European Medicines Agency
*Evaluation of Medicines for Human Use*

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# WITHDRAWAL ASSESSMENT REPORT FOR

# SPANIDIN

International Nonproprietary Name: Gusperimus

**Procedure No. EMEA/H/C/000809**

D180 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADR | Adverse Drug Reaction |
| ALT | Alanine Transaminase |
| ANA | Anti-Nuclear Antibodies |
| ANCA | Anti-Neutrophil Cytoplasmic Antibody |
| ATC | Anatomical Therapeutic Chemical Classification System |
| AUC | Area Under the Curve |
| AZA | Azathioprine |
| BVAS | Birmingham Vasculitis Activity Score |
| BW | Body weight |
| c-ANCA | Cytoplasmic staining pattern of Anti-Neutrophil Cytoplasmic Antibody |
| CHMP | Committee for Human Medicinal Products |
| CL | Clearance |
| $C_{max}$ | Maximum Concentration |
| CRF | Case Report Form |
| CS | Corticosteroids |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTC | Common Toxicity Criteria |
| CVA | Cerebrovascular accident |
| CYC | Cyclophosphamide |
| D, d | Day |
| DSG | 15-deoxyspergualin |
| ECG | Electrocardiogram |
| EMEA | European Medicines Agency |
| EOS | End of Study (Visit) |
| EULAR | European League Against Rheumatism |
| EUVAS | European Vasculitis Study Group |
| F, f | Female |
| F1 | Follow Up 1 (Visit, other numbering respectively) |
| GC | Glucocorticoids |
| GCSF | Granulocyte Colony-Stimulating Factor |
| GN | Glomerulonephritis |
| ICH | International Conference on Harmonisation |
| INR | International Normalised Ratio |
| ITT | Intent to treat |
| i.v. | Intravenous (ly) |
| M, m | Male |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMF | Mycophenolate mofetil |
| MPA | Microscopic Polyangiitis |
| MS | Multiple Sclerosis |
| MTX | Methotrexate |
| NA | Not Available |
| NOAEL | No observed Adverse effect level |
| p-ANCA | Perinuclear staining pattern of Anti-Neutrophil Cytoplasmic Antibody |
| PIL | Patient Information Leaflet |

| | |
|---|---|
| PK | Pharmacokinetics |
| PSUR | Periodic Safety Update Report |
| QT | Interval between the start of the Q wave and the end of the T wave in an electrocardiogram |
| QTc | Heart rate-corrected QT interval |
| RA | Rheumatoid Arthritis |
| RT | Renal transplantation |
| SAE | Serious Adverse Event |
| s.c. | Subcutaneous (ly) |
| SF-36® | Short-Form-36® |
| SPC | Summary of Product Characteristics |
| $t_{½}$ | Half-life |
| $t_{max}$ | Time to Maximum Concentration |
| VDI | Vasculitis Damage Index |
| $V_A$ | Apparent volume of distribution |
| WBC | White Blood Cell |
| WG | Wegener's Granulomatosis |

# I. RECOMMENDATION

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety and efficacy, the CHMP considers that the application for Spanidin, an orphan medicinal product in the treatment of refractory Wegener's granulomatosis, is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of outstanding issues (Section VI).

# II. EXECUTIVE SUMMARY

## II.1 Problem statement

Wegener´s Granulomatosis (WG) is a form of primary systemic vasculitis, with granulomatous inflammation involving the respiratory tract together with a necrotising vasculitis affecting small to medium sized vessels. Although primarily affecting respiratory tract, lungs and kidney, almost every organ can be involved. WG is a rare disease with an estimated prevalence between 42 and 63 per million inhabitants in the European Union. Formerly, the prognosis was poor, with a mortality of 80 % within one year.

The introduction of the Fauci-scheme with cyclophosphamide (CYC) and prednisolone in 1983 greatly improved patient survival rates. Improvement or remission can be achieved in 75% to 90% of patients, however, the disease remains life threatening with common relapses and treatment is needed on a long-term basis with a high treatment-related morbidity and mortality. Therefore, new treatment strategies are warranted, particularly in frequent relapsing or refractory patients and in those suffering from side effects of cyclophosphamide.

