A Phase I, Randomized, Single-Center Study to Investigate the Safety, Tolerability, Pharmacodynamic and Pharmacokinetic Profiles of Single and Multiple Doses of R924548 in Healthy Human Subjects

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Primary: to investigate the safety and tolerability in healthy subjects of single and multiple ascending oral doses of R548 formulated and dosed as an aqueous suspension or aqueous solutionSecondary: - to characterize the single dose and steady…

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

Summary

ID

NL-OMON37424

Source
ToetsingOnline

Brief title
R924548 SAD/MAD study

Condition

- Autoimmune disorders

Synonym
immune-mediated diseases, rheuma

Research involving

Human

Sponsors and support

Primary sponsor: Rigel Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Rigel Pharmaceuticals;Inc.;USA

Intervention

Keyword: Healthy subjects, Immune-mediated diseases, R924548

Outcome measures

Primary outcome

Criteria for evaluation

Safety and tolerability: adverse events, vital signs, ECG-parameters,

laboratory parameters, physical examination

Stopping rules:

Dosing for any individual subject will be stopped if the subject experiences a

possible Drug-related serious adverse event (SAE) or a possibly Drug-related

significant non-serious AE that in the opinion of the Investigator or Sponsor*s

medical representative, warrants discontinuation

from the Study for that subject*s well-being.

Progression to the next higher dose level will be stopped if 1 or more subjects

experience a possible Drug-related SAE or a possible Drug-related significant

non-serious AE that, in the opinion of the Investigator or Sponsor*s medical

representative, warrants discontinuation of dose

escalation or stopping the Study.

In Groups A1-A4 only, if S370 (the Ames positive metabolite isolated in dog

feces) is found in any subject*s feces at an amount *3.6 mg, then escalation to the next dosing group will only occur following approval by the Investigator , Sponsor*s medical representative and the EC.

Secondary outcome

Criteria for evaluation

Pharmacodynamics: IL-2 stimulated pSTAT5 in blood lymphocytes and GM-CSF stimulated pSTAT5 in granulocytes

analysis of blood lymphocyte subsets

Pharmacokinetics: plasma R548 and its metabolite R507 and R689 concentrations.

metabolite profiling in urine and feces (in Groups A1-A4 only), pharmacokinetic parameters, plasma caffeine and paraxanthine concentrations, pharmacokinetic parameters

Study description

Background summary

The study drug to be given, R548, is a new investigational drug that may eventually be used for the treatment of immune-mediated diseases such as rheumatoid arthritis. R548 is a study drug that will convert in the body into an inhibitor of Janus kinase 1 (JAK1) and Janus kinase 3 (JAK3), which are enzymes that contribute to the development of inflammation in rheumatoid arthritis.

This new study drug is not registered and approved for sale as a drug and this is the first time that this study drug is being given to humans.

Study objective

Primary:
to investigate the safety and tolerability in healthy subjects of single and multiple ascending oral doses of R548 formulated and dosed as an aqueous suspension or aqueous solution

Secondary:
- to characterize the single dose and steady state pharmacokinetic (PK) profiles of R548 and its active metabolite R507
- to characterize the single dose PK profiles of R548 and its active metabolite R507 in R548 formulated as an immediate release and an enteric-coated tablet.
- to characterize the food effect on the PK of R548 formulated as an immediate release tablet.
- to characterize the single dose and steady state pharmacodynamics (PD) profile of R548
- to evaluate the potential PK interaction between a CYP1A2 substrate (caffeine) and R548 at steady state in healthy human subjects
- to profile the metabolites of R548 in the plasma, urine and feces

Study design

Design
Part A: a randomized, placebo-controlled, single-ascending dose study with four groups of four healthy male subjects (Groups A1-A4) each receiving a single oral dose of R548 or placebo (three active and one placebo); two groups of eight healthy male subjects (Groups A5-A6) each receiving a single oral dose of R548 or placebo (six active and two placebo; Group A1 will be sub-divided in two groups of two subjects (one active and one placebo in the first group, and two active in the second group, which will therefore be single-blind) separated by a minimum of two days.

