A Multicentre, Interventional Treatment, Randomised, Double-Blind, Single Group Assignment, Placebo Controlled Study to Evaluate the Efficacy and Safety of Two Different Doses of Nefecon® in Primary IgA Nephropathy Patients at Risk of Developing End-Stage Renal Disease

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Objectives:The objective of the trial is to evaluate efficacy and safety of two different doses of Nefecon® in the treatment of patients with primary IgA nephropathy (IgAN) at risk of developing end-stage renal disease, under rigorous blood pressure...

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

Summary

ID

NL-OMON39659

Source
ToetsingOnline

Brief title
The NEFIGAN Trial

Condition

- Nephropathies

Synonym
Berger's disease, IgA Nephropathy

Research involving
Human

Sponsors and support

Primary sponsor: Pharmalink AB
Source(s) of monetary or material Support: pharmaceutical company (Sweden)

Intervention

Keyword: budenoside, IgA, Nephropathy, Renal disease

Outcome measures

Primary outcome

Primary Efficacy Endpoint(s)

The primary endpoint is the mean reduction in UPCR at 9 months compared to baseline UPCR values. The mean reduction will be measured as ratio of UPCR at 9 months compared to baseline.

Secondary outcome

Secondary Efficacy Endpoint(s)

- remission defined as Complete Remission (<0.3g/g UPCR), Partial Remission (>=0.3g/g to <1.0g/g + 50% reduction in UPCR from baseline), Treatment Failure (>=1.0g/g OR <50% reduction in UPCR from baseline) at Month 9
- percentage change in urine albumin creatinine ratio (UACR) and urine albumin from baseline at Month 9
- achieving reduction by >=50% in UPCR at Month 9 compared to baseline
- percentage change in serum creatinine, chronic kidney disease epidemiology collaboration equation (CKD-EPI) estimated glomerular filtration rate (eGFR), modification of diet in renal disease study equation (MDRD) eGFR and creatinine clearance from baseline at 9 months

Tertiary Efficacy Endpoint(s)

- achieving defined reductions (>=30%, >=35%, >=40%, >=45%, >=50%, >=55%, >=60%) of

UPCR, UACR and urine albumin at Month 9 compared to baseline

- achieving defined reductions (>=30%, >=35%, >=40%, >=45%, >=50%, >=55%, >=60%) of

UPCR, UACR and urine albumin from baseline at Months 1, 3, 5, 7, 10.5 and 12

- percentage change in UPCR, UACR and urine albumin from baseline at 1, 3, 5,

7, 10.5 and 12 months

- percentage change in serum creatinine, CKD-EPI eGFR, MDRD eGFR and creatinine

clearance from baseline at 1, 3, 5, 7, 10.5, and 12 months

- percentage change in Cystatin C-based eGFR from baseline at Months 9 and 12

- microhematuria at Months 9 and 12

Exploratory Efficacy Endpoint(s)

The exploratory analyses listed below are planned but may not be conducted if

deemed to be obsolete during later stages of the trial; other exploratory

analyses may be added.

- Percentage change from baseline at 9 and 12 months on exploratory

markers/biomarkers

- Urine and serum total IgA1/2, secretory IgA, IgA */**ratios, IgA1

monomer/polymer ratio, IgA1 O-glycosylation, IgA-CD89 immune complex levels

- Urine IL-6/EGF ratio, NAG, NGAL, KIM-1, RBP levels

- Serum or plasma IgA anti-gliadin, IgA anti-ovalbumin, IgA anti-BSA, AOPP,

MAdCAM-1, NGAL, hsCRP, PDGF-BB, PDGF-DD, mannose binding lectin levels,

25-hydroxycholesterol levels and non-standard complement assays

Study description

Background summary

Doctors have discovered that, in many cases, patients with IgA nephropathy very slowly progress to kidney failure, often referred to as end-stage renal disease. At end-stage renal disease the damage to the kidney is permanent, with patients requiring dialysis or kidney transplantation. It has been estimated that about 20 to 40% of all patients with IgA nephropathy develop kidney failure within 5 to 30 years following diagnosis. It is difficult to predict which patients are likely to progress to kidney failure. Research, however, has shown that patients with persistently high levels of protein in their urine (often referred to as proteinuria) are at greater risk of progressing to kidney failure. In addition, patients with high blood pressure are also at greater risk.