Over the last 20 years, a lot of treatment options and agents have been investigated. Nowadays, "standard care" (current treatments applied in the hospital) has changed and includes besides the "Fauci regimen", treatment with pulse CYC and various other treatments with immunosuppressive drugs like methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), infliximab, leflunomide, rituximab and intravenous Immunoglobulin (IVIg).

However a subgroup of approximately 10 % of patients exists who do not respond to CYC and corticosteroids. Furthermore patients exist who cannot tolerate the treatment, or who continue relapsing. These patients are severely ill and suffering from dramatic symptoms and a clear unmet medical need for induction of remission is identified for this population.

## II.2 About the product

**Classification**
Gusperimus (trade name Spanidin) is a chemically synthesised selective immunosuppressive agent.

**Mode of action**
Although the precise mechanism of action of gusperimus has not been elucidated, several pharmacological effects have been noted. On a molecular basis, gusperimus specifically binds to member(s) of the heat shock protein (hsp) 70 family and prevents translocation of NF-κB from cytoplasm into the nucleus of the cell. Gusperimus therefore hinders transcription of several immunologically relevant genes such as those coding for the kappa light chain, IL-6, TNFα, and IL-2 receptor α chain. Moreover, some investigations have revealed that gusperimus can induce apoptosis in lymphocytes which may be related to deactivation of Akt-kinase and p70 S6-kinase, a key molecule of protein synthesis, as well as inhibition of mitochondrial respiratory function. Consequently, gusperimus could influence different functions within the overall immune response. Gusperimus appears to affect the cellular immune response *via* inhibition of cytotoxic T-cell generation, and the humoral immune response *via* impairment of specific B-cell activation resulting in inhibition of antibody secretion. Furthermore, both parts of a specific immune response may be

influenced by interference of gusperimus with antigen processing and presentation. In general, gusperimus can be considered as an inhibitor of proliferation and/or differentiation.

**Indication and posology**
The originally proposed indication was:

Spanidin is recommended as therapy in refractory Wegener's granulomatosis (WG), unresolved by standard treatment, where:
- patients have an active unresponsive disease and their condition is otherwise not brought under control by the course of treatment already administered
- patients have an active and constant grumbling disease with frequent relapses (history of intractable course)
- patients are intolerant to current standard immunosuppression treatment, i.e. have received a high cumulative dose of cyclophosphamide (CYC).

which was changed to:

Spanidin (0.5 mg/kg body weight (BW)) is indicated as therapy for induction of remission in adult patients suffering from refractory Wegener's granulomatosis, unresolved by standard treatment with cyclophosphamide and glucocorticoids according to EULAR recommendations, where:
- patients have an unchanged or increased disease activity after four weeks of treatment with standard therapy, or
- patients are unresponsive to standard treatment, defined as ≤ 50% reduction in the disease activity score and/or lack of improvement of at least one major item after 4-6 weeks of standard treatment, or
- patients have chronic persistent disease, defined as presence of at least one major or three minor items on the disease activity score list (e.g. BVAS or BVAS/WG) despite 8 weeks of standard treatment.

The recommended daily dose of gusperimus is: "0.5 mg/kg body weight (BW) until white blood cell count reaches 3,000 /µl or for up to 3 weeks, followed by a rest of 7 days (washout phase) or until at least a WBC count of 4,000 /µl is reached again. This treatment regimen can be repeated up to 6 cycles."

The posology is for subcutaneous use only.

## II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

The non-clinical investigation of gusperimus has been performed since 1985 and revealed its immunosuppressive actions and effectiveness in autoimmune diseases in various non-clinical models.

Gusperimus was approved in Japan in 1994 (with the trade name Spanidin) as a new immunosuppressant for treatment of acute and accelerated rejection crisis after renal transplantation. Further Marketing Authorisations for the same indication were granted in Argentina (1996), Czech Republic (1998) and Poland (1999).

