1 STUDY SYNOPSIS

Name of Sponsor/Company: Nordic Pharma France	Individual Study Table Referring to Part of the Dossier For Regulatory use only	(For National Authority Use only) For Regulatory use only
Name of Finished Product: Spanidin	Volume: Not applicable	
Name of Active Ingredient: Gusperimus	Page: Not applicable	
Title of study: Randomised, Evaluator-Blinded, Multicentre, International, Parallel-Group, Active-Controlled Clinical Trial of Gusperimus versus Conventional Therapy in Relapse of Granulomatosis with Polyangiitis (Wegener's Granulomatosis).		
Study code: NO005 – NK103 **EudraCT number: 2011-001219-30** **IND No: 106879**		
Coordinating Investigator: : Dr. David Jayne, Consultant in Nephrology and Vasculitis, Addenbrookes Hospital, Cambridge CB2 2QQ, UK **Investigators:** See appendix 16.1.4		
Study centre/s: Multicentre Study – approximately 40 clinical centres within the European Union, Russia and the USA were planned to recruit a total of 216 patients. Ultimately only 4 patients were recruited: 2 in Spain and 2 Czech Republic		
Studied period: Date of first enrolment: December 2011 Date of last planned completed patient : Q2 2014 Enrolment discontinuation: April 2012	**Phase of development:** III	
Objectives: Primary Variables: The aim of the study is to assess the efficacy (superiority testing) of gusperimus compared to conventional treatment in patients with a relapse of WG with or without ongoing Glucocorticoids (GC) and/or immunosuppressive therapy (AZA/MMF/MTX or LEF) Secondary Variables: To evaluate the safety and quality of life of gusperimus treatment compared to standard treatment in patients with relapse of WG receiving GC		
Study design and methodology: Randomised, evaluator-blinded, multicentre, international, parallel-group, active-controlled, phase III superiority trial. The aim of the study is to assess the efficacy (superiority testing) and safety of gusperimus compared to conventional treatment in patients with a relapse of WG, with or without ongoing glucocorticoids (GC), and/or immunosuppressive therapy (AZA, MMF, MTX orLEF).		

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The total study duration was estimated to be 25 months:

- a maximum estimated recruitment period of 12 months
- a 12-month treatment period,
- a 4-week follow-up period

Patients of both severity subgroups (severe and non-severe) were randomly assigned (1:1 ratio) either to the test group using gusperimus or to the control group.

The test group: both severity subgroups were treated with gusperimus + GC.

The control group:
Severe subgroup; were planned to receive intravenous CYC pulses for at least 13 weeks and 22 weeks at maximum, followed by MTX + GC after achieving a response with BVAS ≤ 2. Patients intolerant to MTX and patients with impaired renal function (eGFR $\leq$ 60 mL/min/1.73 m2) will receive AZA + GC.

Non-severe subgroup: receive MTX + GC (or AZA + GC for those previously intolerant to MTX or with impaired renal function, i.e. eGFR $\leq$ 60 mL/min/1.73 m2).

The expected proportion of treatments given to the control group was 70% MTX and 30% AZA (10% MTX-intolerant patients, 20% of patients with eGFR $\leq$ 60 mL/min/1.73 m2). Proportions will be similar in both severity subgroups

BVAS was assessed by a blinded evaluator at each of the clinical centres. Evaluators were trained centrally, using a training manual and assessing training cases. Patients were required to attend an initial screening visit, followed by scheduled visits for efficacy and safety assessments.

After 16 weeks of treatment, the GC dose was reduced stepwise to 5mg/day in accordance with the protocol. This dose should have been maintained until the end of the study.

Patients who could not achieve a reduction in disease activity corresponding to BVAS ≤ 2 after 24 weeks from trial entry, who experienced a new severe relapse at any stage during the trial, or who failed to adhere to the GC reduction regimen, was regarded as a treatment failure.

After Week 52 (Day 28 Cycle 13) gusperimus responders were supposed to continue with the drug administration (expanded access programme for which a separate protocol was planned to be designed) or change to an alternative maintenance therapy at their physician's discretion.

The study end was supposed to be at week 56 (a follow-up visit) - four weeks after the last administration of the study medication in patients who finish the study.

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All patients leaving the trial before Week 52 were followed-up four weeks after the last administration of the study medication and at Week 56.

Control group patients who failled to meet the primary endpoint at Week 24 and/or who experienced a severe adverse event related to CYC, MTX or AZA at any time were regarded as a treatment failure. They were allowed to switch to gusperimus, if available at that time.

