PHASE 3B/4 RANDOMIZED SAFETY ENDPOINT STUDY OF 2 DOSES OF TOFACITINIB IN COMPARISON TO A TUMOR NECROSIS FACTOR (TNF) INHIBITOR IN SUBJECTS WITH RHEUMATOID ARTHRITIS

Published: 25-02-2014
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The primary objective of this endpoint study is to evaluate the safety of tofacitinib at two doses versus TNFi; the co-primary endpoints are adjudicated major adverse cardiovascular events (MACE) and adjudicated malignancies excluding non-melanoma...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON41518

Source
ToetsingOnline

Brief title
9002/0194; A3921133

Condition

- Autoimmune disorders
- Synovial and bursal disorders

Synonym
Rheumatoid Arthritis; arthritis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Phase 3B/4, Randomized Safety Endpoint Study, Rheumatoid Arthritis, Tofacitinib

Outcome measures

Primary outcome

Endpoints

This study will use independent endpoint adjudication committees for the adjudication of events of interest (EoI), including the co-primary endpoints. For those events meeting the co-primary endpoint pre-defined criteria, the Steering Committee will be responsible for ongoing analysis of these events and for informing the Sponsor of recommendations made (eg, to continue the study or to stop the study). All other adjudicated events (eg, opportunistic infections, hepatic events, non-primary CV or malignancy events) will be reported in the usual fashion (See Section 8 Adverse Event Reporting).

The investigator for the site of incidence will be notified of any malignancy or cardiovascular event reported as an EoI that is adjudicated by the Endpoint Adjudication Committee as NOT meeting endpoint criteria; the investigator at the study site must re-evaluate the EoI and report the event to Pfizer. SAEs must be reported in accordance with the timeframes described in the Serious

Adverse Event Reporting Requirements section of this protocol (See 8.12.1 and 8.12.4). The investigator*s SAE awareness date in this instance is identified as the date that the investigator site of incidence receives the notification that an EoI does not meet endpoint criteria. Handling SAEs in this manner will allow Pfizer to meet its Sponsor reporting obligations to regulatory authorities upon receipt of such SAEs. Any EoI that are pending adjudication at the annual safety report cutoff date will not be included in the safety tables of the annual report.

Safety Endpoints

The safety endpoints will be collected and analyzed for all subjects in the study, through the

end of the study.

Co-Primary Safety Endpoints

The following co-primary safety endpoints will be analyzed to provide comparative rates for

tofacitinib vs. the combined TNFi:

* Malignancies, excluding non-melanoma skin cancers (adjudicated)

* Major adverse cardiovascular events (MACE) (adjudicated). The definitions of MACE used in this study are consistent with those outlined in the Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials with the exclusion of cardiovascular death due to pulmonary embolism. The following events are included, as defined:

* Cardiovascular death

* Death due to acute myocardial infarction (MI)

* Sudden cardiac death

* Death due to heart failure

* Death due to stroke

* Death due to cardiovascular procedures

* Death due to cardiovascular hemorrhage

* Death due to other cardiovascular causes: peripheral artery disease

* Non-fatal myocardial infarction (MI)

* Non-fatal stroke of any classification, including reversible focal neurologic defects with imaging evidence of a new cerebral lesion consistent with ischemia or hemorrhage

Secondary outcome

Secondary Safety Endpoints

The secondary safety endpoints will include an evaluation of the following events:

* Opportunistic infection events including tuberculosis (adjudicated)

* Hepatic events (adjudicated)

* Cardiovascular events other than MACE (adjudicated)

* All adverse events (AEs), including serious adverse events (SAEs)

Clinically significant abnormal laboratory parameters

* All cause mortality (adjudicated)

* Reasons for permanent or temporary discontinuation of study medication

Efficacy Endpoints

Efficacy endpoints will include:

* Change from baseline to each post-baseline scheduled visit in DAS28-4 (CRP).

Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index

(CDAI).

* Rate of remission at each post-baseline scheduled visit including:

* ACR-EULAR Boolean remission (defined as the subject satisfying all of the

following: tender joint count * 1, swollen joint count *1, C-reactive protein

*1 mg/dl,

patient global assessment *1 on a 0-10 scale)

* SDAI * 3.3

* CDAI *2.8

* Rate of low disease activity (LDA) at each post-baseline scheduled visit

including:

