A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO ASSESS THE EFFICACY AND SAFETY OF TOCILIZUMAB VERSUS PLACEBO IN PATIENTS WITH SYSTEMIC SCLEROSIS

Published: 21-09-2015
Last updated: 20-04-2024

EFFICACY OBJECTIVESThe primary efficacy objective for this study is as follows:* To evaluate the efficacy of TCZ compared with placebo on skin sclerosis, as measured by mRSS at Week 48The secondary efficacy objectives for this study are as follows...

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

Summary

ID

NL-OMON43973

Source
ToetsingOnline

Brief title
WA29767, FocuSSced

Condition

- Autoimmune disorders
- Connective tissue disorders (excl congenital)

Synonym
scleroderma, skin thickening, systemic sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: farmaceutisch industrie F. Hoffmann la Roche

Intervention

Keyword: phase III, systemic sclerosis, tocilizumab

Outcome measures

Primary outcome

Efficacy Outcome Measures

The primary efficacy outcome measure for this study is as follows:

* Change in mRSS from baseline to Week 48

The secondary efficacy outcome measures for this study are as follows:

* Proportions of patients with *20%, * 40%, and * 60% improvement in mRSS at

Week 48 compared with baseline

* Change in FVC from baseline to Week 48

* Change in HAQ-DI from baseline to Week 48

* Change in Patient's Global Assessment from baseline to Week 48

* Change in Physician's Global Assessment from baseline to Week 48

* Time to treatment failure, defined as the time from randomization to the time

of one of the following events (whichever occurs first) during the 48-week

double-blind treatment period: death, decline in percent-predicted FVC > 10%

relative to baseline, > 20% increase in mRSS and an increase in mRSS of * 5

points occurrence of a predefined SSc-related complication as adjudicated by

the Clinical Adjudication Committee

Secondary outcome

Safety Outcome Measures

The safety outcome measures for this study are as follows:

* Frequency of deaths

* Nature, frequency, and severity of adverse events

* Incidence of specific laboratory abnormalities

* Change from baseline in digital ulcer count 3.4.3 Immunogenicity Outcome

Measures

The immunogenicity outcome measures for this study are as follows:

* Incidence of anti-TCZ antibodies during the study relative to the prevalence

of anti-TCZ antibodies at baseline

* Correlation between anti-TCZ*antibody status and efficacy, safety, or PK

outcome measures

Pharmacodynamic Outcome Measure

The PD outcome measure for this study is as follows:

* Predose ESR and serum IL-6, sIL-6R, and CRP levels at baseline and at

subsequent timepoints after initiation of study drug

Pharmacokinetic Outcome Measures

The PK outcome measures for this study are as follows:

* Predose serum TCZ concentration at baseline and at specified timepoints

thereafter

* Correlation between PK parameters for TCZ and efficacy, safety, or immunogenicity outcome measures

Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

* Proportions of patients who achieve a response, as determined by the investigator using CRISS, at Week 48
* Change in the VAS component of the SHAQ from baseline to Week 24 and baseline to Week 48
* Change in WPAI-GH score from baseline to Week 24 and baseline to Week 48
* Change in EQ-5D-3L score from baseline to Week 24 and baseline to Week 48
* Change in total score and subscores of Saint George*s Respiratory Questionnaire from baseline to Week 48
* Change in FACIT-Fatigue score from baseline to Week 48.
* Change in HRCT fibrosis score from baseline (based on HRCT scan performed within 3 months prior to screening) to Week 48
* Change in DLCO from baseline to Week 48
* Proportion of patients with * 15% decline in observed DLCO at Week 48
* Proportion of patients with * 15% decline in percentage of predicted DLCO at Week 48
* Change in FVC from baseline to Week 24
* Proportion of patients with * 10% decline in observed FVC at Week 24 and at Week 48

* Proportion of patients with * 10% decline in percentage of predicted FVC at

Week 24 and at Week 48

* Change in mRSS from baseline to Week 24 and Week 96

* Change in observed and percentage of predicted FVC from baseline to Week 96

* Correlation between non-inherited biomarkers (serum levels of CCL18, sVCAM-1,

COMP, and autotaxin; plasma levels of CXCL4; and whole blood gene signatures

associated with plasmablasts and IFN) and efficacy, safety, PK, or

immunogenicity outcome measures

Study description

Background summary

SSc is a rare and devastating disease with no approved treatment options. To date, no therapy has been shown to modify overall disease progression in SSc. The data from Study WA27788, a double-blind, placebo-controlled study, demonstrated a clinically meaningful effect of TCZ on mRSS and FVC, as well as improvements in HAQ-DI, Physician's Global Assessment, and Patient's Global Assessment at Week 48. This
Phase III study is designed to confirm clinically and statistically the findings from Study WA27788. Overall, no new or unexpected safety signals were observed in Study WA27788. The benefit*risk profile for TCZ in SSc is considered to be positive on the basis of clinically meaningful, albeit not statistically significant, effects of TCZ on skin sclerosis and pulmonary function, the concordance of positive clinical and
patient-reported outcomes (PROs), as well as the absence of safety findings that would be prohibitive of further development.

