# A Phase 2B, Double-Blind, Randomized, Placebo-Controlled, Parallel Group, Dose Ranging Study of Oral PF-06651600 and PF-06700841 as Induction and Chronic Therapy in Subjects with Moderate to Severe Ulcerative Colitis [VIBRATO]

Published: 19-07-2017
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Primary Objective: - To evaluate the efficacy of PF-06651600 and PF-06700841 at Week 8 in subjects with moderate to severe UC. Secondary Objective(s): - To evaluate the safety and tolerability of PF-06651600 and PF-06700841 in subjects with moderate...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Will not start |
| **Health condition type** | Gastrointestinal ulceration and perforation |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON48602

**Source**
ToetsingOnline

**Brief title**
Pfizer B7981005
(9002/0472)
Vibrato

### Condition

- Gastrointestinal ulceration and perforation

**Synonym**
moderate to severe ulcerative colitis

**Research involving**
Human

## Sponsors and support

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

## Intervention

**Keyword:** colitis ulcerosa, PF-06651600 / PF-06700841, Phase 2B

## Outcome measures

### Primary outcome

Primary Endpoint: Total Mayo score at Week 8.

### Secondary outcome

Secondary Endpoint(s):

- Incidence and severity of adverse events, serious adverse events and withdrawals due to adverse events.

- Incidence of serious infections for definition).

- Proportion of subjects achieving remission based on total Mayo score of * 2 with no individual subscore >1 at Week 8.

- Total Mayo score at Week 32.

- Proportion of subjects in remission based on total Mayo score of * 2 with no individual subscore >1 at Week 32.

- Proportion of subjects achieving improvement in endoscopic appearance (defined as a Mayo endoscopic subscore of *1) at Week 8 and/or at Week 32.

- Proportion of subjects achieving clinical response at Week 8.

- Proportion of subjects in endoscopic remission at Week 8.

- Proportion of subjects in symptomatic remission at Week 8.

- Proportion of subjects achieving deep remission at Week 8.

- Partial Mayo scores and change from baseline over time at Weeks 2, 4 and8.

- Change from baseline at Week 8 in total Mayo score.

- The scores and change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) Total score and domains (Bowel Symptoms, Systemic Symptoms, Emotional Function and Social Function) at Weeks 4and 8.

- The proportion of subjects with IBDQ total score * 170 at Weeks 4and 8.

- The proportion of subjects with * 16 point increase in IBDQ total score from baseline at Weeks 4 and 8.

- Proportion of subjects with improvement in IBDQ bowel symptom domain at Weeks 4 and 8. The improvement is defined as an increase of at least 1.2 points from baseline in average score among IBDQ bowel symptom domain (items 1, 5, 9, 13, 17, 20, 22, 24, 26, 29).

- The scores and change from baseline in Short Form 36 version 2, acute (SF-36v2) (physical and mental component summary scores: PCS & MCS, and 8 domain scores) at Weeks 4 and 8.

- The scores and change from baseline in EuroQoL 5 Dimensions (EQ-5D-3L & EQ-5D VAS) at Weeks 4 and 8.

See protocol for Tertiary/Exploratory Endpoint(s)

# Study description

**Background summary**

The Janus kinase (JAK) family kinases mediate signal transduction via interactions with type I and type II cytokine receptors. Upon binding of the cytokine to its receptor, the associated JAKs are activated, and phosphorylate each other and the receptor. The phosphorylated receptors serve as docking sites for the signal transducers and activators of transcription (STAT) family (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) of transcription factors. The STATs are then phosphorylated by the co-localized JAKs, which stabilize homo- or heterodimeric STAT complexes that translocate the nucleus where they bind to specific gene promoters and activate transcription of a range of target genes.