Gusperimus was discovered by the Institute of Microbial Chemistry, and developed by Takara Shuzo and Nippon Kayaku in Japan and was out-licensed for US and European development to Bristol Myers and Behringwerke respectively. Several indications were investigated based on a high-dose short term intravenous regimen but efficacy was not convincingly shown (cancer, organ transplantation, RA or multiple sclerosis (MAA to Germany)). As a consequence of results of non-clinical studies using autoimmune animal models and of data obtained from a clinical study in patients with glomerulonephritis (GN) it was suggested that gusperimus may be effective in treating systemic vasculitis with a low-dose long term regimen. So, initially Euro Nippon Kayaku GmbH (ENK) has focused the development on ANCA- (antineutrophil cytoplasmic antibodies) associated systemic vasculitis including WG and microscopic polyangiitis (MPA).

An application for Marketing Authorisation was first submitted to the EMEA through the Centralised Procedure (EMEA/H/C/000544), in 2003. Major issues on the quality of Spanidin® as well as on the non-clinical and clinical data submitted were identified. The major clinical objections concerned the non-homogeneity of the patient population and the uncontrolled design of the pivotal study as well as the lack of a comparative trial versus CYC and ENK withdrew the MAA on 06 August 2004.

Protocol assistance from the CHMP focussing on the design of the new phase II clinical trial was sought in Nov 2002 (EMEA/CHMP/5875/02). In December 2005 results from an interim analysis of the first 21 patients included in study 102 were submitted for further protocol assistance. In these procedures, the limitations of comparisons based on historical data were highlighted and it was anticipated that the development might be sufficient only if it is considered, after the appropriate comprehensive evaluation, that sound efficacy data with acceptable safety is demonstrated in a subset of patients with no other therapeutic alternatives. The CHMP recommendations were only partially followed. Follow-up protocol assistance was requested in August 2006 concerning eligibility for conditional approval.

## II.4 General comments on compliance with GMP, GLP, GCP

GMP: According to the information submitted by the company the Takasaki Plant, Nippon Kayaku Co. Ltd was inspected in December 2003, by Regierung der Oberpfalz, Bayern, Germany; Ref. No.CPMP/3321/03. Copy of the GMP Certificate has been provided. A GMP inspection was performed and the inspectors recommended that there are no GMP reasons to stop the Spanidin application to be granted (MHRA, UK, 24th July 2007).

GLP: All investigations cited in the Primary Pharmacodynamic section are published studies not performed under GLP conditions. Safety pharmacology studies were conducted before GLP guidelines came into force, but were performed in line with concepts of GLP and are of acceptable quality. All pivotal toxicity studies were GLP compliant.

GCP: Study 101 and Study 102 were performed following the requirements of Good Clinical Practice (GCP) and the local requirements. In Study 102, an external audit of two centres as well as audits of the Project Master File and the Data Management/Database was performed

## II.5 Type of application and other comments on the submitted dossier

This application is an application for conditional approval within the centralized procedure. Major objections were identified which pertained mainly to the definition of the patient population and possible confounding effects of co-medication (glucocorticoids) on efficacy. The applicant did a detailed work-up of the patient-population which allowed a case by case analysis based on the new definition by EULAR (The European League Against Rheumatism) as requested in the Day120 LoQ and during clarification meeting at BfArM on 14th August 2007.

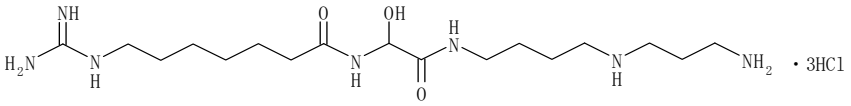
The applicant proposes a randomised trial of gusperimus versus cyclophosphamide or methotrexate in patients with refractory WG defined by EULAR as a conditional study post-approval (No. 103). The outlined study protocol disproves the applicant's original argumentation that a controlled study in the intended indication is not feasible.

# III. SCIENTIFIC OVERVIEW AND DISCUSSION

## III.1 Quality aspects

### Drug substance

Gusperimus is a polyamine made synthetically. It is an immunosuppressive agent not described in any Pharmacopoeia with the following structural formula:



Information about the manufacturing process is included in the dossier. Details of the commercial synthetic process are given both in the form of a flow chart and a narrative description. The description of the manufacturing process is properly documented.