Screening:
V0 –Screening (Day -14 – Day -1)
Patients signed the Informed Consent form and the following information were collected: vital signs, physical examination, current medication, Inclusion and Exclusion criteria, serum chemistry parameters (CRP, urea/BUN, creatinine/eGFR, ALT, AST, bilirubin, ALP, Na, K, Ca, glycaemia), haematology (RBC, platelets, HB, HCT, WBC with differential, ESR), urinalysis (protein, blood, glucose, ketones, leukocytes, nitrites, pH, specific gravity), Hepatitis B, C and HIV-test, pregnancy test (if applicable), determination of BVAS.

V1 - Baseline (Week 1, Day 1)
Demographic data, history of WG including previous treatments with immunosuppressants, physical examination, vital signs, weight and height, confirmation of Inclusion and Exclusion criteria, determination of BVAS and Vasculitis Damage Index (VDI), SF-36 questionnaire, EQ5D questionnaire, serum chemistry parameters (CRP, urea (BUN), creatinine/eGFR, ALT, AST, bilirubin, ALP, Na, K, Ca, glycaemia), haematology (RBC, platelets, HB, HCT, WBC with differential, ESR), the central assessment of ANCA, ANA anti-GBM Ab and complement, IgG, urinalysis (protein, blood, glucose, ketones, leukocytes, nitrites, pH, specific gravity), ECG and a chest X–ray. BVAS assessment, serum chemistry parameters, haematology and urinalysis do not have to be repeated if the screening assessments have been performed in $\leq$ 2 days before V1. Randomisation, AE assessment, concomitant medications, dispensing of study medication, training on the preparation and administration of study medication by the patient and/or by a third person (for patients in the gusperimus group).

V2, V3, V4, V5, V6, V8, V9 (Weeks 4, 8, 12, 16, 20, 32, 40 Day 6 or 7)
Physical examination, vital signs, weight, BVAS, serum chemistry parameters (CRP, urea (BUN), creatinine/eGFR, ALT, AST, bilirubin, ALP, Na, K, Ca, glycaemia), haematology (RBC, platelets, HB, HCT, WBC with differential, ESR), urinalysis (protein, blood, glucose, ketones, leukocytes, nitrites, pH, specific gravity), AE assessment, report of concomitant medications, drug accountability, dispensing of study medication.

V7, V10, Vx (Week 24 Day 6 or 7; Week 53, Day 1-3; Day of relapse visit/early termination)
BVAS and VDI, SF-36 questionnaire, EQ5D questionnaire, pregnancy test (if applicable), physical examination, vital signs, weight, serum chemistry parameters (CRP, urea (BUN), creatinine/eGFR,

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ALT, AST, bilirubin, ALP, Na, K, Ca, glycaemia), haematology (RBC, platelets, HB, HCT, WBC with differential, ESR), the central assessment of ANCA and Complement, IgG, urinalysis (protein, blood, glucose, ketones, leukocytes, nitrites, pH, specific gravity), ECG, AE assessment, report of concomitant medications, drug accountability, dispensing of study medication (V7 only)

Vfu – Follow-up (4 weeks after the last trial medication, Week 56*)*
BVAS and VDI, EQ5D questionnaire, SF-36 questionnaire, serum chemistry parameters (CRP, urea (BUN), creatinine/eGFR, ALT, AST, bilirubin, ALP, Na, K, Ca, glycaemia), haematology (RBC, platelets, HB, HCT, WBC with differential, ESR), urinalysis (protein, blood, glucose, ketones, leukocytes, nitrites, pH, specific gravity), AE assessment, report of concomitant medications..

Number of subjects (planned and analysed):
Planned 216 subjects, estimated drop-out rate: 10% = 194 evaluable subjects.
At date of premature termination 4 patient had been included.
Nordic Pharma faced difficulties enrolling patients due to the availability of rituximab which is only registered in the US for the treatment of Wegener's Granulomatosis and off label used in this indication in some European countries.
In April 2012, Nordic Pharma took the decision to put the SPARROW study on hold and started working on an amendment to the current protocol based on discussions with the EMA.
The inclusion of patients was discontinued on 17 April 2012; it was decided that the patients already enrolled would continue their treatment as per the study protocol. Three patients were withdrawn from the Sparrow study, of which one due to treatment failure and 2 because of adverse events (patient's decision). The remaining patient in the test group continued his treatment as per the study protocol on a named-patient basis under the prescriber's responsibility. This patient subsequently died of respiratory failure in the
context of nosocomial infection by multiresistant Pseudomonas and underlying interstitial lung disease and emphysema. All clinical sites, regulatory authorities and ethic committees were notified of these discontinuations.

