3 (DR3).
The TL1A/DR3 pathway has been implicated in the regulation of pathogenic Th1, Th2, Th9
and Th17 T-cells, and of NK and NK-T cell responses, in immune-mediated

diseases. The
TL1A expression on antigen-presenting cells (monocytes, macrophages, dendritic cells) and
DR3 expression on effector cells (ILC2, T-cells, NK and NK-T cells) is highly dependent on
pro-inflammatory conditions. Moreover, data from non-clinical species and humans implicate TL1A in the pathophysiology of IBD. Taken together, PF-06480605 presents an
orthogonal mechanism of action to existing IBD therapies that could represent an important
addition to the existing IBD armamentarium.
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 disease.

3. POTENTIAL RISKS
Protocol mandated monitoring and discontinuation criteria are designed to identify and
follow laboratory changes that may be associated with PF-06480605 treatment. The potential risks associated with PF-06480605 identified are based on the totality of nonclinical
and clinical data across the entire PF-06480605 development program, with the clinical data
coming from studies in the healthy volunteer population.
No significant clinical findings have emerged from the completed Phase 1 first-in-human
(FIH) study that would impact subject safety. A total of 92 subjects, 60 and 32 subjects in
single ascending dose (SAD) and multiple ascending dose (MAD) periods, respectively, were
assigned to and received study treatment (PF-06490605 or placebo) in the first-in-human
Study B7541001. PF-06480605 doses of up to 800 mg administered intravenously in the
single ascending dose period, up to 300 mg X 3 administered subcutaneously, and 500 mg
X 3 administered intravenously at 2-week intervals in the multiple ascending dose period
were generally safe and well-tolerated in healthy subjects. There were no deaths, SAEs,
severe AEs, AEs resulting from ADA/NAbs, or subjects with dose reduced or temporary
discontinuations due to AEs during the FIH study with PF-06480605.
Preliminary embryo, fetal, and developmental toxicity studies (pEFD) are being conducted.
At this time, it is not known whether PF-06480605 can cause fetal harm when

administered
to pregnant women. It is also not known whether PF-06480605 can affect male or female
fertility, or whether PF-06480605 is secreted in human milk. Because of the investigational
nature of this product, PF-06480605 should not be administered to pregnant women or
women who are nursing an infant. Women of childbearing potential will be excluded from
the B7541002 study until the pEFD toxicity studies are completed and the data support
inclusion of this population of women. Investigators will be notified of the results of the
pEFD toxicity studies upon their completion.

4. ADDITIONAL RELEVANT INFORMATION
Pfizer believes that the current PF-06480605 Investigator*s Brochure (dated March 2016)
appropriately describes the known benefits and risks of PF-06480605. Safety and efficacy
data will continue to be closely monitored in all clinical trials, and any new safety concerns
will be promptly reported, as required.

5. CONCLUSION
In conclusion, Pfizer considers that the results of the nonclinical toxicity and safety
pharmacology studies, together with the clinical experience obtained to date with
PF-06480605, support the further investigation of PF-06480605 for the treatment of
moderate to severe ulcerative colitis, in subjects who have failed or are intolerant to at least
one conventional ulcerative colitis treatment.
Inflammatory bowel disease is a serious and potentially life-threatening disease. The
benefits to subjects participating in this study will be potential control of their ulcerative
colitis disease activity, as evidenced by improvement in the signs and symptoms of their
disease, and translating in overall improvement in quality of life. Study subjects may also
benefit from learning about their health as confirmed by study tests and assessments.
A more detailed discussion of PF-06480605 can be found in the Investigator*s Brochure.

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

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:;1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.;2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.;3. Male and/or female subjects between *18 and *75 years of age at the time of informed consent.;4. Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use two highly effective methods of contraception throughout the study and until the Week 26 visit (or 98 days after the last dose of IP).;Women of childbearing potential (WOCBP) will be eligible for this study provided these women use two highly effective
methods of contraception throughout the study and until the Week 26 visit (or 98 days after the last dose of IP), as outlined in Section 4.3. ;Female subjects who are not of childbearing