The quality of the starting materials is suitable for its use in the production of the gusperimus drug substance. The purification phases include the use of different column chromatography processes in order to remove impurities. Multiple HPLC methods are employed throughout synthesis and work up to assess in-process controls. The crystallization process is controlled to confirm that the β-form is obtained, since the crystalline form is an important factor for the stability of the drug substance.

The chemical structure of Gusperimus trihydrochloride is well characterised. The molecule has an asymmetric carbon and exists as a racemic mixture. The chiral centre is the sensitive site of hydrolytic degradation.

Gusperimus trihydrochloride is a white crystalline powder, freely soluble in water (1g/ml). [d1]Regarding polymorphism two identified crystalline forms, α-form and β-form, exist.

The specified impurities are qualified at the level proposed.

The absence of the class 2 solvents used during the manufacture has been demonstrated according to the CPMP/QWP/450/03 Guideline.

The drug substance specification has been established taking into account the relevant ICH Guidelines for setting new chemical entity specifications. The specification proposed is suitable to control the quality of the drug substance manufactured using the current process.

All analytical methods, used in routine control, have been satisfactorily described and validated following the ICH Q2 R1Guideline.

The container closure system has been chosen taking into account the stability studies.

The formal stability studies have been performed under ICH Q1A conditions. The parameter studied and the analytical methods used are stability indicating. Taking into account the results obtained in the accelerated and long term stability studies, the proposed retest period is approvable.

### Drug Product

Spanidin is available as a white lyophilised sterile powder for solution for injection containing 50 mg gusperimus trihydrochloride per vial.

It contains commonly used excipients and the container system proposed is widely used for this type of formulation; their specifications have been established with reference to EP monographs.

In the pharmaceutical development of this formulation all relevant physicochemical properties have been considered.

The manufacturing process is standard for these types of formulations and has been described in detail.

The drug product specification has been established taking into account the relevant ICH Guideline for setting a new product specification. The specification proposed is suitable to control the quality of the drug product manufactured using the proposed process. The shelf-life specification is the same as the release specification.

All analytical methods, used in routine control, have been satisfactorily described and validated following the ICH Q2 R1Guideline.

Taking into account the impurity results of batches used in safety studies, the acute toxicological studies, genotoxicity studies on individual impurities and genotoxicity studies on a mixture of gusperimus with high concentration of impurities, it is suitable to conclude that the specified impurities are considered qualified at the level proposed.

The formal stability studies have been conducted - in accordance to the ICH Q1A (R2) guideline - on production scale batches of Spanidin 50 manufactured by the current process.

The packaging material used in these studies was the same as that proposed for commercialisation. The parameters checked are considered stability indicating.

The shelf-life applied, 2 years at 2ºC - 8ºC ("Do not freeze"), is supported by the updated results submitted.

## III.2 Non-clinical aspects

### Pharmacology

Primary pharmacodynamics: Difficulties in evaluation of the mechanisms of action of gusperimus in *in vitro* studies may have been due to a quick hydrolysis of gusperimus in neutral aqueous solutions and the oxidative degradation of gusperimus by polyamine oxidase in the presence of foetal calf serum, a common supplement of cell culture media.

Nevertheless, in a series of in vitro and in vivo studies gusperimus was shown to have immunosuppressive actions and to be active in preventing and regressing the inflammation and organ damage caused by the immune reaction. Based on published literature, gusperimus widely influences the functions of (cytotoxic) T-lymphocytes, B-lymphocytes, monocytes/macrophages and dendritic cells (DC). Observed pharmacodynamic effects related to immunosuppression include suppression of proliferation and activation of T-lymphocytes, suppression of antibody production by B-cells, inhibitory effects on monocytes/macrophages and their antigen-presenting function and induction of apoptosis in B- and T-lymphocytes.

Beneficial effects in autoimmune disease models such as spontaneously developing autoimmune-prone mice, multiple sclerosis, rheumatoid arthritis, crescentic glomerulonephritis, Goodpasture's syndrome and graft-versus-host disease have been documented. In addition, inhibitory effects of gusperimus on tissue rejection after transplantation have been shown in rats, dogs and primates.

