A PHASE I STUDY, TO DETERMINE THE SAFETY, TOLERABILITY, PHARMACOKINETICS AND FOOD EFFECT OF SINGLE AND MULTIPLE DOSES OF ORALLY ADMINISTERED HM71224 IN HEALTHY, ADULT MALE VOLUNTEERS

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Primary:To evaluate the safety and tolerability, and if possible to determine the maximum tolerated dose (MTD) of HM71224 after single and multiple ascending dose administration in healthy subjects.Secondary: To determine the pharmacokinetics (PK)...

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

Summary

ID

NL-OMON40064

Source
ToetsingOnline

Brief title
HM71224 SAD/FE/MAD study

Condition

- Other condition

Synonym
Rheuma, Rheumatoid Arthritis

Health condition

Reumatoide Arhtritis/Chronisch Inflammatoire aandoening

Research involving
Human

Sponsors and support

Primary sponsor: Hanmi Pharmaceutical Co. Ltd.
Source(s) of monetary or material Support: Pharmaceutische industrie

Intervention

Keyword: Food Effect, HM71224, Multiple Ascending Dose, Single Ascending Dose

Outcome measures

Primary outcome

Safety; AEs, vital signs, 12-lead ECG, clinical laboratory, physical

examination; and Part C only: DLCO, SpO2, Lung auscultation, and Sp-D.

Secondary outcome

PK: plasma and urine HM71224 concentrations: plasma and urine PK parameters.

Exploratory PD : BTK occupancy, CD63+ (Part C only)

Study description

Background summary

HM71224 is a new investigational compound that may eventually be used for the treatment of Rheumatoid Arthritis (RA). HM71224 blocks an enzyme (Bruton*s tyrosine kinase [BTK]) which is present in certain white blood cells (B-Cells). In patients with autoimmune diseases like RA these B Cells react against the own body. Lowering the sensitivity of these cells can reduce the reaction against the own body. This is the first time that this compound is being given to humans.

Study objective

Primary:
To evaluate the safety and tolerability, and if possible to determine the maximum tolerated dose (MTD) of HM71224 after single and multiple ascending dose administration in healthy subjects.

Secondary:
To determine the pharmacokinetics (PK) of HM71224 and selected metabolites (M1 and M2) following single and multiple oral dose administration of HM71224.

To assess whether the PK of HM71224 is affected by food.

To assess the BTK occupancy by HM71224 after multiple oral administration of HM71224

Study design

A double-blind, randomized, placebo-controlled study, consisting of a single ascending dose (SAD) with a food
effect part, and a multiple ascending dose (MAD) part. In the SAD part of HM71224 to be taken as a tablet,

In Part A SAD: 2 groups of 9 subjects (6 subjects on active and 3 on placebo) will be treated with escalating doses in an
alternating panel design with a washout of at least 7 days between dose administrations. In the first dose cohort, for risk
mitigating purposes, initially 2 subjects (one active, one placebo) will be dosed and after a 24-hour safety monitoring
window, the remainder of the first cohort will be dosed.

In Part B FE: 1 group of 8 subjects (8 subjects on active) will be treated with a single oral dose of HM71224 in an open label, cross over design; with HM71224 being administered in one treatment period under fasted conditions and on the other treatment period under fed conditions.

In Part C MAD: 7 groups of 8 subjects (6 subjects on active and 2 on placebo) will be treated with escalating sequential doses of HM71224.This means that there are two additional MAD groups included to evaluate .

Procedures and assessments
Screening and follow-up:
demographics, clinical laboratory (including clinical chemistry, hematology, prothrombin time [PT], activated partial thromboplastin time [aPTT], lipid panel and urinalysis), full physical examination (including height and body weight), vital signs (including supine systolic and diastolic blood pressure, pulse rate and body temperature), 12-lead electrocardiogram (ECG), previous and concomitant medication, medical history, drug and alcohol screen, Hepatitis B Surface Antigen (HBsAg), anti Hepatits C Virus (HCV) and anti- Human

Immunodeficiency Virus 1 and 2 (HIV 1/2); Part C: Lung function test and High-resolution CT and X-Ray thorax scan. During follow-up a low-dose CT scan will be performed if deemed necessary. Fecal occult blood (from Group 6 onwards).

Each admission : drug and alcohol screen, AEs, and previous and concomitant medication

Observation period :
Part A SAD: 3 periods in the clinic from Day -1 up to 48 hours after the last dose
Part B FE: 2 periods in the clinic from Day -1 up to 48 hours after the last dose
Part C MAD: 1 period in the clinic from Day -3 up to 48 hours after the last dose

Blood sampling: for PK: each period pre*dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36 and 48 h post*dose. Group 9 and 10: pre-dose, 1, 2, 8 and 24 hours after first dose on Day 1, pre-dose on Day 7, and pre-dose, 2 and 24 hours after dose on Day 14.
Part C PD: BTK occupation, CD63+)): Day 1 pre-dose and 4 and 24 h post dose, Day 14 pre-dose and on Day 21. For Group 8 only: additional CD63+ assessments on Day 7 pre-dose, and on Day 14 at 4 h and 24 h post-dose. Group 9 and 10: Group 9 and 10: additional BTK Samples 1, 2, 12 hours post-dose on Day 1, Day 3 predose and 2 hours post-dose , and Day 15, 17, and 21, no 24 hour sample after first dose on Day 1 and pre-dose sample on Day 14 are taken.