Study objective

EFFICACY OBJECTIVES
The primary efficacy objective for this study is as follows:
* To evaluate the efficacy of TCZ compared with placebo on skin sclerosis, as measured by mRSS at Week 48
The secondary efficacy objectives for this study are as follows:
* To evaluate the efficacy of TCZ compared with placebo on pulmonary function, as measured by FVC at Week 48

* To evaluate the efficacy of TCZ compared with placebo on PROs, as measured by the HAQ-DI and Patient's Global Assessment at Week 48
* To evaluate the efficacy of TCZ compared with placebo, as measured by the Physician's Global Assessment at Week 48
* To evaluate the efficacy of TCZ compared with placebo by assessment of time to treatment failure (death, worsening of mRSS and/or FVC [see Section 4.4.1.1], or clinically significant SSc complication) up to Week 48

SAFETY OBJECTIVES
The safety objectives for this study are as follows:
* To evaluate the safety of TCZ compared with placebo, focusing on the nature, frequency, and severity of serious and non-serious adverse events, the frequency of SSc-related complications, and effects on vital signs, physical findings, and clinical laboratory results
* To evaluate the safety of TCZ compared with placebo by assessing the number of digital ulcers
* To assess the long-term safety of TCZ

IMMUNOGENICITY OBJECTIVES
The immunogenicity objectives for this study are as follows:
* To characterize the immunogenic potential of TCZ by measuring anti-TCZ antibodies
* To assess the potential relationship between development of anti-TCZ antibodies and efficacy, safety, or pharmacokinetic (PK) outcome measures

PHARMACODYNAMIC OBJECTIVE
The pharmacodynamic (PD) objective for this study is as follows:
* To compare changes in levels of PD biomarkers following treatment with TCZ versus placebo

PHARMACOKINETIC OBJECTIVES
The PK objectives for this study are as follows:
* To characterize the pharmacokinetics of TCZ
* To evaluate potential relationships between PK parameters for TCZ and efficacy, safety, or immunogenicity outcome measures

EXPLORATORY OBJECTIVES
The exploratory objectives for this study are as follows:
* To evaluate the efficacy of TCZ compared with placebo on skin sclerosis, as measured by mRSS at Week 24
* To evaluate the efficacy of TCZ versus placebo measured by the proportion of responders as defined by the Combined Response Index for Systemic Sclerosis (CRISS) at Week 48
* To evaluate the efficacy of TCZ compared with placebo, as measured by the visual analog scale (VAS) component of the Scleroderma Health Assessment Questionnaire (SHAQ) at Weeks 24 and 48
* To evaluate the efficacy of TCZ compared with placebo, as measured by the

Work Productivity and Activity Impairment*General Health (WPAI-GH) questionnaire at Weeks 24 and 48
* To evaluate the efficacy of TCZ compared with placebo, as measured by the EuroQol 5-Dimension Questionnaire with three levels of severity (EQ-5D-3L) at Weeks 24 and 48
* To evaluate the efficacy of TCZ compared with placebo, as measured by Saint George*s Respiratory Questionnaire at Week 48
* To evaluate the effect of TCZ compared with placebo on fatigue as measured by Functional Assessment of Chronic Illness Therapy*Fatigue (FACIT-Fatigue) score at Week 48.
* To evaluate the efficacy of TCZ compared with placebo on the basis of change in pulmonary fibrosis, as determined using high-resolution computed tomography (HRCT) scans at Week 48
* To evaluate the efficacy of TCZ compared with placebo, as measured by diffusion capacity of the lung for carbon monoxide (DLCO) at Week 48 and FVC at Week 24
* To evaluate the maintenance of efficacy of TCZ, as measured by mRSS and FVC at Week 96
* To assess whether non-inherited biomarkers are predictive of response to TCZ (i.e., predictive biomarkers), susceptibility to developing adverse events, or progression to a more severe disease state (i.e., prognostic biomarkers), can provide evidence of TCZ activity, or can increase the knowledge and understanding of disease biology

Study design

This Phase III, multicenter, randomized, double-blind, placebo-controlled, two-arm, parallel-group study is designed to assess the efficacy and safety of TCZ in patients with SSc. The study consists of two periods: a 48-week, double-blind, placebo-controlled period, followed by a 48-week open-label treatment period. Patients will be randomized in a 1:1 ratio to receive SC injections of 162 mg of TCZ QW or placebo QW for 48 weeks during the double-blind treatment period. During the open-label treatment period, all patients will receive SC injections of 162 mg of TCZ QW for up to 48 weeks. Patients receive their first dose of open-label treatment at Week 48.