Concerning the underlying molecular mechanism of action, it has been hypothesised that gusperimus, by binding to the heat shock protein 70 (hsp70) may impair the function of hsc70 as a chaperon. Hsc70 is believed to act as a molecule for loading peptide antigens to major histocompatibility complex class I and II molecules. Therefore, the binding of gusperimus to hsc70 may be responsible for the down-regulation of antigen expression in antigen-presenting cells (APC) and, in addition, inhibit activation of NF-κB and NF-κB-dependent processes.

In summary, although the mechanism of action has not been fully clarified and an animal surrogate model of WG is not available, the provided pharmacodynamic data clearly indicate that gusperimus has profound immunosuppressive effects and suggest that gusperimus could be efficacious in the treatment of WG.

As an immunosuppressant, the pharmacologically active form of gusperimus is the S(-) optical isomer, while the R-(+) isomer is pharmacologically inactive. The racemate is proposed for marketing.

Secondary pharmacodynamics: Inhibitory effects of gusperimus on proliferation of various tumour cell lines in vitro and on experimentally induced tumours in mice in vivo have been shown. Also, a weak antibacterial activity has been reported, although these effects need further reassurance.

Safety pharmacology: The Applicant has conducted a core battery of safety pharmacology studies. During first MAA assessment of gusperimus three points of concern had been raised with respect to the safety pharmacology studies and were resolved by the Applicant: (i) it was clarified that, although conducted before formal establishment of GLP, the safety pharmacology studies are of sufficient quality; (ii) it was verified that a statistically significant haemolytic effect identified in vitro was not of clinical relevance; (iii) the clinical relevance of a putative vasodilative effect of gusperimus on peripheral blood vessels at high plasma concentrations was corroborated by human clinical data. An increase in femoral artery blood flow at a dose of 0.1 mg/kg or more and a decrease in blood pressure and increase in heart rate at a dose of 0.3 mg/kg or more were observed in dogs. The vasodilative effect of gusperimus was transient but dose-dependent. The potential vasodilative effect of gusperimus is unlikely to cause any serious adverse reaction in patients with WG at the proposed therapeutic dose. On the other hand, hypotension has been addressed at clinical level and it has been listed as a common side effect, in the SPC.

According to ICH guideline S7B ("The non-clinical evaluation of the potential for delayed ventricular repolarisation by human pharmaceuticals"), the potential of a new drug substance for QT-interval prolongation should be evaluated in non-clinical safety pharmacology studies. No such data have been provided for gusperimus. Furthermore, clinical data for evaluation of potential for QT-interval prolongation in accordance with ICH guideline E14 ("The clinical evaluation of QT/QTc interval prolongation and proarrhytmic potential for non-antiarrhythmic drugs") have also not been provided.

Pharmacodynamic drug interactions: A prolonged graft survival in transplantation models was observed when gusperimus was given in combination with cyclosporin A or prednisolone.

**Pharmacokinetics**

In non-clinical studies, absorption, distribution, metabolism and excretion of gusperimus have been investigated and characterised in the rat, dog and monkey.

Method of analysis: Several assays have been established for the determination of gusperimus plasma levels. An application of LC/MS/MS technology enabled microdetermination of gusperimus and its metabolites with 10-100 times higher sensitivity and enhanced specificity compared with conventional GC/MS and HPLC methods.

Absorption: Bioavailability of orally applied gusperimus is very low. Therefore gusperimus must be administered parenterally. In toxicological studies gusperimus has been applied i.v., s.c. and i.p. High bioavailability of gusperimus following s.c. administration has been shown in different animal species and gusperimus is also applied s.c. in the clinical situation.

Distribution: Protein binding ratio of gusperimus was low and similar in animal species and man. Gusperimus was distributed rapidly to the major organs, reaching the highest concentration in kidneys, but did not readily cross the blood-brain barrier and its passage across the placenta was low.

