2. SYNOPSIS

Name of Sponsor/Company: Pharmalink AB **Name of Finished Product:** Nefecon™ **Name of Active Ingredient:** Budesonide	**Individual Study Table Referring to Part of the Dossier** Volume: Page:	*(For National Authority Use Only)*

Title of Study: 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.

The NEFIGAN Trial.

Investigators: Prof Bengt Fellström (Coordinating Investigator).

Study Centres: 61 study sites across 10 European countries (Belgium, Czech Republic, Denmark, Finland, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom).

Publications: None at the time of report.

Studied period (years):	**Phase of Development:**
First patient first visit: 11 December 2012 Last patient last visit: 25 June 2015	Phase IIb

Objectives:

Primary Efficacy Objective: To investigate whether patients on Nefecon™ (budesonide; hereinafter referred to as NEFECON) achieved a larger mean reduction in urine protein creatinine ratio (UPCR) compared to patients who received placebo during the 9 months trial.

Due to greater eligibility after the run-in phase than anticipated, it was decided to perform an interim analysis after 90 patients had completed the 9-month treatment phase to evaluate the primary objective while the total sample size was increased from 90 patients to 150 patients.

Secondary Efficacy Objectives: To evaluate if other urine protein response criteria and other laboratory parameters used to estimate glomerular filtration rate (GFR) were in favour of NEFECON compared with placebo at 9 months.

Tertiary Objectives: To evaluate if other response criteria and time-points were in favour of NEFECON compared with placebo.

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

Methodology: This was a multicentre, interventional treatment, randomised, double-blind, single group assignment, placebo-controlled study with an interim analysis performed for the primary endpoint after 90 patients completed the treatment phase. Upon fulfilment of the screening inclusion criteria, patients underwent a 6-month run-in phase, during which treatment with angiotensin converting enzyme inhibitors (ACEIs) and/or angiotensin II type I receptor blockers (ARBs) was optimised to a maximum tolerated dose to target blood pressure to <130/80 mm Hg. Patients who completed the run-in and fulfilled the randomisation criteria were randomised to receive: NEFECON 8 mg/day, NEFECON 16 mg/day or placebo. Treatment was administered orally as 4 capsules (NEFECON or placebo) taken once daily for 9 months. Patients continued

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to take ACEI and/or ARB therapy throughout the treatment phase.

Number of patients (planned and analysed): Approximately 200 patients were planned to be included in the run-in phase

In total, 207 patients were enrolled into the 6-month run-in phase and 153 patients were randomised into the treatment phase (51 in each treatment group). Of these, 150 patients were treated and 120 patients completed the treatment and follow-up phases as planned. An interim analysis was conducted after 90 patients completed the 9-month treatment phase.

Diagnosis and main criteria for inclusion: Screening inclusion criteria included female or male patients, 18 years of age or older, with biopsy-verified immunoglobulin A nephropathy (IgAN). Patients had to have a UPCR ratio ≥0.5 g/g (56.5 mg/mmol) or urine protein ≥0.75 g/24 hours; and a GFR ≥50 mL/min per 1.73 m^2 or ≥45 mL/min per 1.73 m^2 for patients on a maximum recommended or maximum tolerated dose of an ACEI and/or ARB. Patients were excluded from screening if there was a presence of other nephropathy or gastrointestinal disorder, or were receiving treatment with other forms of corticosteroids.

Randomisation inclusion criteria included completion of the run-in phase, with maintenance of UPCR or urine protein at the levels specified above, and a GFR ≥45 mL/min per 1.73 m^2.

Test product, dose and mode of administration: Four capsules (4 NEFECON [NEFECON 16 mg/day] or 2 placebo + 2 NEFECON [NEFECON 8 mg/day] or 4 placebo) each day for the duration of the 9 month treatment phase of the trial.

Criteria for evaluation:

Efficacy: Urine samples were taken to determine the amount of protein, albumin and creatinine in the urine throughout the treatment and follow-up phases. The quotients protein/creatinine and albumin/creatinine were determined. Creatinine clearance was calculated using standard equations. Twenty-four hour albuminuria was calculated. A spot urine sample was used to determine presence or absence of microhaematuria. Blood samples for serum creatinine and cystatin C assessments were taken throughout the treatment and follow-up phases.

Safety: Reporting of AEs, changes in vital signs and laboratory evaluations including haematology and clinical chemistry assessed safety.

Statistical methods:

The primary comparison was to investigate differences in mean reduction of UPCR between NEFECON (16+8 mg/day) versus placebo in 90 patients (who had completed the 9-month treatment phase). If the primary comparison was statistically significant (at the 1.58% one-sided level at the interim analysis [$p<0.0158$] and 1.52% one-sided level at the final analysis [$p<0.0152$]), the following comparisons were (in order) NEFECON 16 mg/day versus placebo; NEFECON 8 mg/day versus placebo; and NEFECON 16 mg/day versus NEFECON 8 mg/day. With the addition of an interim analysis, the type I error of 2.5% one-sided was protected by performing a hierarchical structure of analysis with closed tests of

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hypotheses.