Urine sampling : for PK: each period pre-dose and 0-4, 4-8, 8-12, 12-24, 24-36, and 36-48 h post-dose

Safety assessments :
AEs: throughout the study; vital signs: each period at pre*dose and 0.5, 1, 2, 3, 4, 6, 8, 12, 36 and 48 h post-dose; 12-lead ECG: each period at pre*dose and at 2, 4, 6, 8, 24 and 48 h post*dose; clinical laboratory: each period at pre* dose and 24 h post*dose; physical examination: each period at 48 h post*dose. For Part C there are additional safety assessments: (DLCO), and lung function test, SpO2, ; Lung auscultation (Listening to the lungs) and additional clinical laboratory ((including CRP, WBC and surfactant, Sp-D). For Group 8 there are additional safety assessments: Body temperature: in the afternoon of Day -2, Day 1, Day 2 to 6, Day 8 to 13, Day 15 and at discharge; skin inspection : once daily from Day -2 to discharge on Day 16

Bioanalysis : by PRA: analysis of plasma samples for HM71224 using a validated LC-MS method, analysis of Surfactant, pulmonary-associated protein D (Sp-D) using a validated ELISA method: by ABL: analysis of BTK occupancy using a validated 2-step ELISA method.

Intervention

Part A SAD:
Group Period Treatment No. of
tablets How often
1 1 10 mg HM71224 or placebo 2 x 5 mg Single dose
2 40 mg HM71224 or placebo 2 x 20 mg Single dose
3 160 mg HM71224 or placebo 8 x 20 mg Single dose
2 1 20 mg HM71224 or placebo 1 x 20 mg Single dose
2 80 mg HM71224 or placebo 4 x 20 mg Single dose
3 200 mg HM71224 or placebo 10 x 20 mg Single dose

Part B FE:
Group Food status Treatment
How often
3 Fasted 60 mg HM71224 Single dose
3 Fed 60 mg HM71224 Single dose

Part C MAD:
Group Day Treatment Breakfast How
often
4 1 10 mg HM71224 or placebo No Once daily
2 -13 10 mg HM71224 or placebo No Once daily
14 10 mg HM71224 or placebo No Once daily
5 1 20 mg HM71224 or placebo No Once daily
2 -13 20 mg HM71224 or placebo No Once daily
14 20 mg HM71224 or placebo No Once daily
6 1 40 mg HM71224 or placebo No Once daily
2 -13 40 mg HM71224 or placebo No Once daily
14 40 mg HM71224 or placebo No Once daily
7 1 80 mg HM71224 or placebo No Once daily
2 -13 80 mg HM71224 or placebo No Once daily
14 80 mg HM71224 or placebo No Once daily
8 1 120 mg HM71224 or placebo No Once daily
2 -13 120 mg HM71224 or placebo No Once daily
14 120 mg HM71224 or placebo No Once daily
9 1 40 mg HM71224 of placebo No Twice daily
3 up to 13 40 mg HM71224 of placebo No* Once daily
14 40 mg HM71224 or placebo No Once daily
10 1 60 mg HM71224 or placebo No Twice daily
3 up to 13 60 mg HM71224 of placebo No* Once daily
14 60 mg HM71224 ro placebo No Once daily
* Ontbijt wordt 1 uur na inname geserveerd.

Study burden and risks

During the investigation, various assessments can be experienced as more or less stressful.

Blood draw, indwelling canula:
During this study blood will be drawn. Each period 1 time an indwelling canula will be used (2 times for the MAD part) and a number of blood draws will be drawn by direct puncture of the vein. The insertion of the canula may be associated with pain, minor bleeding, bruising, possible infection.

Collection of urine; Urine will be collected until 48 hours after administration of HM71224 (thus until Day 3).

Heart trace (ECG*s): ECG*s will be made regularly: specifically on Day 1 of each period.

As HM71224 was administered to men for the first time in this study, to date only limited information on adverse effects in man have been reported. In Part A and B of this study the following adverse effects have been reported: loose stools, nausea, stomach rumble, and headache. In one of the groups of Part C of this study, one event of generalized skin rash associated with itching, covering the whole body (diagnosed as serum sickness-like reaction) was reported in 1 participant. This episode resolved completely after treatment. HM71224 has been studied in animals. From animal studies and the expected activity of HM71224 the following adverse reactions may be expected: increased risk of infections, hepatic- gastro-intestinal symptoms such as abdominal pain, abdominal distension and constipation and also respiratory tract symptoms such as difficulty in breathing (dyspnea), rapid breathing (tachypnea), chest pain and finally skin rash. With the dose(s) used in this study no serious adverse effects are expected.

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

Gender: male
Age: 18 * 65 years, inclusive
BMI: 18.5 * 30.0 kg/m2, inclusive
Non-smokers for at least 60 days: (Part A and B) or 2 years (Part C).

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 the study. In case of donating blood or significant loss of blood within 60 days of the start of drug dosing.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-01-2013
Enrollment:	82
Type:	Actual

Ethics review

Approved WMO Date:	01-11-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-11-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-07-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-07-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-09-2013
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-09-2013

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-02-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-02-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-08-2014
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	EUCTR2012-004353-92-NL
CCMO	NL42361.056.12