A Multicenter, Double-blind, Randomized, Parallel, Placebo-controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of 2 Oral Doses, 25 mg Twice Daily and 100 mg Twice Daily, of PG 760564 in Adult Patients with Rheumatoid Arthritis Receiving Methotrexate

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Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON30408

Source
ToetsingOnline

Brief title
RACER

Condition

- Other condition

Synonym
rheumatoid arthritis

Health condition

gewrichtsaandoeningen

Research involving
Human

Sponsors and support

Primary sponsor: Procter & Gamble
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: rheumatoid arthritis

Outcome measures

Primary outcome

The primary efficacy endpoint will be the proportion of patients meeting the

ACR 20 response criteria at 12 weeks.

Secondary outcome

The secondary efficacy endpoints will include:

• ACR 50 and ACR 70 responses at 12 weeks (Appendix 2);

14• Change from baseline in DAS 28 scores at 12 weeks (Appendix 3);

• Change from baseline at 12 weeks in:

o Tender joint count

o Swollen joint count

o Physician*s global assessment

o Patient*s global assessment

o Patient*s assessment of pain

15o HAQ score (Appendix 4)

o Acute phase reactants (ESR and CRP)

o TNF-α, IL-1, and IL-6

o Duration of morning stiffness

o RF titer;

• Time to ACR 20.

Study description

Background summary

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis with a worldwide prevalence of 0.5% to 1%.1,2 Rheumatoid arthritis causes substantial morbidity: approximately 50% of patients are unable to work within 10 years of disease onset.3 Rheumatoid arthritis is a systemic inflammatory disorder and RA patients may also develop extra-articular manifestations in different organ systems.
The importance of pro-inflammatory cytokines in the pathogenesis of RA has been shown in clinical trials of biologic agents that block tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1) activity.4,,,567 Although anti-TNF-α therapies have been reported to increase the risk of infection, they have shown significant efficacy in RA and have set a new standard in the management of RA. There are 3 TNF-α antagonists currently approved for RA in the US.
PG-760564 [2-(4-Fluorophenyl)-6,7-dihydro-3-(2-phenoxy-4-pyrimidinyl)-1H,5H-pyrazolo(1,2-a)pyrazol-1-one] is a cytokine synthesis/release inhibitor with p-38 mitogen-activated protein (MAP) kinase inhibition activity that is being investigated as a treatment for RA. PG-760564 has been shown to inhibit p-38 MAP kinase directly and has been shown to inhibit the release of TNF-α and IL-1 from a number of cell types. Oral administration of PG-760564 was effective in both the prevention and treatment components of the rat collagen-induced RA model. Histological examination of the joints showed statistically significant inhibition of pannus, inflammation, cartilage damage, and bone resorption at 2.5 mg/kg in the treatment model.

Study objective

The objectives of this study are as follows:
Primary Efficacy Objective:

• To assess the effect of PG-760564 on the proportion of patients meeting the American College of Rheumatology 20 response criteria (ACR 20) at 12 weeks;11
Secondary Efficacy Objectives:
• To assess the effect of PG-760564 on the proportion of patients meeting the ACR 50 and ACR 70 responses at 12 weeks;
• To assess the effect of PG-760564 on the change from baseline in 28-joint Disease Activity Score (DAS 28) at 12 weeks;
• To assess the effect of PG-760564 on the change from baseline at 12 weeks in the following parameters:
o Tender joint count
o Swollen joint count
o Physician*s global assessment
o Patient*s global assessment
o Patient*s assessment of pain
o Health Assessment Questionnaire (HAQ) score
o Acute phase reactants [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)]
o TNF-α, IL-1, and IL-6
o Duration of morning stiffness
o Rheumatoid factor (RF) titer;
• To assess the effect of PG-760564 on time to ACR 20.
Safety Objectives:
• To assess the safety and tolerability of PG-760564 in patients with RA.

Study design

This will be a 12-week, double-blind, randomized, placebo-controlled, parallel group, multicenter study to evaluate the safety, efficacy, and PK of oral administration of PG-760564 in adult patients with active RA receiving treatment with MTX. The study will be conducted in North America and Europe at approximately 50 to 60 sites. Approximately 270 patients will be randomized, of which 189 are expected to complete the study. If the dropout rate is >30%, up to an additional 30 patients total could be randomized, to ensure 63 completed patients per treatment group. Two oral doses of PG-760564 will be evaluated: 25 mg BID and 100 mg BID.
Due to concomitant treatment with MTX, all patients will be required to take either 5-7 mg/week of folic acid or 2.5 mg/week of folinic acid. Higher doses will not be allowed.