In IgA nephropathy patients, the kidneys become inflamed and damaged by IgA that gets trapped in the kidneys. IgA stands for immunoglobulin A, which is type of antibody that normally helps your body fight off infections. Much of the IgA that gets trapped in the kidney in IgA nephropathy patients comes from cells originating from the lining of the gut (intestine). Instead of being secreted into the gut lumen to protect this part of the body, some of the IgA in IgA nephropathy patients ends up in the bloodstream, eventually getting deposited in the kidney. Slowly and over a long period of time, due to this deposition the kidney becomes damaged and starts to leak protein and sometimes blood into the urine. The drug being studied is specifically designed to reduce the production of IgA in the gut in order to reduce the amount of IgA getting into the blood and that then gets trapped in the kidney.

There are many kidney diseases that cannot be cured with the medications available today. Treatment often focuses on slowing or stopping the disease progression and on preventing complications which can promote disease progression. One such complication is high blood pressure. For patients with IgA nephropathy, the usual medical treatment is giving drugs that control blood pressure and which at the same time reduce the amount of protein in the urine. There are two types of blood pressure medications that have been shown to be effective in this. These two types are angiotensin-converting-enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Even with these treatments some patients still have high levels of protein in their urine and remain at risk of progressing to kidney failure. For these patients, doctors may

recommend a 3 to 6-month course of treatment with high doses of systemic steroids. Steroids are medicines used for a variety of illnesses that involve inflammation in the body and *systemic* means that the medication affects all parts of your body. This form of steroid treatment may help to reduce urine protein levels and preserve kidney function. However, as these drugs also enter the bloodstream and are given at such high doses they can affect the entire body. Long-term use of such systemic steroids may be associated with several side effects (some of them potentially serious) which your doctor can explain for you.

Study objective

Objectives:
The objective of the trial is to evaluate efficacy and safety of two different doses of Nefecon® in the treatment of patients with primary IgA nephropathy (IgAN) at risk of developing end-stage renal disease, under rigorous blood pressure control with an angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin 2 receptor blocker (ARB).

Primary Efficacy Objective:
To investigate whether patients on Nefecon® achieve a larger mean reduction in urine protein creatinine ratio (UPCR) compared to patients on placebo during a 9 months trial.

Secondary Efficacy Objective:
To evaluate if other urine protein response criteria and other laboratory parameters used to estimate glomerular filtration rate (GFR) are in favour of Nefecon® compared with placebo at 9 months.
Tertiary Objective:
To evaluate if other response criteria and time-points are in favour of Nefecon® compared with placebo.

Safety Objective:
To evaluate safety in terms of adverse events, changes in vital signs and laboratory tests during the trial.

Evaluation of the safety of Nefecon® will be based upon the assessment of adverse events, including glucocorticoid-related side-effects, and clinically important changes in laboratory parameters (incl. HbA1c). Changes in urine cortisol levels on 24 hour urine collections will be evaluated to assess the extent of adrenal suppression in response to Nefecon®. Particular attention will be given to those events which result in discontinuation of study medication or which are serious in nature.

Study design

Trial Design:
A Multicentre, Interventional Treatment, Randomised, Double-Blind, Single Group Assignment, Placebo Controlled Study to Evaluate the Efficacy and Safety of Two Different Doses of Nefecon® in Primary IgA Nephropathy at Risk of Developing End-Stage Renal Disease

Nefecon® is an add-on treatment to other medications for nephropathy symptoms and kidney function, including ACEI and/or ARBs. Rigorous blood pressure control will be achieved over a 6-month Run-in Phase in which ACEI and/or ARB will be dosed to target a blood pressure of <130/80 mm Hg and urine protein creatinine ratio < 0.5 g/g (56.5 mg/mmol). Patients who complete the Run-in Phase and fulfil all of the inclusion and none of the exclusion criteria will be eligible for randomisation and entering the treatment phase of the trial. Patients will remain on their ARB and/or ACEI dosing regimen for the duration of the trial.