potential (ie, meet at least 1 of the following criteria):;* Have undergone a documented hysterectomy and/or bilateral oophorectomy;;* Have medically confirmed ovarian failure; or;Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state.;5. A diagnosis of UC for *4 months. A biopsy report must be available to confirm the histological diagnosis in the subject*s source documentation. In addition, a report documenting disease duration and extent of disease (eg, proctosigmoiditis, left-sided colitis, and pancolitis) based upon prior endoscopy must also be available in source documentation.;6. Subjects with moderate to severe active UC as defined (via screening colonoscopy) by a total Mayo score of *6, with a rectal bleeding subscore of *1 and an endoscopic subscore of *2 on the Mayo.;7. Active disease beyond the rectum (>15 cm of active disease at the screening colonoscopy).;8. Must have inadequate response to, loss of response to, or intolerance to at least one conventional therapy for UC:;* Steroids;;* Immunosuppressants (AZA [azathioprine], 6-MP, or MTX [methotrexate]);;* Anti-TNF inhibitors (eg, infliximab, adalimumab, or golimumab);;* Anti-integrin inhibitors (eg, vedolizumab).;For subjects in The Netherlands: Subjects must have inadequate response to, loss of response to, or intolerance to at least one biological therapy, such as an anti-TNF inhibitor.;Note: The information below is provided as guidance. Local standards of care, as well as investigator assessment should be considered.;Inadequate response to, loss of response to, or intolerance to corticosteroid treatment is defined as one or more of the following:;* Steroid refractory: persistent symptoms of active disease despite treatment with at least one 4-week induction regimen that included a dose of *30 mg prednisone (oral) daily for at least 2 weeks or IV for at least 1 week within the previous
5 years;;* Steroid dependent: two failed attempts to taper steroids below a dose equivalent to 10 mg prednisone (oral) daily;;* Steroid intolerant: history of intolerance to corticosteroids (including but not limited to Cushing*s syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, infection) within the previous 5 years.;Inadequate response to, loss of response to, or intolerance to prior immunosuppressant treatment is defined by one or more of the following:;* Persistent signs and symptoms of active disease despite a history of at least one 12-week regimen of oral AZA (*2-2.5 mg/kg/day) or 6-MP (*1-1.5 mg/kg/day) and/or MTX (*25 mg/week) within the previous 5 years;;* History of intolerance to AZA, 6-MP, or MTX (including but not limited to nausea/vomiting, abdominal pain, pancreatitis, LFT [liver function testing] abnormalities, lymphopenia, TPMT [thiopurine methyltransferase] genetic mutation, infection) within the previous 5 years.;Inadequate response to, loss of response to, or intolerance to prior anti-TNF inhibitors and anti-integrin inhibitors is defined as one or more of the following:;* Persistent signs and symptoms of active disease despite at least one 8-week regimen of infliximab (3 intravenous doses *5 mg/kg), or adalimumab (subcutaneous doses of 160 mg at Week 0 and 80 mg at Week 2 followed by a dose of *40 mg every 2 weeks), or golimumab (subcutaneous doses of 200 mg at Week 0 and 100 mg at Week 2, followed by 50 mg or 100 mg every 4 weeks), or vedolizumab (intravenous doses of 300 mg at Weeks 0, 2, and 6).;Note: There is no specific requirement for a subject to *washout* of a current treatment and no patient should be actively removed from prohibited medications in order to meet study inclusion/exclusion criteria.;9. Subjects currently receiving the following treatment for UC are eligible provided they have been on stable doses as described below:;* Oral 5-ASA or sulfasalazine stable dose for at least 4 weeks prior to baseline. If oral 5-ASA treatment has been recently discontinued, it must have been stopped for at least 2 weeks

prior to total Mayo score screening procedures.;* Oral corticosteroids (prednisone equivalent up to 20 mg/day; budesonide up to
9 mg/day) stable dose for at least 2 weeks prior to baseline. If oral corticosteroids have been recently discontinued, they must have been stopped at least 2 weeks prior to total Mayo score screening procedures. Decreases in steroid use due to AEs are allowed.;* 6-MP or AZA (*2.5 mg/kg) stable dose for 8 weeks prior to baseline. Decreases due to AEs are permitted.

Exclusion criteria

Subjects with any of the following characteristics/conditions will not be included in the study:;1. Subjects with a diagnosis of indeterminate colitis, ischemic colitis, radiation colitis, diverticular disease associated with colitis, microscopic colitis or CD. Subjects with clinical findings suggestive of CD (eg, fistulae, granulomas on biopsy) are also excluded.;2. Subjects with an imminent need for surgery or with elective surgery scheduled to occur during the study.;3. Subjects with colonic dysplasia or neoplasia.;4. Subjects with toxic megacolon.;5. Subjects with primary sclerosing cholangitis.;6. Subjects with known colonic stricture.;7. Subjects with history of colonic or small bowel stoma.;8. Subjects with a history of colonic or small bowel obstruction or resection.;9. Abnormal findings on the chest x-ray film performed routinely before initiating a new biologic therapy, such as presence of tuberculosis (TB), general infections, heart failure, or malignancy. Chest x-ray examination may be performed up to 12 weeks prior to screening. Documentation of the official reading must be located and available in the source documentation.;10. Any current evidence of untreated latent or active TB infection, evidence of prior or currently active TB by chest x-ray, residing with or frequent close contact with individual(s) with active TB. Subjects who have a positive Mantoux (PPD) tuberculin skin test or a positive Interferon Gamma Release Assay (IGRA to be tested
at the site*s local lab where feasible) during screening or within 12 weeks prior to randomization. The following are acceptable assays: QuantiFERON*-TB Gold test (QFT-G), QuantiFERON*-TB Gold In-Tube test (QFT-GIT) and T-SPOT*-TB test during screening or within 12 weeks prior to screening.;* A positive Mantoux tuberculin skin test is defined as *5 mm of induration (or as defined by country specific or local standards) at 48-72 hours without consideration of prior Bacillus Calmette-Guerin (BCG) vaccination. Documentation of the dose and product used for the Mantoux tuberculin test as well as the official test reading must be obtained and available in the subject*s source documentation.;* An IGRA is preferred for subjects with a prior BCG vaccination (to be tested by a site*s local lab where feasible), but may be used for any subject. Documentation of IGRA product used and the test result must be in the subject*s source documentation.;* If results of the IGRA are indeterminate, the test may be repeated, and if a negative result is obtained, enrollment may proceed. A positive test on repeat is exclusionary.;* Subjects with repeat indeterminate IGRA results may be enrolled after consultation with pulmonary or infectious disease specialist that determines low risk of infection (ie, subject would be acceptable for immunosuppressant
(eg, anti-TNF) treatment without additional action).;* Subjects with adequately treated latent tuberculosis infection may be enrolled regardless of Mantoux or IGRA results.;11. Presence of active enteric infections (positive stool culture and sensitivity). The presence of Clostridium difficile or pseudomembranous colitis. Known active invasive fungal infections such as histoplasmosis or parasitic infections. Subjects with clinically significant underlying disease