Diagnosis and main **criteria for inclusion:**

Inclusion Criteria were

1. Documented diagnosis of WG according to the ACR classification criteria.
2. Diagnosis of WG at least 6 months before entry and initial induction therapy with a combination of GC and an immunosuppressive (CYC or MTX) or rituximab.
3. Relapse of WG with or without ongoing GC, and/or immunosuppressive therapy with AZA/MMF/MTX or LEF. The minimum disease activity is defined by the presence of one new/worse major or three new/worse minor BVAS (version 3) items.

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4. Patients between 18 – 75 years.
5. Medically acceptable and reliable contraception method during the study course. (Women should not become pregnant for at least 6 months after CYC treatment).
6. Written informed consent for study participation given by the patient.
7. Patients able and prepared to self-administer the study medication or having a relative/third person able to do it.
8. Ability to read, understand and record information required by protocol.

Exclusion Criteria were:

1. Other multi-system autoimmune disorders, including systemic lupus erythematosus and anti-GBM disease.
2. Systemic vasculitis due to a viral infection.
3. CYC therapy intolerance, hypersensitivity or contraindication to CYC (active substance or any of the excipients) in patients with severe relapse of WG.
4. Hypersensitivity or contraindication to
   - Spanidin (active substance or any of the excipients) orboth MTX (active substance or any of the excipients) and AZA (active substance or any of the excipients) ormethylprednisolone, prednisolone or other corticosteroids (active substance or any of the excipients).
5. Underlying medical conditions, which in the opinion of the Investigator place the patient at an unacceptable risk level for participating in a study.
6. Previous randomisation in this study.
7. CYC, intravenous immunoglobulin, anti-cytokine biologic therapies, plasma exchange or Abatacept in the three months prior to entry to the trial. Rituximab, Alemtuzumab or stem cell transplantation is not permitted in the six months prior to entry to the trial.
8. Previous treatment with gusperimus.
9. Participation in another clinical trial with investigational drugs within the last 3 months before screening or during the present trial period.
10. Pregnant or breast-feeding females.
11. Active bacterial/viral infection (HIV, Hepatitis B, Hepatitis C, Tuberculosis).
12. Patients with eGFR < 15 mL/min/1.73m2 (MDRD equation).
13. ALT, AST, bilirubin, and ALP levels above 2 x the upper normal limit.
14. Inadequate bone-marrow function: WBC < 4000/mm3, haemoglobin < 8 g/dL, neutrophils < 2500/mm3, platelets < 100 000/mm3.

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Test product, dose and mode of administration, batch number:

SPANIDIN
Gusperimus, powder for solution for injection, is a white lyophilized powder. It is presented in a glass vial containing 50 mg gusperimus for reconstitution in 0.9ml sterile water for injection (EP) to a 50mg/ml solution.

Gusperimus will be dosed at 0.5 mg/kg/day and administered by the patients themselves s.c. in 28-day cycles (every four weeks throughout the study):

21-day treatment period with gusperimus will be followed by a seven-day resting period. If the WBC count falls below 4000/mm3 during the full 21-day treatment, the first day of gusperimus treatment on which leucopenia (WBC < 4000/mm3) occurs will be noted (X days) and subsequent cycles will be shortened by two days (i.e. X-2). The corresponding washout period will then be extended so that the total cycle length remains 28 days.

Batch used was: A06988
Kit numbers SPA100846-100932 and SPA101081-101096 were used in the Czech Republic
Kit numbers SPA100991, SPA100993-100996, SPA100998, SPA101520-101523, SPA101525-101528, SPA101530-101536 and SPA101538-101541 were used in Spain

Duration of treatment:
The total study duration is estimated to be 25 months:
- a maximum estimated recruitment period of 12 months
- a 12-month treatment period,
- a 4-week follow-up period

The longest follow-up was 36 weeks

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Reference therapy, dose and mode of administration, batch number:

