A randomised, double-blind, placebo-controlled trial for establishing safety, tolerability, pharmacokinetics, pharmacodynamics and clinical efficacy of multiple subcutaneous doses of BI 655064 in healthy volunteers and in rheumatoid arthritis patients with prior inadequate response to methotrexate therapy

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

Summary

ID

NL-OMON40579

Source
ToetsingOnline

Brief title
1293_2

Condition

- Autoimmune disorders

Synonym
Rheumatoid arthritis

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: Boehringer Ingelheim BV

Intervention

Keyword: BI 655064, Methotrexate, Monoclonal antibody, Rheumatoid Arthitis

Outcome measures

Primary outcome

Safety, tolerability, pharmacokinetics, pharmacodynamics and clinical efficacy.

Clinical efficacy: ACR20 response rate at Week12 from the initiation of study

treatment

Secondary outcome

- ACR50 and 70 response rates at Week 12

- EULAR Response Criteria (DAS28 4v-CRP and DAS28 4v-ESR) at Week 12

- percentage of patients with a decrease in DAS28 4v-CRP of >1.2 at Week 12

compared to baseline

- change in DAS28-4v at Week 12 (Day 85) compared to baseline

Study description

Background summary

RA is a chronic, autoimmune condition which mainly affects the joints in the body. Current therapy for RA consists of medications called standard disease-modifying anti-rheumatic drugs (DMARDs) and biologic DMARDs. These medications have the potential to reduce or prevent joint damage and preserve joint function. The most common standard DMARD is called Methotrexate (MTX) and it is generally the first line medication used to treat RA. However, not everyone responds well enough to treatment with MTX alone or even with other standard DMARDs added to MTX or substituted for MTX. These people need the addition of a biologic DMARD to MTX in order to control their disease more effectively. BI 655064 is a biologic DMARD which is being researched in this study. The most common approved biologic DMARDs used first in combination with MTX are medications which act against a molecule in the human body called Tumour Necrosis Factor-Alpha (anti-TNF alpha) however there are also other biologic DMARDs approved for the treatment of RA.
BI 655064 is a type of medication called a monoclonal antibody. A monoclonal antibody is a protein made in the laboratory that can bind to substances in the body. BI 655064 works by binding to a protein called CD40 and modifying its normal function. CD40 is present on the surface of some human blood cells, the most important being called B-lymphocytes or B-cells.

Study objective

This study has two parts. The main purpose of Part 2 of this study is to see how safe and effective different doses of BI 655064 are as well as to look at the pharmacokinetics (the amount of medication in your blood) and the pharmacodynamics (the way in which the medication binds to CD40 proteins on your blood cells and modifies the normal function of CD40) in patients with RA.
In Part 1, BI 655064 was tested in healthy male and female volunteers, a requirement for all investigational medications. The purposes of Part 1 were the same as for Part 2 except for looking at the effectiveness of BI 655064 * this is not possible in people without the disease.

Study design

This clinical study is to be conducted at approximately 35 centres in approximately 7 countries with a maximum total of approximately 106 subjects.
In Part 2, you will be randomly assigned by chance (like pulling a number out of a hat) to one of four treatment groups and will receive treatment for 12 weeks. It is planned that approximately 44 subjects will be included in the treatment group receiving 120 mg BI 655064 subcutaneously (s.c.) every week for 12 weeks and 22 subjects will be included in the treatment group receiving placebo s.c. every week for 12 weeks. You will have a 2 out of 3 chance to receive active medication and a 1 out of 3 chance to receive placebo.

Intervention

BI 655064 / placebo dosed 120 mg s.c. every week from randomisation in RA patients (2:1). This is to be administered on days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78.

