A multi-center, phase 1, open-label evaluation of the effect of PF-00547659 (anti MadCam monoclonal antibody) on cerebrospinal fluid (CSF) lymphocytes in volunteers with Crohn*s Disease or Ulcerative Colitis who are anti-TNF inadequate responders.

Published: 13-12-2011
Last updated: 28-04-2024

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

Summary

ID

NL-OMON39430

Source
ToetsingOnline

Brief title
A7281008 Crohn Disease: TOSCA (9002/0017)

Condition

- Gastrointestinal inflammatory conditions

Synonym
Crohn's Disease, Inflammatory Bowel Disease

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Crohn□s Disease, Open-Label, PF-00547659, Phase 1, Ulcerative Colitis

Outcome measures

Primary outcome

Percent change from baseline (pre treatment) in absolute lymphocyte count in

CSF in subjects with CD/UC after receiving 3 monthly doses of PF 00547659.

Secondary outcome

Secondairy Endpoints

* Safety of PF 00547659: the frequency of on treatment adverse events,

withdrawal due to adverse events, and serious adverse events (SAEs) will be

reported.

* Proportion of subjects developing anti drug antibodies (ADA) to PF 00547659.

* Frequency and severity of injection site reactions and other hypersensitivity

reactions.

Exploratory Endpoints

* Change in biomarkers in blood and CSF at each lumbar puncture (LP) by FACS

and LSC.

* *4*7+ T cells, CD4+ T cell count, CD8+ T cell count, CD4+:CD8+ ratio, CD34+,

CD3 and B cell repertoire.

* Soluble MAdCAM, ICAM 1 and VCAM 1 concentration.

* Change total PF 00547659 serum concentration over time.

* Proportion of subjects with a decrease in HBI *3 points from baseline after 3

doses of PF 00547659.

Optional Exploratory Endpoints

* Change in biomarkers in endoscopic biopsy specimens

* *4*7+ T cells, CD4+:CD8+ ratio, CD34+, CD3 and B cell repertoire by

immunohistochemistry (IHC).

* Tissue MAdCAM expression by IHC.

* Mucosal healing (SES CD) in the endoscopic biopsy substudy.

* Presence of JC virus DNA and anti JC antibody in the blood and CSF before and

after treatment with PF 00547659.

Study description

Background summary

The purpose of this study is to confirm the hypothesis that treatment with PF 00547659 will not alter the number or type of lymphocytes in the CSF or reverse the CD4+:CD8+ ratio, thus indicating that it is unlikely to impair CNS immune surveillance. No studies of CSF T lymphocyte populations have been published to date in patients with Crohn*s disease or Ulcerative Colitis. Therefore, baseline values will be examined to determine whether they are consistent with those in the normal population, or demonstrate evidence of impaired immune surveillance due to prior or concomitant treatment with Immunosuppressants and/or anti TNFs which have been reported to be associated with opportunistic infections as well as demyelination syndromes.

Normal individuals have approximately 2000 3000 WBCs/mL in the CSF of which approximately 90% are lymphocytes. Of these lymphocytes, 66% 75% of them are CD4+ cells. In order to have enough cells for FACS analysis, 10 mL CSF will be

centrifuged to concentrate the cells. This should allow for approximately 25,000 cells for analysis. The supernatant may be used for determination of soluble MAdCAM, VCAM 1 and ICAM 1.

In order to assess the effects of PF 00547659 on peripheral blood and CNS lymphocyte trafficking, a panel of T and B cell markers will be tested by FACS analysis as well as by LSC in samples of CSF and blood.
Lymphocyte trafficking in the gut will be assessed in an exploratory fashion in the optional Endoscopic Biopsy Substudy (see Section 7.6). This will confirm the mechanism by which PF 00547659 reduces intestinal inflammation. Thus, this study will simultaneously investigate T cell trafficking into all 3 compartments, CSF, gut and blood in subjects with active Crohn*s disease or Ulcerative Colitistreated with PF 00547659.