The study will consist of a screening visit followed by a washout period for all disease-modifying antirheumatic drugs (DMARDs) and anti-cytokine therapies except MTX (see Appendix 5). The washout period will be 4 weeks for sulfasalazine, hydroxychloroquine, azathioprine, D-penicillamine, etanercept, and anakinra, 8 weeks for gold, infliximab, and adalimumab, and 12 weeks for abatacept.
After the washout period, the patients will be randomized if they fulfill all inclusion and exclusion criteria. Patients determined to be eligible will be

randomized to receive either 25 mg BID or 100 mg BID of oral PG-760564, or placebo for 12 weeks. There will be 6 treatment visits (Weeks 1, 2, 4, 6, 8, and 12) and a follow-up visit 4 weeks after the last treatment visit (Week 16). Patients will not initiate new therapies until after the 4-week follow-up is completed. Liver function tests will be evaluated at every visit.
If dose-limiting toxicity is seen in patients receiving the 100 mg BID dose (based on recommendation from the IDMC), the 100 mg BID dose will be discontinued and patients in this dose group will have their dose decreased to 50 mg BID. In that case, new patients randomized to the 100 mg BID dose will be given a 50 mg BID dose instead.
The primary efficacy endpoint will be the proportion of patients meeting the ACR 20 response criteria after 12 weeks of treatment.

Intervention

use of PG-760564 en methotrexate

Study burden and risks

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Contacts

Public
Procter & Gamble

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Scientific
Procter & Gamble

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients who meet all of the following criteria are eligible for participation in the study:
a. Men and women, 18 to 70 years of age, inclusive, at screening;
b. Who meet ACR criteria for RA, with a documented diagnosis of RA for at least 6 months;
c. Whose functional capacity is class I, II, or III according to the revised criteria of the ACR (Appendix 6);12
d. Who have active disease despite treatment with MTX before washout of any DMARDs other than MTX. Active disease for this study will be defined as follows:
• At least 6 swollen joints and 6 tender joints; AND,
• At least one of the following 3 criteria must be present:
* ESR of at least 28 mm/hour
* Elevated CRP
* Morning stiffness lasting at least 45 minutes;
e. Who have been treated with MTX for at least 24 weeks. The dose of MTX must be stable for at least 8 weeks, at 15-20 mg/week, or at 10 mg/week if that is the maximal tolerated dose, before starting study medication;
f. If female, must be (as documented in the patient notes):
• Post menopausal (>= age 50 and at least 1 year without spontaneous menses), or
• Surgically sterile (if by tubal ligation, must have been performed at least 3 months before entry into the study), or
• Using acceptable contraception (e.g., oral, intramuscular, or implanted hormonal contraception, intra-uterine device) for at least 3 months prior to randomization and for the duration of the study including the follow-up period, in conjunction with a barrier method (e.g., condom and spermicide, diaphragm and spermicide) for the duration of the study and during the follow-up period; NOTE: All contraception precautions for MTX must be followed.
g. If sexually-active male, must be surgically sterile (e.g., non-reversed vasectomy with confirmed azoospermia) or use condom during the study and during the
(PG-760564) follow-up period;
NOTE: All contraception precautions for MTX must be followed.
h. Who are willing and able to participate in the study and provide signed informed consent.

Exclusion criteria

Patients with any of the following will not be entered into the study:
a. Active or latent tuberculous infection as defined below:
1. History of tuberculosis (TB), or