In lactating rats, drug-related radioactivity was detected in milk following administration of radiolabelled gusperimus. Concentrations in milk were similar to maternal plasma concentrations. This issue should be addressed in the SPC which should state that gusperimus is contraindicated in breast-feeding women.

Metabolism: All human metabolites are also formed in dogs, whereas in rats only low and inconsistent amounts of human metabolites were found. Even though a more extensive metabolism was observed in dog when in rat, the terminal half-lives of gusperimus following s.c. and i.v. administration were approximately 2 hours in both animal species. In rat and dog, the metabolic profile of gusperimus in plasma and urine and total exposure to gusperimus and its metabolites were similar following s.c. administration and i.v. administration. The metabolic profile after s.c. administration did not change after repeated administrations in both animal species. Serum amine oxidases appear to participate in gusperimus metabolism.

At Day 180 of the initial MAA, an outstanding issue that should have been addressed was the quantitative information on extent of circulating metabolites formed in rats and dogs compared with humans. No such information has been provided in module 2.4, 2.6 or 4 of this MAA. However, taking into account that there is no outstanding concern related to the genotoxic potential of gusperimus metabolites, this issue is not considered as of crucial importance.

Excretion: Gusperimus is excreted mainly (about 90%) via the kidney, either in form of metabolites (dog) or largely in unchanged form (rat), whereas excretion via faeces in both species remains below 10%.

Pharmacokinetic drug interactions: Pharmacokinetic drug interaction studies are not available. The lack of such data has been justified by the Applicant with reference to (i) non-clinical studies, describing the absence of gusperimus-related induction or inhibition of human liver CYP isoforms, (ii) the availability of clinical data for the concomitant application of gusperimus and a number of agents commonly used in the treatment of WG.

Other pharmacokinetic studies: WG patients often suffer from renal impairment. In nephrectomised rats, extraction of both lobes of the kidney induced the accumulation of gusperimus inside the body, the major storage organ being the liver, and the drug was excreted via bile, biliary excretion being hardly observed in normal rats. In nephrectomised dogs, gusperimus was as rapidly metabolised or excreted as in normal dogs. However, with dialysis, gusperimus concentrations in the blood decreased more rapidly.

**Toxicology**

All studies were largely performed according to currently valid guidelines. However, concomitant toxicokinetic measurements are, with the exception of some acute toxicity studies, missing, which is considered an important drawback.

Acute toxicity: The acute toxicity of gusperimus has been assessed in a number of species and by various routes of administration. In single-dose toxicity studies, the death of mice, rats and dogs were attributed to respiratory suppression. Toxic signs at very high, non-lethal dose levels were mainly sedation, muscle relaxation, respiratory suppression with cyanosis, and convulsions in mice and rats and ataxia, tremor, suppressed respiration with cyanosis and irregular heart beat in dogs, indicating effects on the central and, possibly, the peripheral nervous system. Animals that survived recovered rapidly and completely. No signs of immunosuppression or bone marrow suppression were observed in surviving animals, suggesting that these effects need drug administration for a longer time. In dogs, the total tolerated dose of gusperimus could be increased by continuous i.v. infusion compared to i.v. bolus injection.

Repeat dose toxicity studies: The majority of subchronic and chronic repeat dose toxicity studies in rats and dogs were carried out using i.p and i.v. administration, respectively. In short term repeat

dose toxicity studies relatively high doses were applied to find a toxic dose, whereas in longer term studies lower dose levels were used to estimate the NOAEL.

In the repeat dose toxicity studies, the effects of gusperimus were mainly characterised by the inhibition of cell proliferation in rapidly proliferating tissues. In accordance with the intended pharmacodynamic activity, a marked suppression of the proliferation of cells of the immune system, with lymphocyte depletion in spleen and thymus (main organs of the immune system), but also in blood and bone marrow occurred. In addition, a general suppression of bone marrow cell proliferation, resulting in anaemia (decreased red blood cell counts, decreased haemoglobin, decreased haematocrit), decreased white blood cell counts and decreased platelet counts was observed. Furthermore, inhibition of proliferation of other rapidly proliferating cells such as hair follicles and the cells of the oral and intestinal mucosa can be assumed based on observed alopecia and gastrointestinal adverse effects such as diarrhoea and occasional oral erosion.