Patients entering the treatment phase will be administered Nefecon® (8 mg/day OR 16 mg/day) OR placebo for a phase of 9 months. A 3-month follow-up phase will follow on from the treatment phase, of which the first 2 weeks will be used to taper the dose of those patients that received 16 mg/day dosing to 8 mg/day, with the placebo and 8 mg/day groups receiving placebo to retain blinding.

Run-in Directives
Patients eligible after screening will enter a 6 month Run-in Phase in which anti-hypertensive therapy is to be provided to reduce blood pressure and proteinuria to target levels. Antihypertensive therapy is to follow current clinical guidelines.
ACEI and/or ARBs are to be used as a first-line therapy with a target to reduce
- blood pressure to <130/80 mm Hg
- UPCR to <0.5 g/g
ACEI and/or ARBs are strongly recommended to be increased to the maximum tolerated dose but are not permitted to exceed the maximum recommended daily dose. Combination ACEI and ARB therapy to achieve the blood pressure and UPCR targets may be used at the discretion of the Investigator.
Investigators are strongly advised to introduce changes to ACEI and/or ARB therapy early on in the Run-in Phase rather than towards the conclusion of this period. Antihypertensive medications other than ACEI and ARBs, including diuretics, aldosterone antagonists, calcium-channel blockers and ß-blockers can be used at any time-point during Run-in Phase at the discretion of the Investigator, but with a recommendation for any change to be made early in the Run-in Phase.
A similar approach is advised for introductions or changes to medications or lifestyle that could influence endpoint variables, with an early rather than late introduction. These include non-steroidal anti-inflammatory drugs (NSAIDs), statins, certain antibiotics, over-the-counter medications,

complementary medicines, fish-oils, dietary habits including salt intake, fluid intake, smoking habits and exercise. Prohibited medications include systemic immunosuppressive or systemic corticosteroid drugs (excluding topical or nasal steroids) and inhaled corticosteroids.

Run-In Phase Visit Schedule
- Patients entering the Run-in phase NOT on a maximum recommended dose (or maximum tolerated dose) of an ACEI and/or ARB
A minimum of 3 Run-in visits over the 6 month Run-in Phase are to be conducted, with a further 3 optional visits depending on extent of changes that are required for the patient. Of the 3 mandatory visits, 2 are to be conducted in the first 3 months after screening, while the third mandatory visit is to be made within the final 3 months of the Run-in Phase.
- Patients entering the Run-in phase already on a maximum recommended dose (or maximum tolerated dose) of an ACEI and/or ARB
A minimum of 2 Run-in visits over the 6 month Run-in phase are to be conducted, with a further 4 optional visits. Of the 2 mandatory visits, 1 is to be conducted in the first 3 months after screening, while the second mandatory visit is to be within the final 3 months of the Run-in phase.

Treatment and Follow-up Phase Directives
Changes in doses of ACEIs, ARBs and/or antialdosteronic agents (eg. Spironolactone, Eplerenone) should be avoided during the treatment and follow-up phases of the trial, and introductions and changes in other anti-hypertensive therapy should be avoided during the treatment and follow-up phases, unless deemed necessary by the Investigator. In the case of ACEI specific side-effects, ARBs should be used to retain blood pressure control. In the case of hypotension, withdrawal of non-ACEI/non-ARB medications should be considered before these drug classes to achieve the target blood pressure of 130/80 mm Hg.
In addition, patients should avoid introductions and changes to other medications and lifestyle choices that could influence end-point variables. These include NSAIDs, statins, certain antibiotics, over-the-counter medications, complementary medicines, fish-oils, dietary habits including salt intake, fluid intake, smoking habits and exercise. Introductions and changes are permitted at the discretion of the Investigator. Prohibited medications include systemic immunosuppressive or systemic corticosteroid drugs (excluding topical or nasal steroids), inhaled corticosteroids and inhibitors of CYP3A (e.g. ketoconazole). Patients should be instructed to avoid grapefruit and grapefruit juice.