2. Chest X-ray suggestive of former or current tuberculous infection, or
3. Positive tuberculin skin test with purified protein derivative of tuberculin (PPD) >=5 mm in a patient without history of vaccination with bacillus Calmette-Guérin (BCG), or
4. In Europe, vaccination with BCG and positive PPD >8 mm, or
5. In Europe, vaccination with BCG and positive PPD >=5 mm but <=8 mm and any of the following risk factors:
i. silicosis
ii. residents and employees of high-risk congregate settings
iii. weight loss >10% of ideal body weight
iv. gastrectomy
v. jejunoileal bypass, or
6. In US, vaccination with BCG and positive PPD >=5 mm;
b. Active listeriosis;
c. History of episode of infection requiring hospitalization within 30 days before screening or episode of infection requiring intravenous (IV) antibiotics within 30 days before screening or current active infection;
d. History of chronic or recurrent infections, or immunodeficiency;
e. Indwelling catheters;
f. Bronchiectasis;
g. History of uveitis or other inflammatory eye disease;
h. Autoimmune diseases other than RA [mixed connective tissue disease (MCTD), seronegative spondyloarthropathy, systemic lupus erythematosus (SLE), undifferentiated connective tissue disease (UCTD), psoriatic arthritis, sarcoidosis, etc.], except Sjogren*s syndrome secondary to RA;
i. Chronic liver diseases, serologic evidence for infection with hepatitis B or hepatitis C [positive hepatitis B surface antigen (HepBsAg) or hepatitis C antibody (HepCAb)];
j. History of alcohol or drug abuse;
k. Abnormal hepatic and renal functions (LFTs and serum creatinine values elevated above the Central laboratory normal reference range on screening or baseline visits); patients with known elevations of transaminases greater than 1.2 times the upper limit of normal (ULN) on 2 or more occasions in the 6 months before screening will be excluded.
l. Platelets <100 x 109/L;
m. Abnormal WBC and/or significant abnormalities in other complete blood count (CBC) values. Hemoglobin (Hgb) <10 mg/dL;
n. Joint surgery within 2 months of screening;
o. History of lymphoma, leukemia, or lymphoproliferative disorders;
(PG-760564)
p. History of other malignancies other than treated basal cell carcinoma of the skin;
q. History of demyelinating diseases;
r. History of heart failure, New York Heart Association (NYHA) class III or IV (Appendix 7);
s. Pregnant or lactating women, or women who plan to become pregnant;
t. Personal or family history of prolonged QT syndromes. Family history of sudden cardiac death due to arrhythmia or unknown cardiac problems (presumed QT problems);
u. Other risk factors for torsade de pointes (TdP), e.g., history of significant arrhythmias including history of ventricular tachycardia or fibrillation [unless patient has implantable cardiac defibrillator (ICD)]; atrial fibrillation or flutter; history of sick sinus syndrome or significant heart blocks (unless patient has pacemaker); ECGs showing prolongation of QTc

interval (>440 msec);
v. Hypokalemia, hypomagnesemia, or hypocalcemia;
w. Drugs known to cause prolongation of QT interval (must be off for at least 5 half-lives to be enrolled) (see list in Appendix 8);
x. Demonstrated likelihood not to comply with protocol requirements ;
y. Current participation in another clinical trial involving active intervention;
z. Known allergy to components of the study medication;
aa. History of efficacy failure with etanercept, infliximab, adalimumab, anakinra, and abatacept;
bb. History of treatment with B-cell depleting therapies (rituximab) and immunoadsorption (Prosorba Column);
cc. History of treatment with p-38 MAP kinase inhibitors;
dd. History of treatment with cyclosporine, cyclophosphamide, or other alkylating agents;
ee. Other diseases requiring immunosuppressive therapy;
ff. Treatment with leflunomide within 6 months prior to study entry;
gg. Intra-articular or intramuscular steroids within 4 weeks before screening;
hh. Change in non-steroidal anti-inflammatory drug (NSAID) and/or corticosteroid doses within 30 days prior to entry into the study (Day 1 of the washout period);
ii. Treatment with any experimental/investigational therapy within the last 2 months for chemical and 6 months (from screening date) for biologic drugs;
jj. Use of the following inducers of CYP 3A4 (carbamazepine, phenobarbital, phenytoin, St John's Wort and troglitazone) or inhibitors of CYP 3A4 (diltiazem, fluvoxamine, grapefruit juice, itraconazole, ketoconazole, mibefradil, nefazodone, troleandomycin, cimetidine, and verapamil); the washout period for these drugs will be 5 days except for phenobarbital for which it will be 21 days;
kk. Patients not treated with folic or folinic acid.
Any other conditions, including important concurrent illnesses (e.g., hypothyroidism) that, in the opinion of the Investigator would jeopardize the study. The Investigator should call the Medical Monitor should there be any questions.

Study design

Design

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:	Pending
Start date (anticipated):	01-11-2006
Enrollment:	30
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	methotrexate
Generic name:	methotrexate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nog niet bekend
Generic name:	PG-760564

Ethics review

Approved WMO Date:	09-03-2007
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-06-2007
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2006-002216-10-NL
Other	geen nummer
CCMO	NL14158.058.06