A MULTICENTER OPEN-LABEL EXTENSION STUDY TO ASSESS LONG-TERM SAFETY OF PF-00547659 IN SUBJECTS WITH ULCERATIVE COLITIS (TURANDOT II)

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Primary Objective* The primary objective of this study is to monitor the safety and tolerability of PF 00547659 during long term treatment. Secondary Objective* The secondary objective is to assess pharmacokinetics and immunogenicity of PF 00547659...

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

Summary

ID

NL-OMON44981

Source
ToetsingOnline

Brief title
TURANDOT II

Condition

- Gastrointestinal inflammatory conditions

Synonym
inflammatory bowel disease, Ulcerative colitis

Research involving
Human

Sponsors and support

Primary sponsor: Shire

Source(s) of monetary or material Support: by the sponsor as described in question B6/B7.

Intervention

Keyword: Open-label extension study, PF-00547659, Ulcerative colitis

Outcome measures

Primary outcome

Frequency of on treatment AEs, AEs leading to withdrawal, and SAEs.

Secondary outcome

Secondary Endpoints

Immunogenicity

* Frequency of the development of anti drug antibodies (ADAs) and neutralizing

antibodies (Nabs).

Pharmacokinetics

* Serum trough concentrations of PF 00547659 via listings and plots.

Mucosal Healing

* Proportion of subjects with mucosal healing at Week 16 (defined as absolute

Mayo subscore for endoscopy of 0 or 1).

Exploratory Efficacy Endpoints

* Assessment of the durability of response based upon Clinical Remission and

Clinical Response based upon Total Mayo score assessed at Week 16 [28 weeks

from initial dose] in subjects with a Clinical Response in study A7281009.

* Non-Responders from study A7281009 will also be assessed at Week 16 for

Clinical Remission and Clinical Response. * Assessment of Clinical Remission

and Clinical Response based upon the partial Mayo Score in all subjects at Week 40, Week 92 and Week 144.

* Simple Clinical Colitis Activity Index (SCCAI) will be assessed at monthly visits.

* Partial and Mayo subscores will also be assessed.

Exploratory Pharmacodynamic Endpoints

* Blood samples will be collected prior to dosing at baseline and every 4 weeks to Week 24, Week 32 and Week 72 to measure hsCRP. Also, stool samples will be collected at the time points noted above to measure fecal calprotectin. Blood samples will be collected at baseline, Week 4 (Visit 2) and Week 16 (Visit 5) to measure soluble MAdCAM.

Exploratory Biomarkers

* Analyses relevant to the understanding and treatment of UC may be conducted on the portion of stool samples remaining after calprotectin analysis.

* Blood will be collected at Visits 2, 5 and 19 for multiplex analyses of RNA transcripts and proteins associated with UC, inflammation and mechanism of drug activity.

* Optional biopsies will be taken at Visit 5 to assess RNA transcripts and proteins associated with UC, inflammation and mechanism of drug activity.

Study description

Background summary

PF 00547659 is a fully human IgG2* anti-MAdCAM-1 monoclonal antibody that binds to human MAdCAM to reduce lymphocyte homing to the gut and GI inflammation and is under development for the treatment of Crohn*s Disease (CD) and Ulcerative Colitis (UC).

PF 00547659 has been shown to block the MAdCAM pathway which decreases leukocyte homing to gut by inhibiting the key interactions between MAdCAM and the *4*7+integrin expressed on lymphocytes. Although the selectively targeting of the MAdCAM receptors is a novel approach, the basic interference of lymphocyte homing by preventing the binding of these *4*7+ lymphocytes to the MAdCAM receptor and the resultant efficacy in UC is well established. The main differentiation being that PF 00547659 blocks the interaction of *4*7+ lymphocytes to the MAdCAM receptor by selectively binding to the receptor. Principal sites of the MAdCAM expression on normal tissue includes intestine, pancreas, stomach, esophagus, spleen and to a lesser extent lung, liver, and bladder but not in the central nervous system (CNS). PF 00547659 also does not bind to VCAM and is therefore not expected to be effective for the treatment of Multiple Sclerosis or affect lymphocyte homing or surveillance in the CNS.

Study objective

Primary Objective
* The primary objective of this study is to monitor the safety and tolerability of PF 00547659 during long term treatment.

Secondary Objective
* The secondary objective is to assess pharmacokinetics and immunogenicity of PF 00547659.

Exploratory Objectives
* Exploratory objectives include an assessment of the durability of response with long term treatment with PF 00547659 based upon Clinical Remission and Clinical Response based upon the Mayo Score performed at Week 16 in Clinical Responders from study A7281009.
* Explore relationships between PK of PF 00547659, PD and clinical endpoints.

Study design

This is a multi center Phase 2, open label, safety extension study for study A7281009. Study A7281009 is a Phase 2b study to evaluate PF 00546759 vs placebo in subjects with moderate to severe ulcerative colitis who have failed at least 1 conventional therapy. Two dose levels of PF 00547659 will be investigated in this open label extension study. Subjects eligible for this study will have completed the 12 week double blind induction period in study

A7281009. All subjects entering this study must have discontinued immunosuppressant therapy. They will then be randomly assigned to receive either 75 mg or 225 mg subcutaneously every 4 weeks without unblinding treatment assignment from study A7281009, and without regard to responder status in that study.

After the active treatment period, the subjects will enter a 24 month follow up period including 6 monthly visits followed by 18 month extended contact (every 6 month telephone contacts). At the last onsite visit (Week 96), subjects will undergo an End of Study visit but will continue the every 6 month telephone contacts until Week 168.

After completion of Open Label Treatment Period 1, all subjects will be permitted to continue in Open Label Treatment Period 2 (Weeks 76-144) and will receive the 75 mg dose on a every four weeks basis for a further 18 months.

