An international prospective, double-blind, placebo-controlled phase III RCT in which patients with moderate to severe psoriasis vulgaris are treated with s.c. methotrexate using an optimized treatment schedule.

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Primary objective: to evaluate the efficacy of subcutaneous application of methotrexate in patients with moderate to severe Psoriasis compared to Placebo as assessed by achieving the primary endpoint PASI 75 after a 16 week treatment phase....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Epidermal and dermal conditions
Study type	Interventional

Summary

ID

NL-OMON39795

Source
ToetsingOnline

Brief title
METOP

Condition

- Epidermal and dermal conditions

Synonym
psoriasis, psoriasis vulgaris

Research involving
Human

Sponsors and support

Primary sponsor: Prof. Kristian Reich
Source(s) of monetary or material Support: medac GmbH Hamburg Germany

Intervention

Keyword: international, methotrexate, optimized dosing scheme, Psoriasis

Outcome measures

Primary outcome

Difference in PASI75 responder rate after week 16 between treatment arms

Secondary outcome

• PASI75 after 52 weeks treatment

• PASI50 and 90 after 15 and 52 weeks treatment

• PASI75 after 32 weeks treatment in placebo arm (cross-over)

• NAPSI, BSA, PGA, PsA and questionnaires as , PSAT metex®, DLQI and EQ-5D after 16 and 52 weeks treatment

• Safety and tolerability assessed by AE/SAE, laboratory values and local tolerability at the site of administration

• ONLY FOR GERMAN SITES APPLICABLE: Changes of levels of molecular biologic analysis (UBC and B2M as housekeeping gens; TNF-α, IL-17, IL-4, IFN-gamma) and immunohistochemistry analysis (CD3, CD1a, Ki67) at baseline and after 16 weeks (at 2-3 sites for approx. 30 patients)

Study description

Background summary

For decades Methotrexate has been used to treat psoriasis. Clinical experience in the treatment with MTX is greater than documentation from studies. Until today, despite its common use, no recommendations for a standardized dosing regimen of MTX in psoriasis exists. The current SmPC recommends to start with an initial dose of 7,5mg MTX that is gradually increased.
The data derived from clinical trials that were recently performed indicate that neither the safety nor the efficacy profile benefits from a slow up-titration of MTX. Additionally, MTX is not even a comparatively cheap therapy option but even one of the most conventional therapy options for treatment of moderate to severe psoriasis, SO ?. WHAT DO YOU MEAN WITH THIS LAST SENTENCE.
The present study is initiated to further increase the knowledge about the optimal dosing regimen and to thus optimize the efficacy and safety of MTX treatment for patients with moderate to severe psoriasis.

For more details on the study background please refer to the study protocol section 7.

Study objective

Primary objective: to evaluate the efficacy of subcutaneous application of methotrexate in patients with moderate to severe Psoriasis compared to Placebo as assessed by achieving the primary endpoint PASI 75 after a 16 week treatment phase.

Secondary objectives: safety, tolerabilityand efficacy of the optimized treatment schedule. Up to week 16 analyzed between verum and placebo arm. From week 16 to 52 long term treatment effects analyzed for verum only.

Study design

A prospective, randomized, placebo-controlled, multi-center, international Phase III, double-blind study of an optimized treatment schedule with MTX (12 centers planned: Germany 9, France, the Netherlands and the UK 1 center in each country respectively).

Two study arms:
Arm1: verum -verum
Arm2: placebo-verum (from week 16 onwards patients of arm two will receive verum as well)

--> see section 9 study protocol

Intervention

Verum (MTX) versus placebo for the first 16 weeks of treatment. From week 16 to week 52 all patient will receive verum.

Study burden and risks

Burden/ Risks:
There is a risk for short-term haematological events connected with MTX treatment. This appears to be associated with certain genetic variations (Caliz 2012). In this study we do not assess any genetic markers. To minimize the risk for severe short term haematological issues we perform a blood test 5 days after the first injection of MTX. The second dose will only be administered by the patient if the blood results do not reveal any abnormal values or a clinically relevant unfavourable trend compared to baseline. This safety criterion is exclusively set up for this study following internal discussions with international MTX experts e.g. Alan Menter (Dallas, USA).
Administration of MTX comprises the risk of hepatotoxicity due to the reduced purine synthesis. As combination of folic acid demonstrably reduces this risk, 5mg of folic acid will be administered 24h after each injection.

For a detailed outline of undesirable effects of MTX treatment please refer to the metex® SmPC.
In-/ and Exclusion criteria have been well chosen to exclude any patient for whom known side-effects may become harmful.

Benefit:
Due to data of clinical trials done with MTX in psoriasis as indication it is assumed that by applying the new developed dosing scheme tested in this clincal trial, an accelerated onset of therapy is achieved leading to a faster improvment of patients condition.
Study data may lead to validation of the proposed dosing scheme and thereby giving doctors an optimized tool for treating the applicable patient population.