Intervention

not applicable

Study burden and risks

not applicable

Contacts

Public
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Stockholm SE-114 26,
SE
Scientific
Pharmalink AB

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Screening Inclusion Criteria: ;1. Female or male patients >=18 years;2. Biopsy-verified IgA nephropathy;3. Urine protein creatinine ratio >=0.5 g/g (56.5 mg/mmol) OR urine protein >=0.75 g/24 h;4. Estimated GFR (using the CKD-EPI formula) OR measured GFR >=50 mL/min per 1.73 m2 OR >=45 mL/min per 1.73 m2 for patients on a maximum recommended or maximum tolerated dose of an ACEI and/or ARB;5. Willing to change antihypertensive medication regimen if applicable;6. Willing and able to give informed consent;Randomisation Inclusion Criteria:;1. Completion of the Run-in Phase;2. Urine protein creatinine ratio >=0.5 g/g (56.5 mg/mmol) OR urine protein >=0.75 g/24 h;3. Estimated GFR (using CKD-EPI formula) OR measured GFR >=45 mL/min per 1.73 m2

Exclusion criteria

Screening Exclusion Criteria: ;1. Secondary forms of IgA nephropathy as defined by the treating physician (for example, Henoch-Schönlein purpura patients and those with associated alcoholic cirrhosis);2. Presence of crescent formation in >=50% of glomeruli assessed on renal biopsy;3. Kidney transplanted patients;4. Severe gastrointestinal disorders (including peptic ulcer disease and inflammatory bowel disease) which may impair drug effect, or other conditions which could modify the effect of the trial drug as judged by the Investigator;5. Consumption of an investigational drug within 30 days prior to enrolment;6. Hyperlipidaemia defined as unacceptable levels of lipids according to the discretion of the Investigator;7. Morbid obesity defined as a body mass index (BMI) >45 kg/m2;8. Patients currently treated with systemic immunosuppressive or systemic corticosteroid drugs (excluding topical or nasal steroids) or have been previously treated for more than one week within the last 24 months.;9. Patients currently treated chronically (daily dosing) with inhaled corticosteroid drugs or have previously been treated chronically for more than one month within the last 12 months;10. For the treatment of IgA nephropathy, patients treated within the last 24 months with either immunosuppressive agents or systemic corticosteroid drugs ;11. Patients unable to take oral medication or intolerant to budesonide or other corticosteroid preparations;12. Patients with known allergy or intolerance to ACEI and ARB or to any component of the trial drug formulation;13. Patients with acute or chronic infectious disease incl. hepatitis, HIV positive patients and patients with chronic urinary tract infections;14. Severe liver disease according to the discretion of the Investigator;15. Patients with Type 1 or 2 diabetes;16. Patients with uncontrolled cardiovascular disease as judged by the Investigator;17. Patients with current malignancy or history of malignancy during the last three years;18. History or presence of psychological or psychiatric illness (including steroid induced psychosis) which may interfere with the patient*s ability to adhere to the protocol;19. Patients with untreated osteoporosis;20. Patients with glaucoma or cataract;21. Alcohol or drug abuse (present);22. Patients unwilling to meet the requirements of the protocol;23. Other medical or social reasons for exclusion at the discretion of the Investigator;24. Life expectancy < 1 year;25. For women only; pregnant or breast feeding or unwilling to use adequate contraception during the trial (only women of child bearing potential);Randomisation Exclusion Criteria:;1. Unacceptable blood pressure defined as a systolic value >160 mm Hg or diastolic >100 mm Hg;2. eGFR (CKD-EPI method of estimation) loss >30% over the entire duration of the Run-in Phase ;3. Consumption of an investigational drug after screening;4. Medical or social reasons for exclusion at the discretion of the Investigator;5. For women only; pregnant or breast feeding or unwilling to use adequate contraception during the trial (only women of child bearing potential) ;6. For men only; unwilling to use adequate contraception during the treatment and follow-up phase of the trial

Study design

Design

Study phase:	2
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):	17-07-2013
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nefecon
Generic name:	budesonide

Ethics review

Approved WMO Date:	19-10-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-12-2012
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-06-2013
Application type:	Amendment

Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-09-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-09-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-04-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-05-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	09-01-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-01-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-03-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2012-001923-11-NL
CCMO	NL41690.058.12