Additional observations included decreased sodium and potassium plasma concentration, blood in urine, haemorrhage in the urinary bladder, increased creatinine, increased alkaline phosphatase, renal nephrosis, and alveolitis in the lungs.

The extension of the dosing period from subchronic (13 weeks) to chronic (52 - 53 weeks) duration did not produce additional toxic manifestations, however, the general suppression of bone marrow and related anaemia became relatively more prominent in comparison with immunosuppression. With respect to human therapy, these results suggest that the continuous administration of gusperimus for more than three months should be avoided, because upon long-term administration the inhibition of red blood cell regeneration may become more severe than the inhibition of lymphocyte proliferation and may reach a life-threatening severity.

With respect to the clinical situation, secondary infections must be expected at a largely higher incidence than in non-clinical studies, as the contact with pathogenic germs cannot be prevented for patients routinely.

All toxic changes seen in rats and dogs regressed within 5-weeks after withdrawal of gusperimus.

The NOAEL in repeat dose toxicity studies were determined to amount between 0.03 and 1.0 mg/kg/day bw, being in the range of human therapeutic dose levels when calculated on an mg/kg basis. Based on these results, a dose level of 0.5 mg/kg bw as used in human therapy is expected to produce a suppression of lymphocyte proliferation but also some suppression of bone marrow proliferation and gastrointestinal side effects, accompanying the functional immunosuppression.
In accordance, a comparison of Cmax-values and of AUC values at the NOAEL-level in the chronic toxicity studies in rats (53 weeks) and dogs (52 weeks) and at a therapeutic dosage in the clinical setting, showed safety margins of <1, indicating that adverse effects like suppression of lymphocyte and bone marrow proliferation as well as gastrointestinal side effects have to be expected during clinical application of gusperimus.

Genotoxicity: Gusperimus and three of its human metabolites were tested in standard tests for the induction of gene mutations and chromosomal damage. With the exception of an in vitro chromosomal aberration test in CHL cells, all tests were negative. The weight of evidence suggests that the observed in vitro clastogenic effects are without biological relevance. Overall, the available data indicate that gusperimus is devoid of any relevant genotoxic properties. Therefore, with regard to the remaining Q6 from the D180 LOI of the initial MAA, concerns related to the genotoxic assessment of gusperimus are now solved in this MAA.

Carcinogenicity: A carcinogenicity study is not available for gusperimus and has not been required for the proposed indication considering the claimed target population and the intended use of gusperimus as second line therapy in refractory WG. The lack of a carcinogenicity study may be justified taking into account the severity of the disease and the following facts: (i) patients are not expected to be treated continuously for more than six months or in an intermittent manner for more than 6 cycles of 21 days treatment (accordingly, the applicant stated in section 4.2. of SPC that the

"treatment regimen described can be repeated up to 6 cycles"); (ii) gusperimus is devoid of a relevant genotoxic potential; (iii) no signs of carcinogenic activity were observed in the chronic toxicity studies; (iv) all toxic changes seen in rats and dogs regressed after withdrawal of gusperimus.

Nevertheless, the possibility of non-genotoxic carcinogenic effects of gusperimus, related to its immunosuppressive properties, cannot be excluded.

Reproductive and developmental toxicity*:* Gusperimus did not negatively influence male and female fertility in any generation tested (F0, F1). Embryo/foetotoxicity including lethal effects in the F1-generation had been observed in two species after exposure during organogenesis to gusperimus. In rats postnatal survival until postnatal Day 4 was also decreased after in utero exposure during organogenesis, whereas exposure during late gestation (after the end of organogenesis) and lactation did not induce lethal effects in the offspring. Ventricular septum defects had been observed in rat foetuses after exposure during organogenesis. Although this malformation may occur spontaneously in rats, it has to be emphasised that ventricular septum defects had not been seen in any of the control or low dose group foetuses. With the exception of delayed vaginal opening and some effects on avoidance learning in male high dose pups which may be due to the decreased body weights no effects regarding the achievement of landmarks, reflex development, and behavioural tests were seen after exposure during organogenesis.