* SDAI * 11

* CDAI *10

* DAS28-4(CRP) *3.2

* ACR20, ACR50, and ACR70 response rate of at each post-baseline scheduled visit

* Change from baseline to each post-baseline scheduled visit in the HAQ-DI

Study description

Background summary

Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome.1 In kinase assays, tofacitinib, inhibits JAK1, JAK2, JAK3, and to a lesser extent tyrosine kinase 2 (TyK2). In cellular settings where JAK kinases

signal in pairs, tofacitinib preferentially inhibits signaling by heterodimers containing JAK1 or JAK3 (JAK1/3) with functional selectivity over JAK2 homodimer signaling.2 Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain containing receptors for several cytokines, including interleukin (IL)-2, -4, -7, -9, -15, and -21. These cytokines are integral to lymphocyte activation, development, homeostasis, proliferation, and function; therefore, inhibition of their signaling may result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and interferon (IFN)*.3,4 At higher exposures, inhibition of erythropoietin, prolactin, and other hormones can occur via inhibition of JAK2 homodimer signaling. Tofacitinib is efficacious in rodent models of arthritis as assessed by clinical and histological measures of disease progression in the mouse collagen-induced arthritis (CIA) and rat adjuvant-induced arthritis (AIA) models. Tofacitinib is also efficacious in delayed type hypersensitivity models5 and rodent and primate transplant models.5, 6 Thus, tofacitinib shows promise in multiple models of autoimmunity and immune dysregulation. The broad immunosuppressive, immunomodulatory mechanisms of JAK3 inhibition is expected to block cytokine signaling which plays a key role in the pathogenesis of psoriasis, and dampen innate and adaptive immune responses which plays a role in ulcerative colitis.
The anti-inflammatory properties of JAK are expected to inhibit the effect of the infiltrating lymphocytes in the ocular surface and lacrimal gland.

RA is a chronic and debilitating autoimmune disease characterized by inflammation and destruction of the joints, substantial disability, and a significant impact on health status and quality of life; this results in a substantial economic burden to patients and society.8 In kinase assays, tofacitinib inhibits JAK1, JAK2, and JAK3, and to a lesser extent tyrosine kinase 2;
in cellular settings, tofacitinib preferentially inhibits signaling by heterodimeric receptors
associated with JAK3 and/or JAK1 with functional selectivity over JAK2-paired receptors. Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain-containing receptors for several cytokines, including interleukin (IL)-2, -4, -7, -9, -15, and -21,7,9 which are integral to lymphocyte function, and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response.

In Phase 2b dose-ranging studies that evaluated a dose range of 1-15 mg twice daily (BID), tofacitinib demonstrated sustained efficacy and manageable safety over 24 weeks in patients with active RA when used as monotherapy10 or in combination with background methotrexate (MTX).11 Tofacitinib 5 and 10 mg BID were selected as optimal doses for evaluation in Phase 3, which included a broad range of therapeutic scenarios investigating tofacitinib as monotherapy12 or in combination with MTX13,14 and non-MTX nonbiologic disease modifying antirheumatic drugs (DMARDs).15

Phase 3 studies were initiated with two doses of tofacitinib, 5 mg BID and 10 mg BID,
administered as monotherapy or concurrently on a background of non-biologic DMARDs. These studies demonstrated sustained efficacy and manageable safety up to 2 years in patients with active RA. Long-term extension studies have been ongoing since Phase 2 and have enrolled patients who participated in a Phase 2 or Phase 3 study; these open-label studies have demonstrated continued efficacy and a similar safety profile as seen in the controlled clinical trials. The preponderance of long-term data collected in these trials was obtained in patients on 5 mg BID of tofacitinib.

This Post-Authorization Safety Study (PASS) was developed in response to the requirements of the US Food and Drug Administration to further define the safety profile of tofacitinib 5 mg BID and 10 mg BID, especially with respect to major adverse cardiovascular events (MACE) and malignancies, and to provide comparative safety analyses to a TNF inhibitor in an open-label manner.

Study objective

The primary objective of this endpoint study is to evaluate the safety of tofacitinib at two doses versus TNFi; the co-primary endpoints are adjudicated major adverse cardiovascular events (MACE) and adjudicated malignancies excluding non-melanoma skin cancers during
study participation.

Study design

This is a Phase 3b/4 randomized, parallel arm, open-label safety endpoint study. All subjects will be randomized in a 1:1:1 ratio to one of the three treatment arms with approximately 1300 subjects in each treatment arm:
1.Tofacitinib 5 mg BID (oral)
2.Tofacitinib 10 mg BID (oral)
3.TNFi: In the US, Puerto Rico and Canada, subjects randomized to TNFi will receive adalimumab 40 mg every other week (QOW) by subcutaneous injection (SC); in all other countries, subjects randomized to TNFi will receive etanercept 50 mg once weekly by SC injection,
During the study, subjects may require alternate therapies in addition to, or instead of, their randomized drug assignment. All subjects, regardless of their treatment regimen will participate in the study until study completion. (See Sections 5.6.1 and 6.5 of the protocol)
Study completion will be declared when all 3 of the following conditions are met:
1. At least 1500 subjects have been followed for at least 3 years.
2. The targeted number of MACE are observed (See Section 9.2.1 of the protocol)
3. The targeted number of malignancies excluding non-melanoma skin cancers are observed (See Section 9.2.1 of the protocol)

It is expected that approximately 4000 subjects will participate in the study and the expected duration of the study is approximately 5 years following randomization of the first subject. The exact number of subjects and duration of the study will be determined by the pre-specified rules outlined in the charter of the blinded Steering Committee. (See Section 9.6 of the protocol)

Intervention

Subjects will be assigned by chance to receive either tofacitinib 5 mg twice daily or 10 mg twice daily or etanercept 50 mg injection every week in a 1:1:1 ratio.