METHOTREXATE (Metex 2,5 mg Tablets or METOJECT 10 mg/ml,solution injection in pre-filled syringe)
Methotrexate 2.5 mg/tablets, solution 25 mg/unit. The starting dose is 15 mg taken once a week (orally or subcutaneously). If tolerated, the dose may be increased by 2.5 mg/week to reach a maximum of 25 mg/week. Lower target doses are acceptable for intolerant patients. Folic acid (5 mg/week) may be administered to reduce the gastrointestinal and liver toxicity of Methotrexate.
Batch numbers used in Czech Republic: A06991 (tablets, kit numbers MTX500190-500193 and MTX500310-500318) and A06989 (injectons, kit numbers MTX400368-400345)
Batch numbers used in Spain: A06991 (tablets, kit numbers MTX500182-500185) and A06989 (injectons, kit numbers MTX400352-400359)

AZATHIOPRINE (Azathioprin-ratiopharm® 25 mg film tablets)
Azathioprine 25 mg/tablet. The target dose is 2 mg/kg/day. Round dose down to the nearest 25 mg, i.e. 60 kg patient would receive 100 mg/day.
Batch numbers used in Czech Republic: A06990 (Kit numbers AZA300531-300536)
Batch numbers used in Spain: A06990 (Kit numbers AZA300519-300524)

CYCLOPHOSPHAMIDE (Endoxan® 500 mg),
Intravenous CYC at a dose of 15 mg/kg will be administered in control group patients with a severe relapse. The duration of the treatment is minimally 13, maximally 22 weeks – depending on the response (until achieving a response with BVAS $\leq$ 2). The pulsed will be administered at Baseline and Weeks 2, 4, 7, 10, 13, 16, 19 and 22. The dose will be reduced for older patients and patients with renal impairment:

Pulsed CYC dose reduction for impaired renal function and age

Age	eGFR > 30 mL/min/1.73 m^2	eGFR $\leq$ 30 mL/min/1.73 m^2
$\leq$60	15 mg/kg/pulse	12.5 mg/kg/pulse
>60 and$\leq$70	12.5 mg/kg/pulse	10 mg/kg/pulse
>70	10 mg/kg/pulse	7.5 mg/kg/pulse

The CYC dose and frequency of pulse adminstrations were reduced in case of WBC decrease.
Batch numbers used in Czech Republic: A06995 (kit numbers CYC200242-200261)
Batch numbers used in Spain: A06995 (kit numbers CYC200202-200221)

Criteria for evaluation:
The primary efficacy variable was the rate of patients showing, within 24 weeks of trial entry, response with the level of disease activity BVAS $\leq$ 2 that was supposed to be maintained without relapse until the end of the trial (the end of the Week 52).

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The primary efficacy endpoint included

i. Remission - defined as the complete absence of active clinical disease, i.e. a BVAS score of 0, for at least two months on a stable prednisolone dose of ≤ 10 mg/day.
ii. Low activity Disease State (EULAR recommendations, Hellmich) – persistence of up to two minor BVAS items (BVAS ≤ 2).

Secondary Variables:

- Time to response (response is defined as the time from study entry to the first occasion that BVAS is ≤ 2, and there has been adherence to the steroid reduction protocol).
- Response duration defined as time from response with BVAS≤2 to relapse (relapse is defined as the return or first occurrence of one major and/or three minor BVAS items).
- Frequency of severe relapses (defined as at least one major BVAS item).
- Frequency of non-severe relapses (defined as at least 3 minor BVAS items with no major BVAS items).
- VDI score change from baseline to month 12.
- eGFR change from baseline to month 12 in all patients and in a subgroup defined as having a baseline GFR < 60 mL/min (i.e. renal impairment at baseline).
- Frequency of AEs and SAEs. (Total number of AEs per group according to AE category) (Percentage of patients in each group with a severe AE)
- Frequency of severe infection (a severe infection is defined as an infection that requires intravenous antibiotics or hospitalisation). Percentage of patients in each group with a severe infection.
- Pharmacokinetic parameters AUC, Cmax, Tmax and $T_{1/2}$ calculated from the measured plasma samples collected at regular time intervals after administration of gusperimus on the first day of three treatment cycles.
- Pooled physical and mental SF-36 domains change from baseline to month 6.
- Pooled physical and mental SF-36 domains change from baseline to month 12.
- The total corticosteroid exposure.
- Change in EQ5D between baseline and month 12.

Safety endpoints:
Analyses of the incidence and type of AEs that occur during the trial period were not done.

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Statistical evaluation:

Primary Efficacy Analysis

No analysis was done in this study since it was prematurely terminated. In the protocol the following plan for the primary efficancy analysis was stated:

The 95% two-sided confidence interval for the common treatment difference over severity strata was planned to be calculated. The superiority of the test treatment over the reference was considered to be concluded only if the 95% confidence interval completely lies to the right of zero. This approach made a confirmatory directional conclusion possible, which was equivalent to superiority of the test group alternative concluded at the α=0.025 level of significance.