PF 06651600 is an orally bioavailable small molecule that selectively inhibits JAK3 by irreversibly blocking the adenosine triphosphate (ATP) binding site without significantly inhibiting the other three JAK isoforms (JAK1, JAK2, and TYK2). PF-06651600 also inhibits irreversibly the tyrosine kinase expressed in hepatocellular carcinoma (TEC kinase) family (BTK, bone marrow tyrosine kinase on chromosome X (BMX), (interleukin-2-inducible T-cell kinase) ITK, TEC, and tyrosine kinase expressed in T cells (TXK)), with high selectivity over the broader kinome. The selective inhibition of JAK3 will lead to modulation of y-common chain cytokine pathways, such as IL 7, IL 9, IL 15 and IL 21, which have been implicated in the pathophysiology of ulcerative colitis (UC). Furthermore, in vivo PF 06651600 will spare signaling of key immunoregulatory cytokines, such as IL 10, IL 27 and IL 35, which have been shown to be critical to maintain immune homeostasis in the digestive tract. Finally, TEC kinase inhibition will impact cluster of differentiation 8 (CD8)+ T and natural killer (NK) cells cytotoxic functions, which play a role in the pathogenesis of Inflammatory Bowel Disease (IBD). Taken together, it is hypothesized that PF-06651600 could be efficacious in the treatment of UC.

PF-06700841 is an orally bioavailable, small molecule, potent dual inhibitor of human tyrosine-protein kinase 2 (TYK2) and JAK1. JAK1 inhibition will impact the signaling of pro-inflammatory cytokines such as interferon (IFN)-gamma and cytokines signaling through the * -common chain receptor such as IL-7, IL-9, IL-15 and IL-21, while the inhibition of TYK2 will block the production of pro-inflammatory cytokines interferon-gamma and IL-17 through upstream inhibition of the IL-12/Th1 and IL-23/Th17 pathways. Taken together, it is hypothesized that dual inhibition of both TYK2 and JAK1 could be efficacious in the treatment of UC.

Both PF-06651600 and PF-06700841 are under development as induction and chronic therapy for the treatment of inflammatory bowel disease (IBD).

**Study objective**

Primary Objective:
- To evaluate the efficacy of PF-06651600 and PF-06700841 at Week 8 in subjects with moderate to severe UC.

Secondary Objective(s):
- To evaluate the safety and tolerability of PF-06651600 and PF-06700841 in subjects with moderate to severe UC.
- To evaluate the efficacy of PF-06651600 and PF-06700841 in induction of remission at Week 8 in subjects with moderate to severe UC.
- To evaluate the efficacy of PF 06651600 and PF 06700841 at Week 32 in subjects with moderate to severe UC.
- To evaluate the efficacy of PF-06651600 and PF-06700841 for achieving remission at Week 32.
- To evaluate the efficacy of PF-06651600 and PF-06700841 in improvement of endoscopic appearance at Week 8 and/or Week 32 in subjects with moderate to severe UC.
- To evaluate the effect of PF-06651600 and PF-06700841 in induction of other clinical outcomes in subjects with moderate to severe UC.
- To evaluate the effect of PF-06651600 and PF-06700841 in induction on patient reported outcomes (PRO) in subjects with moderate to severe UC.

For Tertiary/Exploratory Objectives see protocol

**Study design**

This is a Phase 2b, randomized, double blind, placebo controlled (for induction period and not for chronic dosing (i.e chronic therapy)), parallel group, multicenter study in subjects with moderate to severe active UC. The first part of the study is a screening period of up to 6 weeks followed by an 8 week double blind induction period. At Week 8, all subjects will continue within their respective treatment cohort (PF 06651600 or PF 06700841) into an additional 24 week active chronic dosing period followed by a 4 week follow up period after the last dose of investigational product for a total of 36 weeks.

Total duration of the study will be approximately 42 weeks, including screening. Approximately 360 subjects in total will be randomized into the study. Following the screening period, subjects who meet the eligibility criteria at the baseline visit will be randomly assigned to receive one of 8 treatments. Three oral dose levels (20, 70, and 200 mg daily) of PF 06651600 plus matching placebo in a 4:4:4:1 ratio and three oral dose levels (10, 30, and 60 mg daily) of PF 06700841 plus matching placebo in a 4:4:4:1 ratio will be investigated. For analysis of the induction period, placebo groups will be combined to yield drug:placebo ratios of 2:2:2:1 for each drug at week 8. See section 3.1.