Study burden and risks

Based on the totality of the non-clinical and clinical data generated thus far, identified risks associated with tofacitinib include infection, lipid elevations, anemia, neutropenia and malignancies. The identified risks for the completed studies with tofacitinib in RA are presented in the XELJANZ® (tofacitinib citrate) Investigator Brochure.

The comparator TNFi, etanercept, is reported to be associated with risks of infection,
malignancy, demyelinating disease, lymphoma, congestive heart failure, pancytopenia or aplastic anemia, anaphylaxis or serious allergic reactions, Lupus-like syndrome or
autoimmune hepatitis. The identified risks for etanercept in RA are presented in the Enbrel® (etanercept) USPI, revised December 2012.

Contacts

Public
Pfizer

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US
Scientific
Pfizer

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1.Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.
2.Must be at least 50 years of age or older.
3.Has moderate to severe rheumatoid arthritis inadequately controlled with methotrexate alone with a score of 6 or greater on the 2010 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Rheumatoid Arthritis
4.Has *6 tender/painful joints on motion and *6 swollen joints (28 joint count)
5.Has a C-reactive protein measured by a high sensitivity assay (hs-CRP) *0.3 mg/dL in the central laboratory
6.Meets Class I, II or III of the American College of Rheumatology (ACR) 1991 Revised Criteria for Global Functional Status in RA where usual self-care activities including dressing, feeding, bathing, grooming, and toileting; avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are subject-desired and age and sex-specific.
7.Has taken methotrexate continuously for at least 4 months prior to the Screening visit and has taken a stable weekly dose of methotrexate with supplemental folic or folinic acid for at least 6 weeks prior to the Baseline visit.
*Methotrexate doses less than 15 mg/week are allowed only in the presence of documented intolerance or toxicity from higher doses
*Doses higher than 25 mg/week are not permitted under any circumstances
*Folic acid doses should be at least 5 mg per week; folinic acid doses should be at least 2.5 mg per week.
8.Have at least one of the following cardiovascular risk factors at screening:
*Current cigarette smoker
*Diagnosis of hypertension
*High density lipoprotein (HDL) <40 mg/dL
*Diabetes mellitus
*Family history of premature coronary heart disease
*Presence of extra-articular disease associated with rheumatoid arthritis, which may include

nodules, Sjögren*s syndrome, anemia of chronic disease and pulmonary manifestations
*History of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina, acute coronary syndrome
9.Subjects must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
10.Male and female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment.
11.Female subjects of childbearing potential must test negative for pregnancy.
12.Female subjects who are not of childbearing potential must meet at least one of the following criteria:
*Have undergone a documented hysterectomy and/or bilateral oophorectomy
*Have medically confirmed ovarian failure or
*Achieved post menopausal status
13.Subjects must screen negative for active tuberculosis or inadequately treated tuberculosis infection (active or latent) as evidenced by the following:
a.Negative QuantiFERON Gold®* In-Tube test performed at screening
This is required unless the subject has been adequately treated for active or latent tuberculosis or a negative QuantiFERON Gold® In-Tube test was previously performed and documented within the 3 months prior to screening.
A negative tuberculin skin test (TST) is one that is <5 mm induration and it can be substituted for the QuantiFERON Gold® In-Tube test only if the central laboratory is unable to perform the test or the test is reported as indeterminate after at least 2 successive attempts.
It is strongly recommended that subjects with a history of Bacille Calmette Guérin (BCG) vaccination be tested with the QuantiFERON Gold® In-Tube test.
b.Chest radiograph taken at screening without changes suggestive of active tuberculosis (TB) infection, unless previously performed and documented within 3 months prior to screening
c.No history of tuberculosis infection unless one of the following is documented:
*Subject with prior or current latent tuberculosis has no evidence of active tuberculosis and must be taking or have completed an adequate course of therapy for latent tuberculosis (9 months of isoniazid in a locale where rates of primary multi-drug resistant TB infection are <5% or an alternative regimen recognized by the World Health Organization) and a chest radiograph is negative for active disease; the chest radiograph must be obtained at screening or, if previously performed and documented, within 3 months prior to screening.
*Subject with prior active tuberculosis has no current evidence of active disease and has completed an adequate course of therapy for active tuberculosis (a multi-drug regimen recognized by the World Health Organization) and a chest radiograph is negative for active disease; the chest radiograph must be obtained at screening or, if previously performed and documented, within 3 months prior to screening