Study burden and risks

During all visits a pregnancy test will be done (if applicable), routine lab tests, inlcuding PK samples, and will BI 655064 be adminstered.
Also during half of all visits questionnaires will be completed (EQ5D, VAS, HAQ) will be completed by the patients and will the swollen and tender joints be counted. Vital signes will be measured and an ECG will be made at the beginning, middle and end of the study.
At v1 (screening) a drugs and infections screening will be done, and a complete physical examination (also at the end of the study).
At v2 (randomisation) ADA sampling will be done, PD samples will be taken, even as biomarkes, farmacogenomic samples. These last three wille be repeated at the end of the study.
For the farmacogenomic samples a separate consent will be given.
Visits will last for 1-2 hours.
For details in the flowchart, please refer to pages 9-11 of the protocol.

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

Part 1 (HVs):;1. Healthy males and females according to the investigator*s assessment, as based on the following criteria: a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests;2. Age * 18 and * 60 years;3. Body Mass Index * 18.5 and * 29.9 kg/m2;4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and the local legislation;5. Female subjects who meet any of the following criteria from at least 30 days before the first study drug administration and until 30 days after trial completion: - using adequate contraception, e.g. any of the following methods plus condom: implants, injectables, combined oral contraceptives, intrauterine device (IUD) - sexually abstinent - have a vasectomised sexual partner (vasectomy at least 1 year prior to enrolment) - surgically sterilised (including hysterectomy) - postmenopausal defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with simultaneous levels of follicle stimulating hormone (FSH) above 40 U/L and estradiol below 30 ng/L is confirmatory);Part 2 (RA Patients):;1. Age * 18 and * 70 years;2. Patients classified as having RA according to the 1987 ACR Classification Criteria;3. Insufficient clinical response to methotrexate defined as moderate/high active disease after oral or s.c MTX treatment given continuously for at least 3 months and for the last 6 weeks before screening at a stable weekly dose *15mg. For patients who do not tolerate the minimum weekly dose of at least 15 mg due to side effects, a stable weekly dose as low as 7.5 mg is also permitted;4. Moderate or highly active disease defined as DAS28 4v-CRP * 3.5 with * 6 tender and * 6 swollen joints out of 68/66 joint count at screening and confirmed by * 6 tender and * 6 swollen joints out of 68/66 joint count at randomisation visit (Visit 2);5. Serum CRP level * 0.8 mg/dL or ESR * 28 mm/1h at screening;6. Anti-CCP2 or Rheumatoid Factor positivity according to the limits of the assay used at screening;7. Female patients who meet any of the following criteria from at least 30 days before the first study drug administration and until at least 6 months after last dose of MTX taken in the current trial: - using adequate contraception, e.g. any of the following methods plus condom: implants, injectables, combined oral contraceptives, intrauterine device (IUD) - sexually abstinent - have a vasectomised sexual partner (vasectomy at least 1 year prior to enrolment) - surgically sterilised (including hysterectomy) - postmenopausal defined as at least 1 year of spontaneous amenorrhea (in questionable cases a blood sample with simultaneous levels of follicle stimulating hormone (FSH) above 40 U/L and estradiol below 30 ng/L is confirmatory) OR Male patients who: - are documented to be sterile or consistently and correctly use a condom while their female partners (if of childbearing potential) agree to use any of the following adequate contraception methods: implants, injectables, combined oral contraceptives, intrauterine device (IUD) from the date of screening until at least 6 months after the last dose of MTX taken in the current trial. - don*t donate any sperm sample for procreation purposes, from the date of screening until at least 6 months after last dose of

MTX taken in the current trial. It is the responsibility of the male patient to ensure that his partner does not become pregnant during all the study duration. Female partners of childbearing potential must perform monthly urine pregnancy tests from the date of screening until at least 6 months after last dose of MTX taken in the current trial.;8. Signed and dated written informed consent prior to admission to the study in accordance with GCP and the local legislation