During the chronic dosing period, all subjects from the induction period PF-06651600 cohort (including subjects who received placebo) will receive 50 mg of PF-06651600, while all subjects from the induction period PF-06700841 cohort (including subjects who received placebo) will receive 30 mg of PF-06700841 for 24 weeks. After completion of the chronic dosing period, subjects will enter the 4 week follow up period.

Any subject who discontinues early from the induction period prior to the Week 8 visit should undergo the procedures for an Early Termination visit on the last day the subject takes the investigational product or as soon as possible thereafter, and will not be permitted to enter the chronic dosing period. For subjects who discontinue early from the chronic dosing period (after the Week 8 visit, but prior to the Week 32 visit), the procedures scheduled for an Early Termination visit will be performed on the last day the subject takes the investigational product or as soon as possible thereafter. After completion of the Early Termination visit subjects will enter the follow-up period.

**Intervention**

PF-06651600 and PF-06700841 tablets and matching placebo for oral administration will be dispensed in blister cards or bottles.

Subjects should take the IP orally for 8 weeks during the induction period and an additional 24 weeks during the chronic dosing period for a total of 32 weeks.

**Study burden and risks**

In conclusion, Pfizer considers that the results of the nonclinical studies together with the clinical experience obtained to date with PF-06651600 and PF-06700841 support the investigation of these IMPs for the treatment of subjects with moderate to severe active UC. Subjects will be monitored closely for rashes and evidence of infection.

Please refer to separate document: OVERALL RISK-BENEFIT ASSESSMENT FOR STUDY and also to the Investigator*s Brochures.

# Contacts

**Public**
Pfizer

300 Technology Square
Cambridge MA 02138
US
**Scientific**
Pfizer

300 Technology Square
Cambridge MA 02138
US

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

1. Male and/or female subjects *18 years to *75 years of age at the time of informed consent. For subjects in Korea: Male and/or female subjects *19 years to *75 years of age at the time of informed consent.
2. Diagnosis (endoscopic and histological) of UC for *3 months prior to entry into the study. A report supporting disease duration and extent (eg, proctosigmoiditis, left-sided colitis, or pancolitis) based upon prior endoscopy including a biopsy report must be available in the source documentation.
3. Subjects with moderate to severe active UC as defined by a total Mayo score of *6, with a rectal bleeding subscore of *1 and an endoscopic subscore of *2. Endoscopy (colonoscopy or flexible sigmoidoscopy) must be performed within 10 days of baseline, preferably 5 to 7 days prior to baseline to allow calculation of Total Mayo Score. The endoscopic subscore assessed by the Central Reader must be available at the baseline visit and will be used to derive the total Mayo score to determine study eligibility.
4. Active disease beyond the rectum (>15 cm of active disease from the anal verge at the screening endoscopy).
5. Must have inadequate response to, loss of response to, or intolerance to at least one conventional therapy for UC:
- Steroids;
- Immunosuppressants (azathioprine [AZA], 6-MP, or methotrexate [MTX]);
- Anti-TNF inhibitors (eg, infliximab, adalimumab, or golimumab);
- Anti-integrin inhibitors (eg, vedolizumab). ;See Appendix 1 of the protocol for guidance only. Local standards of care, as well as investigator assessment should be considered in any assessment.;6. Subjects currently receiving the following treatment for UC are eligible providing 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 baseline.
- Oral corticosteroids (dose equivalent to prednisone up to 25 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 baseline. Decreases in steroid use due to adverse events are allowed.
7. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.
8. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
9. Female subjects of childbearing potential (Women of child-bearing potential: WOCBP) must test negative for pregnancy at screening visit and baseline visit.
10. Female subjects considered to be of non-childbearing potential must meet at least 1 of the following criteria:
a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;
b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
c. Have medically confirmed ovarian failure. ;All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.