Intervention

Subjects will be administered one or more SC doses of the study drug at day 1 (baseline) and then every 4 weeks during the treatment period.

Study burden and risks

The subjects that roll over into this study from A7281009 will have completed Week 12 (Day 84). These subjects have failed at least 1 conventional therapy. This open label extension study will provide additional treatment for these subjects with limited therapeutic options.

Beyond anti-TNFs, patients with inflammatory bowel disease have limited options for biologic therapy. One agent, approved for Crohn*s disease only in the US is natalizumab, which has a 0.1% (1: 1000) incidence of progressive multifocal leukoencephalopathy (PML) which makes it unacceptable to most subjects with Crohn*s disease and their physicians. PF 00547659, an anti MAdCAM monoclonal antibody under investigation for the treatment of both CD and UC, provides a novel mechanism of action that is distinct from natalizumab. There is no interference with central nervous system lymphocyte surveillance since the drug binds to the MAdCAM receptor which is primarily located to venules of the GI tract and to a lesser extent lung, liver and spleen but is not present in the central nervous system. Natalizumab binds to the *4*7+ and *4*1+ lymphocytes and prevents their binding to MAdCAM in the GI tract. Therefore, for subjects with ulcerative colitis the efficacy may be similar. However, natalizumab also prevents these lymphocytes from binding to VCAM6 in the choroid plexus which is responsible for its efficacy in Multiple Sclerosis. PF 00547659 demonstrated a favorable safety profile in the Phase 1 single and multiple dose study conducted in subjects with ulcerative colitis. However, due to the limited safety database, additional precautions will be taken to ensure the safety of

subjects. Subjects will not be allowed long-term co administration with immunosuppressives since IS use has been associated with increased risk of PML in MS patients taking Tysabri. However, the type of IS used is quite different from those used in IBD and it is not known whether or not inflammatory CNS disease makes patients more prone to PML. Since subjects may have stopped immunosuppressives shortly before entering into this study, they may be at increased risk for exacerbation or flare of their ulcerative colitis, especially subjects who enroll from the placebo-treatment arm of study A7281009.

Monitoring of subjects will include standardized focused neurological assessments, and JC virus testing throughout the study and follow up period. Any new unexplained neurological finding will trigger an immediate neurologic consultation with appropriate actions. Samples for JC virus DNA will be taken at monthly intervals throughout the study, and at a minimum tested at baseline and end-of-study visit. In addition, an external Data Monitoring Committee will be in place to adjudicate any subjects with unexplained neurological findings.

Given the lack of therapeutic options for subjects who have failed at least 1 conventional therapy, PF 00547659 with its distinct mechanism of action and known safety profile appears to have a favorable Risk Benefit profile. The added precautions regarding Progressive Multifocal Leukoencephalopathy (PML) are probably unnecessary but will serve to increase the confidence in PF 00547659 in future development.

Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the current 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 this study:
1.Subjects previously enrolled in study A7281009 who have completed the blinded 84-day (12-week) induction period.
2.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.
3.Male and/or female subjects between the ages of 18 and older and 66 years and younger at the time of informed consent if they were previously enrolled in study A7281009.
4. All women of childbearing potential (WOCBP) as determined during study A7281009 (data must be available as source documents for this study) must have a negative urine pregnancy test result at the Baseline visit and throughout the duration of this study (defined as the time of the signing of the ICD through the end of this study).
5. Male and female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the duration of the study (defined as the time of the signing of the ICD through the conclusion of onsite subject participation or for approximately 6 months from the last dose of investigational product for any subject who discontinues early from the study). 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.;*Women of childbearing potential (WOCBP) must have a negative urine pregnancy test result at baseline. WOCBP are defined as women who are biologically capable of becoming pregnant, including women who are using contraceptives or whose sexual partners are either sterile or using contraceptives.;* Women of non-childbearing potential (WONCBP) do not require a urine pregnancy test and must meet at least one of the following criteria:;* Have undergone hysterectomy or bilateral oophorectomy;;* Have medically confirmed ovarian failure; or;* Are medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause).;6. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and

other study procedures.

Exclusion criteria

Subjects presenting with any of the following will not be included in this study:
1. Subjects that have completed Day 84 (Week-12) of study A7281009 but have experienced serious event(s) related to the investigational product, an unstable medical condition, or any other reason, in the opinion of the investigator, would preclude entry or participation in this study.
2. Subjects who are taking any dose of AZA, 6-MP or MTX.
3. Pregnant or breastfeeding women.
4. Males and females of childbearing potential not using higly effective contraception or not agreeing to continue highly effective contraception through the conclusion of onsite subject participation or for approximately 6 months from the last dose of investigational product for any subject who discontinues early from the study).
5. Evidence of right or left heart failure based on echocardiographic assessments conducted as part of a prior study of PF-00547659.
6. 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 entry into this study.
7. Received any prohibited treatment during study A7281009 that, in the opinion of the investigator, compromised the safety or efficacy of this study.
8. Planned live (attenuated) vaccination during the course of the study.
9. Planned major elective medical or surgical procedure during the course of this study.
10. Participation in other interventional studies during participation in this study.
11. The inability to complete any of the five neurological assessments without a clear explanation (e.g. broken leg, sprained wrist, etc).

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-01-2014
Enrollment:	8
Type:	Actual

Ethics review

Approved WMO Date:	22-02-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-05-2013
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-06-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	16-07-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	19-08-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-08-2013

Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	06-09-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-02-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-02-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-05-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	26-05-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-09-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	20-05-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	29-05-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-06-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-02-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-04-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	04-10-2016
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	12-07-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2012-002031-28-NL
ClinicalTrials.gov	NCT01771809
CCMO	NL43060.068.13