Exclusion criteria

Part 1 (HVs):;1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and judged clinically relevant by the investigator;2. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance;3. Any evidence of a concomitant disease judged clinically relevant by the investigator;4. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders;5. Diseases of the central nervous system (such as epilepsy), other neurological disorders or psychiatric disorders;6. History of relevant orthostatic hypotension, fainting spells, or blackouts;7. History of relevant allergy/hypersensitivity (including allergy to the trial medication or its excipients);8. Intake of drugs with a long half-life (>24 hours) within 30 days or less than 10 half-lives of the respective drug prior to administration of trial medication;9. Within 10 days prior to administration of trial medication, use of drugs that might reasonably influence the results of the trial;10. Participation in another trial with investigational drug administration within 60 days prior to administration of trial medication;11. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes/day);12. Alcohol abuse (consumption of more than 140 g/week in females and 210 g/week in males);13. Drug abuse or positive drug screen;14. Blood donation (more than 100 mL within 30 days prior to administration of trial medication or intended during the trial);15. Intention to commence new exercise regimen within one week prior to administration of trial medication or during the trial;16. Inability to comply with dietary regimen of trial site;17. Chronic or relevant acute infections, including but not limited to HIV, Hepatitis B and C and tuberculosis (including a history of clinical TB and/or a positive QuantiFERON TB-Gold test);18. Subject is assessed by the investigator as unsuitable for inclusion e.g. considered not able to understand and comply with study requirements or has a condition that would not allow safe participation in the study;19. Positive pregnancy test, pregnancy or plans to become pregnant within 30 days after study completion;20. Lactation;Part 2 (RA patients):;Part 1 exclusion criteria 7, 9, 12, 13 and 17-20 plus:;1. Current or previous use of more than two anti-TNF biologic drugs or use of other biologic agent targeting any other approved mechanism (any biologic drug with mechanism of action other than direct anti-TNF blockade (e.g. CTLA4, anti-IL6, or anti CD-20) or new oral compounds targeting any other approved mechanism (e.g. JAK inhibitors) for treating RA;2. Current or previous participation in a clinical trial testing an investigational drug for RA within 3 months prior to screening or within 5 half-lives of the investigational drug, whichever is longer except of previous participation in trials testing NSAIDs, corticosteroids, analgesics or patients documented as receiving placebo in previous RA trials;3. DAS28 <3.2 in at least 2 occasions during the last 6 months before screening Note: DAS28 results during the last 6 months before screening visit will be provided as source documents if available. However, patients with less than 2 DAS28 results available

during this time will not be excluded. ;4. RA patients with severe disability (functional class IV) or with confirmed severe systemic manifestations e.g. known amyloidosis, Felty*s syndrome, lymphoproliferative disorders, rheumatoid vasculitis;5. Treatment with any standard DMARD except MTX (including but not limited to sulfasalazine, leflunomide, hydroxychloroquine, D-penicillamine, azathioprine, cyclosporin, gold salts) continuing after randomisation
Note: If patient is on treatment with any other standard DMARD (except MTX) at the time of the screening visit, this should be tapered and stopped before randomisation. MTX should be continued during the screening period at a stable dose between 15-25mg per week. For patients who do not tolerate the minimum weekly dose of at least 15 mg due to side effects, a stable weekly dose as low as 7.5 mg is also permitted;6. Impaired hepatic function, defined as serum AST/ALT, bilirubin or alkaline phosphatase levels > 2 x ULN ;7. Impaired renal function defined as calculated creatinine clearance < 50ml/min;8. Pre-existing blood dyscrasias e.g. bone marrow hypoplasia, significant anaemia, leucopenia or thrombocytopenia;9. Hypersensitivity to MTX or any of its excipients;10. Previous intolerance to MTX as the main cause for stopping treatment (instead of lack of efficacy);11. Any active or suspected malignancy or history of documented malignancy within the last 5 years before screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-04-2014
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	unknown
Generic name:	unknown

Ethics review

Approved WMO Date:	02-05-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-08-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-09-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	30-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2012-004090-16-NL
ClinicalTrials.gov	NCT01751776
CCMO	NL44641.018.13