Efficacy: The primary analysis of the change from baseline in log UPCR was performed on the first 90 patients to complete the 9-month treatment phase and was analysed using a mixed model repeated measures (MMRM) analysis. Baseline log UPCR was included as covariate. The model included treatment group, baseline value, stratification variable (UPCR ≤0.9 g/g and >0.9 g/g), region, visit and visit*treatment group interaction. Secondary and tertiary endpoints were evaluated after all patients had completed the trial and were analysed using analysis of covariance on the log scale and an MMRM analysis. A subgroup analysis was performed on the primary endpoint on the final data. Prior use of steroid treatment was of main interest and subgroups were defined as follows: prior use of immunosuppressive agents or corticosteroid drugs for the treatment of IgAN or not.

Safety: AEs were coded by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA). Chemistry, haematology and urinalysis results were summarised as absolute values and changes from baseline for each visit for continuous variables, and n and percentage for categorical variables. Vital signs were summarised by treatment group.

Results summary:

Demographics: Demographics and baseline characteristics were similar across treatment groups. All patients had a medical history of IgAN. All patients were receiving the maximum recommended or maximum tolerated dose of ACEIs and/or ARBs upon entry into the treatment phase.

Efficacy:

Interim Analysis (after 90 patients had completed the 9-month treatment phase):

Geometric LSmean UPCR was reduced by approximately 24% from baseline (LSmean: 0.756) for NEFECON (16 + 8 mg/day combined) at 9 months based on the estimated back transformed LSmean from the model. Mean UPCR increased by approximately 3% (LSmean: 1.027) in the placebo group. The difference between NEFECON- and placebo-treated patients was statistically significant (p=0.0066).

The primary endpoint was therefore met at the time of the interim analysis and the following comparisons were also made: NEFECON 16 mg/day versus placebo, NEFECON 8 mg/day versus placebo and NEFECON 16 mg/day versus 8 mg/day.

Final Analysis (after all patients had completed the trial):

Of the secondary endpoints, reductions in the relative change from baseline at 9 months in total urine protein/24 hours, UACR, total urine albumin/24 hours, serum creatinine were statistically significantly greater following treatment with NEFECON compared with placebo. Estimated GFR (eGFR) remained stable in the NEFECON treatment groups and declined in placebo-treated patients.

Reduction in the relative change from baseline at 6 months in UPCR was statistically significantly greater following treatment with NEFECON than placebo. Reductions in the relative change from baseline at follow-up visits in UPCR, total urine protein/24 hours, UACR and total urine albumin/24 hours were also statistically significantly greater following treatment with NEFECON compared with placebo. Estimated GFR remained stable in the NEFECON treatment groups and continued to decline in placebo-treated patients. In

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addition, a statistically significant proportion of patients achieved a 40% reduction in UACR at 9 months. The percentage of patients with microhaematuria at 9 months was lower in the NEFECON treatment groups than in the placebo group and similar at 12 months.

Safety:

In total, 133 (88.7%) patients had (unsolicited) TEAEs. There was no dose relationship for the frequencies of patients with at least 1 TEAE. Most TEAEs were mild with only 9 patients with severe TEAEs.

There were no deaths. There were 11 patients with 13 treatment-emergent SAEs: 7 (14.3%) patients in the NEFECON 16 mg/day group, 1 (2.0%) patient in the NEFECON 8 mg/day group, and 3 (6.0%) patients in the placebo group. There was no clear dose relationship in the number of SAEs. Only 4 of the SAEs were considered at least possibly related to treatment by the Investigator; the other SAEs were all considered unlikely to be related.

More patients were withdrawn from the study due to a TEAE in the NEFECON 16 mg/day group (11 [22.4%] patients) than in the NEFECON 8 mg/day group (5 [9.8%]) or in the placebo group (2 [4.0%] patients).

A higher incidence of glucocorticosteroid-related AEs (solicited at each visit [from screening until the end of the study] using a standardised questionnaire) was reported in the NEFECON groups (18 patients in each NEFECON group) than in the placebo group (6 patients) during the treatment phase. The incidence was similar between all treatment groups during the follow-up phase. The frequency of insomnia, moon face, hirsutism, and buffalo hump reported by the patients during the treatment phase was dose-dependent. These effects were reversible.

There was no dose-related trend in the incidence of gastrointestinal events (solicited at each visit (from screening until the end of the study) using a standardised questionnaire); variability between the groups was already reported during the run-in phase.

There were no clinically relevant differences in clinical chemistry, haematology and urinalysis laboratory assessments or in abnormal physical examination findings between the treatment groups. There were no clinically relevant drug-related effects on blood pressure or heart rate and no relevant weight gain for any patients.

Conclusions:

The trial met its primary objective at the planned interim analysis, demonstrating a statistically significant difference in the reduction in UPCR from baseline at 9 months between patients treated with NEFECON and placebo. Analyses in all patients at 9 months showed changes in the 24-hour protein excretion, UACR, and 24-hour albumin excretion were consistent with the primary endpoint results. Data from the 3-month follow-up period demonstrated a persistent treatment effect following withdrawal of the study drug.

Glucocorticosteroid-related AEs were generally more common for NEFECON of which some were dose-related. Discontinuations due to AEs were more common for NEFECON than for placebo and clearly dose-related. There were no relevant differences in clinical laboratory assessments or vital signs between the treatment groups.

This study demonstrated the effect of NEFECON in reducing proteinuria and preventing decline in eGFR

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CKD-EPI (serum creatinine) when compared to placebo with an acceptable safety profile. Date of the Report: 23 May 2016		