A Randomized, Double-Blind, Placebo-Controlled, Single-Dose, Dose-Escalation STUDY of MORAb-022 in Healthy SUBJECTS and Subjects with Rheumatoid Arthritis.

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Primary:to evaluate the safety and tolerability of single escalating intravenous (IV) doses of MORAb-022 in healthy subjects and subjects with rheumatoid arthritis (RA)Secondary:- to evaluate the pharmacokinetics (PK) of single escalating IV doses...

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

Summary

ID

NL-OMON34310

Source
ToetsingOnline

Brief title
MORAb-022 SAD study in HV and patients with RA

Condition

- Other condition

Synonym
chronic inflammatory, rheumatism

Health condition

rheumatoïde arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Eisai
Source(s) of monetary or material Support: Farmaceutische Industrie.

Intervention

Keyword: MORAb-022, rheumatoid arthritis

Outcome measures

Primary outcome

Pharmacodynamics:

Antibodies to MORAb-022, serum/plasma inflammatory markers IL-6, TNF-*, IL-1,

IFN-* concentrations, CD11b receptor expression on neutrophils, circulating

GM-CSF levels, shift in T-cell profiles, and DAS, ACRn and VAS scores.

Pharmacokinetics:

Plasma MORAb-022 concentrations, pharmacokinetic parameters.

Safety:

Adverse events, vital signs, ECG-parameters, laboratory parameters, physical

examination, SP-D levels, PFT.

Secondary outcome

n.a.

Study description

Background summary

The drug to be given, MORAb-022 is a new, investigational compound that may eventually be used for the treatment of rheumatoid arthritis (RA). RA is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks the joints producing an inflammatory reaction (synovitis) that often progresses to destruction of the soft tissue of the joints. RA can also produce diffuse inflammation in the lungs, pericardium (a double-walled sac that contains the heart), pleura (tissue that surrounds the lungs), and sclera (white part of the eye), and also elevations of the skin, most common in subcutaneous tissue under the skin. Although the cause of rheumatoid arthritis is unknown, autoimmunity plays a decisive role in its chronic character and progression.
MORAb-022 is a human monoclonal antibody and is a therapeutic antibody being developed for the treatment of autoimmune diseases including rheumatoid arthritis.

Study objective

Primary:
to evaluate the safety and tolerability of single escalating intravenous (IV) doses of MORAb-022 in healthy subjects and subjects with rheumatoid arthritis (RA)

Secondary:
- to evaluate the pharmacokinetics (PK) of single escalating IV doses of MORAb-022 in healthy subjects and subjects with RA
- to explore the pharmacodynamic (PD) effect of single escalating IV doses of MORAb-022 in healthy subjects and subjects with RA
- to assess the effect of single escalating IV doses of MORAb-022 on the disease activity score (DAS) and American College of Rheumatology scores (ACRn) of subjects with RA

Study design

Design:
A randomized, double-blind, placebo-controlled, single-ascending dose study in healthy male and/or female subjects and subjects with RA; Groups 1-3 will consist of six healthy male and/or healthy female subjects each receiving a single iv infusion of MORAb-022 or placebo (four verum and two placebo); Groups 4-6 will consist of eight healthy male and/or healthy female subjects each receiving a single iv infusion of MORAb-022 or placebo (six verum and two placebo); at the first dose level two subjects (one verum and one placebo) will be dosed and monitored for twenty-four hours before the next two subjects will be dosed (no more than two subjects will be dosed each day in Group 1); in parallel with dose escalation in healthy subjects, there will be a dose

escalation of MORAb-002 in three cohorts (Groups 7-9) of four RA patients each receiving a single iv infusion of MORAb-022 or placebo (three verum and one placebo).

Procedures and assessments
Screening and follow-up:
Clinical laboratory, SP-D level, physical examination, pulmonary function test (PFT), vital signs (including body temperature and respiratory rate), weight, 12-lead ECG; at eligibility screening: chest X-ray, medical history, alcohol and drug screen, GM-CSF autoAb, height, PPD test, HBsAg, anti HCV, anti-HIV 1/2 and serum pregnancy test (females only); physical examination, weight, vital signs (including body temperature and respiratory rate), 12-lead ECG (in triplicate), clinical laboratory, alcohol and drug screen, urine pregnancy test (females only), PFT and SP-D level to be repeated upon admission; follow-up on Day 85; the follow-up visit will be repeated every 2 weeks until MORAb-022 has been cleared 90% from the body.

Observation period:
One period in clinic from -17 h up to 48 h for healthy volunteers (HV) and 24 hr for RA patients after drug administration and ambulatory visits on Days 5, 8, 15, 29, 43 and 57 and a telephonic contact on Day 71.

Blood sampling:
- for pharmacokinetics of MORAb-022 in plasma: pre-dose and 0.25, 0.5 (end of infusion/post-start infusion), 0.75 (post-start infusion), 1, 2, 4, 8 and12 h post-dose (post-start infusion) and once on Days 2, 3 (HV only), 5, 8, 15, 29, 43, 57 and 85 (follow-up)
- for pharmacodynamics of cytokines, IL-1, IL-6, TNF-* and IFN-*: pre-dose and 24 h post-dose and once on Days 3, 8, 15, 29, 43, 57 and 85 (follow-up)
- for pharmacodynamics of antibodies to MORAb-022: pre-dose and once on Days 57 and 85 (follow-up)
- for pharmacodynamics of CD11b in plasma: pre-dose and 8 h post-dose and once on Days 2, 5, 8, 15, 29, 43, 57 and 85 (follow-up)
- for pharmacodynamics of circulating GM-CSF: pre-dose and 0.25, 0.5, 0.75, 2, 4 and 8 h post-dose and once on Days 3 (HV only), 5, 8, 15, 29, 43, 57 and 85 (follow-up)
- for pharmacodynamics of T-cell profile: pre-dose and 4 and 24 h post-dose
- for pharmacodynamics of CRP and SAA (RA patients only): pre-dose and 8 h post-dose and once on Days 2, 5, 8, 15, 29, 43, 57 and 85 (follow-up)
- for DNA: once on Day -1
- for RNA: once on Day -1, post-dose on Day 1 and once on Days 2, 3, 5, 15 , 43, 57 and 85 (follow-up)

DAS, ACRn and VAS scores (RA patients only):
Once on Day -1 and post-dose on Days 2, 5, 8, 15, 29, 43, 57 and 85 (follow-up).