Study objective

The primary objective is to determine whether PF 00547659 alters central nervous system immune surveillance in subjects with active, moderate to severe Crohn*s disease or active, moderate to severe Ulcerative Colitis by altering the absolute lymphocyte count in the CSF

Study design

This is a multi center, phase 1, open label sequential cohort study in volunteers with active, moderate to severe CD/UC who are inadequate responders or intolerant to immunosuppressants (azathioprine [AZA], 6 mercaptopurine [6 MP] and/or methotrexate [MTX]) and anti TNFs. All volunteers must meet all inclusion/exclusion criteria before undergoing a LP (see Section 4 of protocol am 2).

Intervention

Cohort 1
The purpose of Cohort 1 is to determine the baseline CSF characteristics in subjects with active, moderate to severe CD who have failed or are intolerant to immunosuppressants and anti TNFs. Two LPs in 5 subjects will establish the intra and inter subject variability for CSF lymphocytes. If the variability is greater than expected, an additional 5 subjects may be enrolled.
Cohort 1 will consist of approximately 5 10 evaluable CD volunteers meeting all entry criteria for active CD who will undergo 2 lumbar punctures (LPs) (see Section 7.5). If the first LP is acceptable subjects will have a second LP 2 4 weeks later (* 3 days). Subjects who have a traumatic first LP (RBC count is >1/*L) must proceed to dosing. Subject who have a serious complication such as headache requiring a blood patch, may have a second LP, or proceed to dosing without a second LP if they choose. A sufficient number of subjects will be enrolled to replace all subjects without 2 evaluable LPs. If after 48 hours

following the second LP all AE*s have resolved, the subject will then receive the first of 3 monthly doses of PF 00547659 (see Section 6). At Week 12, subjects who have a clinical response to the treatment, (see Section 3.1.5) are eligible to enter the open label extension study (A7281007). Non responders will enter the follow up period of this study.

Cohort 2
Cohort 2 will consist of at least 15 20 evaluable CD or UC volunteers who meet the same criteria as for cohort 1. They will have a LP, receive 3 doses of study drug and then have a second LP if results of the first LP are acceptable, eg, non traumatic (see Section 7.5.1.1). A sufficient number of subjects will be enrolled to ensure at least 15 paired, evaluable, LPs are obtained. Whether or not the LPs are evaluable or both are performed, subjects may receive treatment. At week 12, subjects who have a clinical response to the treatment, (see Section 3.1.5) are eligible to enter the open label extension study (A7281007 for CD subjects or A7281010 for UC subjects). Non responders will enter the follow up period.

Optional Endoscopic Biopsy Substudy
In order to evaluate lymphocyte trafficking in the gut, a substudy will evaluate pre and post treatment lymphocyte subsets and MAdCAM in colonoscopic biopsy samples. This substudy has two arms. Colonic tissue biopsies will be obtained from normal and inflamed mucosa (Arm 1) or from a single site 10 cm distal to the entry point of the scope (anus or stoma) (Arm 2).

Study burden and risks

Subjects will be monitored closely for neurologic symptoms, evidence of infection, evidence of allergy, and evidence of myocardial changes. In addition all subjects receiving the LP's will undergo a 48-hours observation at the treating hospital. Please see the OVERALL RISK_BENEFIT ASSESSMENT which is part of the IMPD (D2 in submission package) for further information.

Contacts

Public
Pfizer

Arcola Road 500
Collegeville, PA 19426 19426
US
Scientific
Pfizer

Arcola Road 500
Collegeville, PA 19426 19426
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Subjects must have acitve, moderate to severe Crohn's Disease or active, moderate to severe Ulcerative Colitis
- Subjects must have failed or are intolerant to anti TNF's
Please see protocol for all inclusion criteria

Exclusion criteria

- Pregnant or breast feeding
- Entero-vesicular fistulae are prohibited due to increased risk of Urinary Tract Infection and sepsis.
Please see protocol for all exclusie criteria

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-10-2012
Enrollment:	3
Type:	Actual

Ethics review

Approved WMO Date:	13-12-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-08-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2013
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:	07-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	03-09-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-11-2013
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	EUCTR2011-001443-74-NL
ClinicalTrials.gov	NCT01387594
CCMO	NL37816.018.11