For any more details please refer to the study 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

1. Are 18 years of age or older at time of informed consent; may be men or women.
2. Are MTX naïve
3. Moderate to severe plaques psoriasis (according rule of ten (PASI >=10 or BSA >= 10 or DLQI >= 10) for at least 6 months with or without psoriatic arthritis (however, highly active psoriatic arthritis is excluded, defined by > 5 swollen tender joints or soles and CRP >2 x UNL) .
4. Women of childbearing potential and all men must be using a highly effective birth control method of contraception (pearl index < 1%) as defined below and must agree to continue to use such measures and not become pregnant or plan a pregnancy until 6 months after receiving the last injection of IMP. Highly effective method is defined as: use of oral, injected or implanted hormonal methods, intrauterine device (IUD) or intrauterine system (IUS), barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicideal foam/gel/film/ suppository.
5. Able to adhere to the study visit schedule and other protocol requirements.
6. Capable of giving informed consent. The informed consent must be obtained prior to any study related procedures.
7. Must avoid prolonged sun exposure and avoid use of tanning booths or other ultraviolet light sources during study.
8. Must agree not to receive a live virus or live bacterial vaccination 4 weeks prior to the first IMP s.c. administration, during the trial and up to 3 months after the last injection.
9. Chest X-ray investigation within the last 6 months prior to first s.c. administration of IMP and show no clinically relevant abnormalities

Exclusion criteria

1. Currently have non-plaque forms of psoriasis (eg, erythrodermic, guttate, or pustular).
2. Have current drug-induced psoriasis (eg, a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, (hydroxy-) chloroquine, or lithium).
3. Are pregnant, nursing, or planning pregnancy (both men and women) while enrolled in the study.
4. Have screening laboratory test results for the following parameters outside the stated ranges (please refer also to :
a. Hemoglobin < 10 g/dL
b. White blood cells < 3.0 x 10E9/L
c. Neutrophils < 1.5 x 10E9/L
d. Platelets < 100 x 10E9/L
e. Creatinine clearance (calculated according to Cockroft-Gault) < 20 mL/min)
f. AST, ALT, and γ-GT levels must be > 2 times the upper limit of normal range
g. Bilirubin > 5mg/dl (85,5 mol/l)
h. Hypalbuminemia <3,5 g/dl
5. Have used any other IMP within the previous 4 weeks or 5 times the half-life of an investigational agent prior to the first s.c. administration of the IMP of this study, whichever is longer.
6. Not able or willing to wash out any prohibited medication as listed below (details given in the protocol). All times with regard to first s.c. administration of the IMP.
- any biologicals: 5 times of half-life
- phototherapie or any systemic medications that could affect the psoriasis: within 4 weeks
- any topical medications that could affect the psoriasis: within 2 weeks
- any systemic immunosuppressants: within 4 weeks
-lithium, antimalarial agents: to be stopped directly prior to first s.c. administration of IMP
- intramuscular gold: within 4 weeks
Patients who take prohibited medications that cannot be washed out within 4 weeks or at least 5 times of the half-life of the investigational agent prior to first s.c. administration of IMP should not be asked to participate in the trial.
7. Have a history of chronic or recurrent infectious disease or had a serious infection or have been hospitalized or received i.v. antibiotics for the treatment of an infection within 2 months prior to screening.
8. History of radiotherapy or planed concomitant radiotherapy.
9. Ulcers of the oral cavity (e.g. ulcerative stomatitis) and/or known gastrointestinal ulcer disease.
10. A known B12/cobalamin deficiency.
11. Known diagnosed ascites or pleural effusions.
12. Have a history of latent or active TB (prior to screening).
13. Have current signs or symptoms of severe, progressive, or uncontrolled renal (specifically with calculated creatinine clearance < 20), hepatic (especially with bilirubin > 5mg/dl (85,5 mol/l), hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease.
14. Have any known malignancy or have a history of malignancy (with the exception of

basal cell carcinoma, squamous cell carcinoma in situ of the skin, or cervical carcinoma in situ that has been treated with no evidence of recurrence, or squamous cell carcinoma of the skin that has been treated with no evidence of recurrence within 5 years prior to the first administration of study agent).
15. Have shown a previous immediate hypersensitivity response, including anaphylaxis, to the folic acid
16. Are unable or unwilling to undergo multiple venipunctures because of poor tolerability or lack of easy access to veins.
17. Are known to have had a substance abuse (drug or alcohol) problem within the previous 12 months.
18. Staff or relatives/partner of any clinical research site

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):	22-02-2013
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	metex
Generic name:	methotrexate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	19-11-2012
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-07-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2012-002716-10-NL
CCMO	NL41745.091.12