Safety assessments:

Adverse events: throughout the study; vital signs (including body temperature and respiratory rate): pre-dose and 1, 2, 4 and 8 h post-dose and once on Days 5, 8, 15, 29, 43 and 57; 12-lead ECG: pre-dose and 2 and 8 h post-dose and once on Days 3 (HV only), 8, 15, 29 and 57; clinical laboratory: 24 h post-dose and once on Days 5, 8, 15, 29, 43 and 57; SP-D level: 24 h post-dose and once on Days 5, 8, 15, 29, 43 and 57; PFT: post-dose on Day 1 and once on Days 2, 3 (HV only), 5, 8, 15, 29, 43 and 57; local tolerability at infusion site: continuously on Day 1 and once on Days 2, 5, 8, 15, 29, 43, 57 and 85 (follow-up).

Bioanalysis:
- analysis of plasma MORAb-022 samples using a validated method by PRA
- analysis of cytokines, IL-1, IL-6, TNF-* and IFN-* samples using validated methods by PRA
- analysis of antibodies to MORAb-022 samples using a validated method by PRA
- analysis of plasma CD11b samples using a validated method by PRA
- analysis of GM-CSF samples using a validated method by PRA
- analysis of GM-CSF auto Ab samples using a validated method by PRA
- analysis of T-cell profile using a validated method by PRA
- analysis of CRP samples using a clinical chemistry method by PRA
- analysis of SAA and SP-D samples using validated methods by PRA
- analysis of DNA samples using a validated method by Sponsor
- analysis of RNA and proteomics samples using a validated method by Sponsor

Intervention

Study Medication
Active substance: MORAb-022
Activity: human monoclonal antibody targeting GM-CSF
Indication: rheumatoid arthritis (RA)
Strength: unknown
Dosage form: iv infusion

Treatments
Healthy subjects
Group 1: a single 30-min iv infusion of 0.0085 mg/kg (absolute dose of approximately 0.6 mg) MORAb-022 or placebo on Day 1
Group 2: a single 30-min iv infusion of 0.042 mg/kg (absolute dose of approximately 3 mg) MORAb-022 or placebo on Day 1
Group 3: a single 30-min iv infusion of 0.12 mg/kg (absolute dose of approximately 10 mg) MORAb-022 or placebo on Day 1
Group 4: a single 30-min iv infusion of 0.36 mg/kg (absolute dose of approximately 30 mg) mg MORAb-022 or placebo on Day 1
Group 5: a single 30-min iv infusion of 0.7 mg/jkg (absolute dose of approximately 60 mg) MORAb-022 or placebo on Day 1
Group 6: a single 30-min iv infusion of 1.4 mg/kg (absolute dose of approximately 120 mg) MORAb-022 or placebo on Day 1

RA patients
Group 7: a single 30-min iv infusion of 0.36 mg/kg MORAb-022 or placebo on Day 1
Group 8: a single 30-min iv infusion of 0.7 mg/kg MORAb-022 or placebo on Day 1
Group 9: a single 30-min iv infusion of 1.4 mg/kg MORAb-022 or placebo on Day 1

Study burden and risks

Procedures:
Pain, light bleeding, heamatoma, possibly an infection.

Medication:
There is no side effect information for humans as MORAb-022 has not been given to humans before. In a previous study with monkeys, in which MORAb-022 was administered daily in very high doses over a period of 4 weeks, the following adverse effects were observed: increase in monocyte counts, increase in liver weights, increase in macrophage infiltration in the lung and a decrease in weight, length and coiling of uterine glands.
An adverse effect, associated with the activity of the compound is Pulmonary Alveolar Proteinosis (PAP). PAP is a rare lung disease and symptoms include dyspnea (shortness of breath), cough, low grade fever and weight loss. Although theoretically these symptoms may occur, this has not been observed yet in preclinical studies.
In the healthy volunteer part, up till cohort 4, MORAb-022 has been well tolerated. There are no significant adverse events reported.

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

Healthy subjects:
Healthy male and postmenopausal female subjects, age between 18 and 65 years, BMI between 18 and 30kg/m2, non-smoker.;Patients:
Male and female subjects with RA, age between 18 and 70 years, BMI is * 35 kg/m2, subjects must be on a stable dose of methotrexate (MTX) for >4 consecutive weeks in the period prior to randomization, at screening the duration of the active disease is of >3 months from the onset of persistent synovitis (i.e. inflammation of the joints), non-smoker or smoke occasionally.

Exclusion criteria

Suffering from: hepatitis B, cancer or HIV/AIDS. In case of participation in another drug study within 60 days before the start of this study or being a blood donor within 60 days from the start of the study. In case of donating more than 1.5 liters of blood (for men)/ more than 1.0 liters of blood (for women) in the 10 months prior the start of this study.

Study design

Design

Study type: Interventional

Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-06-2010
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	n.a.
Generic name:	MORAb-022

Ethics review

Approved WMO Date:	09-04-2010
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	31-05-2010
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-11-2010
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-12-2010
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-01-2011

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	EUCTR2010-018666-23-NL
CCMO	NL32140.056.10