Intervention

Patients will be randomized in a 1:1 ratio to receive SC injections of 162 mg of TCZ QW or placebo QW for 48 weeks during the double-blind treatment period. During the open-label treatment period, all patients will receive SC injections of 162 mg of TCZ QW for up to 48 weeks. Patients receive their first dose of open-label treatment at Week 48.

Study burden and risks

See question E4 and E9.

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

- Age >< = 18 years at baseline (Day 1)
- Diagnosis of SSc, as defined using the American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) criteria (2013)
- SSc disease duration of <<=60 months (defined as time from the first non-Raynaud phenomenon manifestation)
- mRSS of >><=10 and <<=35 units at screening
- Active disease that meets at least one of the following criteria at screening: Disease duration of <<=18 months defined as time from the first non-Raynaud phenomenon manifestation; Increase in mRSS of >><=3 units compared with the most recent assessment

performed within the previous 6 months; Involvement of one new body area and an increase in mRSS of ><=2 units compared with the most recent assessment performed within the previous 6 months; Involvement of two new body areas within the previous 6 months; Presence of at least one tendon friction rub
- Presence of at least one of the following at screening: C reactive protein (CRP) ><=0.6 milligrams (mg) per deciliter (dL) (><=6 mg/Liter [L]); erythrocyte sedimentation rate (ESR) ><=28 millimeter per hour (mm/hr); Platelet count ><=330 x 10^9/L (330,000/microliter)
- Uninvolved or mildly thickened skin at one of the following possible injection site locations: Front, middle region of the thigh; Abdomen, except for the 2-inch area directly around the navel; Outer area of the upper arm (if a patient caregiver is giving the injection)
- For women who are not postmenopausal (><=12 months of non*therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in a failure rate of <1% per year during the treatment period and for up to 3 months after the last dose of study drug
- For men: agreement to remain abstinent or use contraceptive measures and agreement to refrain from donating sperm during the treatment period and for at least 8 weeks after the last dose of study drug

Exclusion criteria

- Pregnant or lactating, or intending to become pregnant during the study
- Major surgery (including joint surgery) within 8 weeks prior to screening or planned major surgery within 12 months following randomization
- Skin thickening (scleroderma) limited to the face or areas distal to the elbows or knees at screening
- Rheumatic autoimmune disease other than SSc, including but not limited to rheumatoid arthritis (RA) (diagnosed using ACR/EULAR criteria), systemic lupus erythematosus, mixed connective tissue disorder, polymyositis, dermatomyositis, eosinophilic fasciitis, primary Sjögren's syndrome, and eosinophilic myalgia syndrome, as determined by the investigator
- History of severe allergic or anaphylactic reactions to human, humanized, or murine monoclonal antibodies
- Evidence of moderately severe concurrent nervous system, renal, endocrine, or gastrointestinal (GI) disease not related to SSc, as determined by the investigator
- Pulmonary disease with FVC <=55% of predicted (best of three measurements) or diffusion capacity of the lung for carbon monoxide [DLCO] (hemoglobin corrected) <=45% of predicted (best of three measurements)
- Class II or higher pulmonary arterial hypertension (PAH), as defined by the World Health Organization
- Evidence of other moderately severe pulmonary disease (e.g., asthma, emphysema), as determined by the investigator
- Cardiovascular disease with significant arrhythmia, congestive heart failure (New York Heart Association Class II-IV), unstable angina, uncontrolled hypertension, cor pulmonale, or symptomatic pericardial effusion
- History of myocardial infarction in the last 6 months prior to screening

- Current liver disease, as determined by the investigator
- History of diverticulitis or chronic ulcerative lower GI disease, such as Crohn disease, ulcerative colitis, or other symptomatic lower GI conditions that might predispose a patient to perforations
- Known active current or significant history of recurrent bacterial, viral, fungal, mycobacterial, or other infections, including but not limited to atypical mycobacterial disease, hepatitis B or C, herpes zoster, infected digital ulcers, and osteomyelitis
- Any major episode of infection requiring hospitalization or treatment with intravenous antibiotics within 4 weeks prior to screening or oral antibiotics within 2 weeks prior to screening
- Significant history of recurrent tuberculosis (TB), active TB requiring treatment within the previous 3 years, or untreated latent TB
- Patients should be screened for latent TB, and, if positive, will be eligible for the study after treatment per local standard practices
- History of or currently active primary or secondary immunodeficiency
- Evidence of malignant disease, or malignancies diagnosed within the previous 5 years (with the exception of local basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix uteri that has been excised and cured)
- Neuropathies or other conditions that might interfere with pain evaluation, as determined by the investigator

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-05-2016
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	RoActemra
Generic name:	tocilizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-09-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-12-2015
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-03-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	29-08-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-09-2016
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-12-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-07-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-01-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2015-000424-28-NL
ClinicalTrials.gov	NCT02453256
CCMO	NL54269.056.15