## Exclusion criteria

1. Female subjects who are pregnant or wish to become pregnant; 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 2 effective methods of contraception (at least one highly affective method) as outlined in the protocol for the duration of the study and for at least 28 days after the last dose of investigational product.
2. Presence of indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, radiation colitis, and diverticular disease associated with colitis, or clinical findings suggestive of Crohn*s disease (eg, fistulae, granulomas on biopsy).
3. Subjects with known colonic stricture and subjects with history of colonic or small bowel obstruction or resection.
4. Subjects with significant trauma or major surgery within 4 weeks of screening.
5. Subjects considered in imminent need for surgery or with elective surgery scheduled to occur during the study.
6. Subjects with a history of bowel surgery within 6 months prior to baseline.
7. Subjects displaying clinical signs of fulminant colitis or toxic megacolon.
8. Subjects with primary sclerosing cholangitis.
9. Subjects with history of colonic or small bowel stoma.
10. Subjects with evidence of colonic dysplasia, adenomas or neoplasia. However, subjects with adenomatous polyps identified on screening endoscopy will be eligible if the polyps have been completely removed and follow-up surveillance per local guidelines is negative.
11. Subjects who meet either of the 2 criteria below are considered at risk for colorectal cancer and must have a colonoscopy prior to randomization. The colonoscopy and pathology reports (if biopsies obtained) must be available in the source documentation:

- If the subject is *50 years of age, a colonoscopy within 10 years of screening is required to exclude adenomatous polyps. Subjects with adenomatous polyps identified on screening endoscopy will be eligible after complete polypectomy and follow-up surveillance per local guidelines is negative.
- If the subject has had extensive (ie, greater than left sided) 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 screening visit is required to survey for dysplasia. Subjects with dysplasia or cancer identified on biopsies will be excluded.
12. Subjects receiving the following therapies within the time period described below or expected to receive any of these therapies during the study period:
- >9 mg/day of oral budesonide or >25 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.
- Azathioprine, 6-mercaptopurine, or methotrexate within 2 weeks prior to baseline.
- Anti-TNF inhibitors (or biosimilars thereof) as described below:
o Infliximab within 8 weeks prior to baseline;
o Adalimumab within 8 weeks prior to baseline;
o Golimumab within 8 weeks prior to baseline.
o Anti-integrin inhibitors (eg, vedolizumab) within 8 weeks prior to baseline.
- Interferon therapy within 8 weeks prior to baseline.
- Subjects with prior treatment with lymphocyte-depleting agents/therapies within 1 year prior to baseline(eg, CamPath® [alemtuzumab], alkylating agents [eg, cyclophosphamide or chlorambucil], total lymphoid irradiation, etc).
- Subjects who have received rituximab or other selective B lymphocyte-depleting agents within 1 year prior to baseline.
- Subjects previously receiving leukocyte apheresis, including selective lymphocyte, monocyte, or granulocyte apheresis, or plasma exchange within 6 months prior to baseline.
- Other marketed immunosuppressants or biologics with immunomodulatory properties within 3 months prior to baseline.
- Other investigational procedures(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.
- Other JAK inhibitors within 3 months prior to baseline. Subjects who have not responded to or have been intolerant of other JAK inhibitors.
Participation in other studies involving investigational drug(s) within 30 days, or 5 half lives of investigational product (IP) (whichever is greater), prior to study entry and/or during study participation.;Please refer to the protocol for additional exclusion criteria

## Study design

## Design

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|---|---|
| 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: | Will not start |
| Enrollment: | 5 |
| Type: | Anticipated |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | PF-06651600 |
| Generic name: | PF-06651600 |
| Product type: | Medicine |
| Brand name: | PF-06700841 |
| Generic name: | PF-06700841 |

# Ethics review

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|---|---|
| Approved WMO Date: | 19-07-2017 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 09-11-2017 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO | |

| | |
|---|---|
| Date: | 15-02-2018 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 22-02-2018 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 25-04-2018 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 09-05-2018 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 13-11-2018 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 28-11-2018 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 05-04-2019 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 17-04-2019 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 01-05-2019 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO | |

| | |
|---|---|
| Date: | 22-05-2019 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |

# 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 | EUCTR2016-003708-29-NL |
| ClinicalTrials.gov | NCT02958865 |
| CCMO | NL62345.028.17 |

# Study results

Results posted: 01-03-2022

**Summary results**
Trial never started

**First publication**
29-10-2021