that could predispose the subjects to infections. A history of serious infection (requiring parenteral antibiotic and/or hospitalization) within 4 weeks before Day 1. Pyoderma gangrenosum is allowed.;12. Known history of human immunodeficiency virus (HIV) based on documented history with positive serological test, or positive HIV serologic test at screening, tested at the site*s local lab. (Note: a documented negative HIV test within 1 year of screening is acceptable and does not need to be repeated).;13. Presence of transplanted organ. Skin grafts to treat pyoderma gangrenosum are allowed.;14. Significant concurrent medical condition as judged by the investigator at the time of screening or baseline visit, including but not limited to the following:
* Any major illness/condition or evidence of an unstable clinical condition (eg, renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary,
immunologic [eg, Felty*s syndrome], or local active infection/infectious illness) that, in the investigator*s judgment will substantially increase the risk to the subject if he or she participates in the study.;* Cancer or history of cancer or lymphoproliferative disease within the previous
5 years (other than resected cutaneous basal cell or squamous cell carcinoma that has been treated with no evidence of recurrence).;* Acute coronary syndrome (eg, myocardial infarction, unstable angina pectoris) and any history of cerebrovascular disease within 24 weeks before screening.;* Subjects with current, or a history of QT prolongation would be excluded.;* Class III or Class IV heart failure.;15. Prior evidence of liver injury or toxicity due to methotrexate.;16. Abnormality in hematology and/or chemistry profiles during screening:;* Positive hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (HBcAb; also referred to as anti-HBc), and/or hepatitis C antibody (HCVAb) with confirmation by hepatitis C virus ribonucleic acid (HCV RNA).;* Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels
1.5 times the upper limit of normal (ULN).; Total bilirubin level *1.5 times the ULN.;* Hemoglobin level *80 g/L (8.0 g/dL).;* Platelet count *100 x 109/L (100,000 cells/mm3) or *1000 x 109/L (1,000,000 cells/mm3).
* White blood cell (WBC) count *3.5 x 109/L (3500 cells/ mm3).
* Absolute neutrophil count (ANC) <2000 cells/mm3.
* Serum creatinine level *177 *mol/L (2 mg/dL).;* Glycosylated hemoglobin (HbA1C) >10%. Screening laboratory tests if considered by the investigator to be transient and inconsistent with the subject*s clinical condition may be repeated once during the screening period for confirmation.;17. Subjects receiving the following therapies within the designated time period or are expected to receive any of these therapies during the study period:;* >9 mg/day of oral budesonide or >20 mg/day of prednisone or equivalent oral systemic corticosteroid dose within 2 weeks prior to baseline.;* IV, IM (parenteral), or topical (rectal) treatment of 5-ASA or corticosteroid enemas/suppositories within 2 weeks prior to baseline.;* Biologics including anti-TNF inhibitors as described below:;* Infliximab within 8 weeks prior to baseline.;* Adalimumab within 8 weeks prior to baseline.;* Golimumab within 8 weeks prior to baseline.;* Anti-integrin inhibitors (eg, vedolizumab) within 12 weeks prior to baseline.;* Other investigational procedure(s) or product(s), such as immunosuppressants used in transplantation (eg, mycophenolate mofetil, cyclosporine, rapamycin, or tacrolimus) or live (attenuated) vaccine within 30 days prior to baseline.;18. Current or history within 2 years of serious psychiatric disease or alcohol or drug abuse.;19. Subjects who are investigational site staff members directly involved in the conduct
of the study and their family members, site staff members otherwise supervised by the

investigator, or subjects who are Pfizer employees directly involved in the conduct of the study.;20. Participation in other studies involving investigational drug(s) within 30 days, or 5 half-lives of IP (whichever is greater), prior to baseline and/or during study participation.;21. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or IP 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.;22. Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant; male subjects able to father children and female subjects of childbearing potential who are unwilling or unable to use two highly effective methods of contraception as outlined in this protocol for the duration of the study and until the Week 26 visit (or 98 days after the last dose of IP) or longer based on the compound*s half-life characteristics.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-10-2017
Enrollment:	4
Type:	Actual

Ethics review

Approved WMO

Date:	16-08-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	17-05-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-06-2017
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	EUCTR2016-001158-16-NL
CCMO	NL58308.018.16