Part B: a randomized, placebo-controlled, multiple-ascending dose study with two to three groups of eight healthy male subjects each receiving a single dose of R548 or placebo (six active and two placebo) on Days 1 and 7 and an oral dose of R548 or placebo twice daily on Days 2-6.

Part C: a randomized, placebo-controlled, multiple dose study with one to two groups of ten healthy male and post-menopausal/surgically sterile female subjects each receiving a single dose of R548 or placebo (eight active and two placebo) on Days 1 and 14 and an oral dose of R548 or placebo twice daily on Days 2-13

Part D: A randomized, open-label (not placebo-controlled), five-treatment period study in 12 healthy male subjects consisting of four-way crossover, followed by a fifth period in which subjects will be randomized to one of two formulations. The four-way crossover component will employ a Williams design with three subjects randomized to receive a different R548 formulation in each period: aqueous suspension in fed state, immediate release 100 mg tablets in fed state, immediate release 100 mg tablets in fasted state, and enteric coated 100 mg tablets in fasted state. In the fifth period, six subjects will be randomized to receive immediate release 200 mg tablets in fasted state, and six subjects will receive enteric coated 200 mg tablets in fasted state. All Part

D doses will be 400 mg R548.

Intervention

Study Medication
Active substance: R548
Activity: janus kinase 1 (JAK1) and janus kinase 3 (JAK3)
Dosage form: aqueous suspension or aqueous solution

Treatments
Part A (SAD)
Group A1: a single oral dose of 50 mg R548 aqueous suspension or placebo on Day 1
Group A2: a single oral dose of 100 mg R548 aqueous suspension or placebo on Day 1
Group A3: a single oral dose of 200 mg R548 aqueous suspension or placebo on Day 1
Group A4: a single oral dose of 100 mg R548 aqueous solution or placebo on Day 1
Group A5: a single oral dose of 350 mg R548 aqueous suspension or placebo on Day 1
Group A6: a single oral dose of 500 mg R548 aqueous suspension or placebo on Day 1

Part B (MAD)
Group B1: a single oral dose of 200 mg R548 on Days 1 and 7 and an oral dose of 200 mg R548 twice daily on Day 2-6, a single oral dose of 150 mg caffeine in the morning of Days -1 and 6
Group B2: a single oral dose of 400 mg R548 on Days 1 and 7 and an oral dose of 400 mg R548 twice daily on Day 2-6, a single oral dose of 150 mg caffeine in the morning of Days -1 and 6

Part C (multiple dose)
Group C1: a single dose of 400 mg R548 on Days 1 and 14 and an oral dose of 400 mg R548 twice daily on Day 2-13

Part D
four times a single oral dose of 400 mg R548 on days 1, 4, 7, 10 and 13, as a suspension (once) or a tablet (four times)

Study burden and risks

not applicable

Contacts

Public
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Scientific
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Part A, B and D:
Healthy male volunteers
18-55 years of age
BMI 19.0-31.0 kg/m2;Part C:
Healthy male 18-55 years of age
Healthy post-menopausal/surgically sterile female volunteers 18-65 years of age
BMI 19.0-31.0 kg/m2

Exclusion criteria

Suffering from: hepatitis B, cancer or HIV/AIDS.

Participation in another drug study within 3 months before the start of this study.
Blood donation within 3 months from the start of this study or in case you have donated more than 1.5 liters of blood (for men) / more than 1.0 liters of blood (for women) in the 10 months before the start of this study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-10-2011
Enrollment:	70
Type:	Actual

Ethics review

Approved WMO Date:	26-09-2011
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-10-2011
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	08-12-2011
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-12-2011
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-12-2011
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-12-2011
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-02-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	07-02-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-03-2012
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-09-2012
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-10-2012
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	EUCTR2011-003096-11-NL
CCMO	NL37876.056.11