Exclusion criteria

1.Subjects who are investigational site staff members directly involved in the conduct of the

trial 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 trial.
2.Subjects who are classified Class IV of the ACR 1991 Revised Criteria for Global Functional Status in RA (ie, are limited in their ability to perform usual self-care, vocational, and avocational activities).
3.Pregnant females; breastfeeding females; sexually active males and females of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after last dose of investigational product.
4.Subjects with infections or history of infections:
a.Any infection requiring treatment within 2 weeks prior to the Baseline visit.
b.Any infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator, within the past 6 months.
c.Infected joint prosthesis at any time with the prosthesis still in situ.
d.Recurrent (more than one episode) herpes zoster or disseminated (a single episode) herpes zoster or disseminated (a single episode) herpes simplex.;
e.Subjects will be screened for human immunodeficiency virus (HIV). Subjects who test positive for HIV will be excluded from the study.
f.Subjects will be screened for hepatitis B virus infection. Subjects with hepatitis B surface antigen (HBsAg) negative testing but who test positive for hepatitis B core antibody (HBcAb) must have further testing for hepatitis B surface antibody (HBsAb). If HBsAb is negative, the subject will be excluded from the study.
g.Subjects will be screened for hepatitis C virus antibodies (HCV Ab). Subjects with positive HCV Ab tests will be reflex tested for hepatitis C virus ribonucleic acid (HCV RNA). Only subjects with negative HCV Ab or HCV RNA will be allowed to enroll in the study.
h.Subjects are excluded for current active tuberculosis infection or prior active or latent tuberculosis that was inadequately treated or cannot be documented (See Section 4.1 Inclusion Criteria #13).
5.Subjects with any current malignancy or a history of malignancy, with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ.
6.Subjects with any uncontrolled clinically significant laboratory abnormality or any of the following laboratory abnormalities:
a.Evidence of hematopoietic disorder or hemoglobin <9 g/dL
b.White blood cell count <3.0 x 109/L (<3000/mm3)
c.Absolute lymphocyte count <0.5 x 109/L (<500/mm3)
d.Absolute neutrophil count <1.0 x 109/L (<1000/mm3)
e.Platelet count <100 x 109/L (<100,000/mm3)
f.Alanine aminotransferase (ALT), or aspartate aminotransferase (AST) >1.5 times the upper limit of normal (x ULN)
g.Estimated glomerular filtration rate (GFR) <60 mL/min using the Cockcroft-Gault formula (Appendix 3).
7.Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks or 5 half-lives (whichever is longer) after discontinuation of the investigational compound before the current study begins and/or during study participation, unless further restrictions to class of compound are specified in Section 4.2 Exclusion Criteria and Section 5.5 Concomitant Medication(s).

8.Subjects requiring or have received any prohibited concomitant medication as outlined in Appendix 2, including:
a.Subjects who have received live or live attenuated vaccines within 6 weeks prior to the first dose of study drug or at any time during treatment or within 6 weeks following discontinuation of study drug (See Section 4.4.2).
b.Subjects who have been previously treated with tofacitinib.
c.Subjects who are being treated with biologic or non-biologic DMARDs other than MTX or antimalarials within their specified washout window at study entry (see Table 1).
d.Subjects who previously experienced inadequate response, intolerance, allergy or hypersensitivity to adalimumab (US, Puerto Rico and Canada) or to etanercept (all other countries) or for whom adalimumab (US, Puerto Rico and Canada) or etanercept (all other countries) are contraindicated.
e.Subjects who are being treated with corticosteroids, other than low dose oral corticosteroids in doses equivalent to *10 mg prednisone per day at study entry.
f.Subjects who require concomitant treatment with medications that are potent inhibitors of cytochrome P450 3A4 (CYP3A4), both moderate inhibitors of CYP3A4 and potent inhibitors of CYP2C19, or potent CYP inducers.
9.Subjects who have Class III or Class IV heart failure according to the New York Heart Association (NYHA) functional classification system.
See protocol for Exclusion criteria 10-16

Study design

Design

Study phase:	3
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):	16-10-2015
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Enbrel
Generic name:	etanercept
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tofacitinib
Generic name:	Tofacitinib

Ethics review

Approved WMO Date:	25-02-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-09-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
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Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
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Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
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Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
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Date:	15-05-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	05-12-2018
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Approved WMO Date:	10-12-2018
Application type:	Amendment
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Approved WMO Date:	02-04-2019
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Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
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Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
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Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
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Date:	11-12-2019
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Approved WMO Date:	04-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2013-003177-99-NL
CCMO	NL47253.048.13