Secondary Efficacy Analysis

No secondary efficacy analysis was performed during this study since it was prematurely terminated. In the protocol the following plan for the secondary efficancy analysis was stated:

Time to response

Response was defined as the first time that BVAS was less than or equal to 2, and there has been adherence to the steroid reduction protocol.

The Kaplan-Meier estimator of distribution function of the time to response was planned be calculated. The log-rank test for censored data should have been performed to compare treatment groups. The test should have been stratified for severity. The patients who would not achieve the response were plannedto be censored at:

- T = 6 months if a treatment failure (as defined in section 5.4) occured within 6 months;
- The time of withdrawal, if the patient was withdrawn from the study due to a reason that was not a treatment failure.

Response duration

The response duration was the time from the response (as defined above) to relapse, or to the end of subject's participation in the study (month 12 or premature withdrawal). Relapse was defined as the return or first occurrence of one major and/or three minor BVAS items. If no relapse occurs, the duration was planned to be censored.

The Kaplan Meier estimator of distribution function of the response duration was planned be calculated. The log rank test for censored data was intented to be performed to compare treatment groups. The test was planned to be stratified for severity. Only responders were planned to be analysed.

Frequency of severe and non-severe relapses

A severe relapse was defined by the recurrence or first occurrence of at least one major BVAS item, all other relapses are non-severe. The proportions of patients with severe and non-severe relapses and the corresponding 95% two-sided confidence intervals for the common treatment differences over severity strata was planned to be calculated.

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Summary statistics by treatment group were planned to be calculated for:

- The change in VDI score from baseline to month 12;
- The change in eGFR from baseline to month 12 (for patients with renal vasculitis at baseline only);
- Frequency of AEs and SAEs. (Total number of AEs per group according to AE category) (Percentage of patients in each group with a severe AE);.
- Frequency of severe infection (a severe infection is defined as an infection that requires intravenous antibiotics or hospitalisation).(Percentage of patients in each group with a severe infection);
- Pharmacokinetic parameters AUC, Cmax, Tmax and $T_{1/2}$ calculated from the measured plasma samples collected at regular time intervals after administration of gusperimus on the first day of three treatment cycles;
- Pooled physical and mental SF-36 domains change from baseline to month 6;
- Pooled physical and mental SF-36 domains change from baseline to month 12;
- The total corticosteroid exposure;
- Change in EQ5D between baseline and month 12.

The statistics were designed to be calculated both for combined data and by strata

Interim Analysis
No interim analyses were done

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Summary of results: Date of the final report 02.04.2015

The study started on December 2011 but Nordic Pharma faced difficulties enrolling patients due to the availability of rituximab, which is registered in this indication in the United States only and also off-label used in some European countries.
On April 2012, Nordic made the decision to put the SPARROW study on hold and started working on an amendment to the current protocol. The situation with the conventional therapy for Wegeners' granulomatosis has recently changed as rituximab (RTX) became one of the available therapeutic options in the treatment of the Wegener's granulomatosis relapse. The RAVE study showed that RTX was superior to cyclophosphamide and should therefore be highly considered in patients with severe Wegener's granulomatosis relapse. Current treatment guidelines strongly recommend RTX for the Wegener's granulomatosis relapse treatment. The inclusion of patients was discontinued on 17 April 2012; the patients already enrolled will continue their treatments as per the study protocol. Three patients were withdrawn from the Sparrow study, one due to treatment failure and 2 because of adverse events (patient's decision). The remaining patient in the test group continued the treatment as per the study protocol on a named-patient basis under the prescriber's responsibility. This patient subsequently died of respiratory failure in a context of nosocomial infection by multi-resistant Pseudomonas and underlying interstitial lung disease and emphysema. All clinical sites, regulatory authorities and Ethics committees were notified of these discontinuations.

Efficacy: The study was carried out according to protocol and strictly followed ICH-GCP guidelines. No efficacy analysis was performed.
Safety: In total, 74 adverse events (AEs) were reported during this study, of which 9 were considered serious adverse events (SAEs). The control group consisted of 1 patient, who experienced 9 non-serious adverse events of which 2 AEs were considered to be related to the study drug. The study group (treated with the study drug) consisted of 3 patients. In these 3 patients, a total of 65 adverse events were reported, of which 26 were considered related to the study drug. Nine of these 65 events were considered SAEs
Conclusion: No analysis was performed because of the early termination of the study.