[$^{3}$H] radioactivity after single i.v. administration of the mixture of [$^{14}$C] NKT-01 and [$^{3}$H] NKT-01 had the highest value at 24 h post-dose in foetal tissues. As gusperimus will be administered repeatedly accumulation in the foetus, foetal kidneys, liver, brain, and heart must be assumed.

Local tolerance: The main toxic findings following single and repeated s.c. application in dogs were inflammation and haemorrhage at the injection site. No local tolerance study has been provided for i.v. administration of gusperimus. Taking into account that i.v. repeat dose toxicity studies have been conducted, the lack of such data may be justified. Installation of gusperimus (0.1 or 5 mg/ml) onto eyes of rabbits caused no ocular irritation.

Other toxicity studies: No relevant additional toxicities were observed in toxicity studies performed with gusperimus degradation products, metabolites and optical isomers. During the initial MAA, concern was expressed that the toxicity of the potential impurity had not adequately been qualified. This issue is now considered resolved, since the potential toxicity of an impurity has been qualified in a 14-day repeat dose toxicity study in rats with a gusperimus preparation containing high concentration of impurities, including four identified impurities, and in *in vivo* and in vitro genotoxicity studies.

In several antigenicity tests, conducted in guinea pigs and rabbits, gusperimus did not show an antigenic potential. Dependence studies have not been performed, which is considered acceptable.

Environmental risk assessment: No further environmental risk assessment is required for the medicinal product Spanidin because the Phase I PEC is below the trigger value of 10 ng/l.

## III.3 Clinical aspects

**Pharmacokinetics**

Gusperimus pharmacokinetics is supported by clinical studies and bibliographical references (13). Pharmacokinetic data were provided from studies in healthy volunteers, autoimmune diseases including rheumatoid arthritis and multiple sclerosis, cancer and renal transplant patients. Additional pharmacokinetic data were provided from a total of 13 patients with WG in study 102 thereby reacting to one of the criticisms of previous assessment.

As gusperimus is poorly absorbed via the gastrointestinal tract, the drug must be administered parenterally. In comparison with IV 3h infusion, sc bolus administration showed a bioavailability of almost 100%. Maximum plasma concentrations following sc administration were 1.5-2 times higher than $C_{max}$ values after IV 3h infusion at the same dose levels.

Posology of this application is intended for the sc route of administration only which in principle is considered acceptable. In the new phase II study (Study 102), although the option to start treatment with IV administration was established in the protocol, no patient received gusperimus by iv application.

Following administration gusperimus exhibited a bi-exponential decay in plasma with a terminal elimination half-life of approximately 1 - 2 hours in patients with normal renal function. Gusperimus showed linear profile with $C_{max}$ and AUC values increasing proportionally with dose up to 10 mg/kg/day. Volume of distribution at steady state was high about (70% total body water) suggesting extensive tissue distribution of the drug.

Rapid plasma clearance and small amounts of unchanged drug in urine indicate extensive metabolism. Renal clearance approximated to glomerular filtration rate with protein binding of about 20%. In blood, 5 metabolites were detected, whereas in urine 6 metabolites were identified, one metabolite having degraded further. There was no single prominent metabolite. Although urinary excretion of unchanged drug was very low (approx. 10%), total urinary excretion of the drug including all metabolites was about 70%, showing this to be the major route of gusperimus elimination. Total clearance, distribution, elimination half-life and urinary excretion rate were independent of the dose. The plasma pharmacokinetic profile of gusperimus in WG patients was higher than that in healthy volunteers, showing approximately twice as much Cmax, a three times higher AUC, and a half total clearance compared to healthy volunteers. No explanation for this can be given at present with the available data.

The pharmacokinetics of gusperimus over the range of doses used in different therapeutic indications has shown to be dose-proportional.

The Applicant has performed a PK analysis in a subset of 13 WG patients included in the phase II Study 102. None of these patients used the IV route of administration during the study. A description of the PK parameters was presented. The results show no differences in Cmax, AUC (0-9) and T1/2 for gusperimus values between Day 1/Cycle 1 and Day 1/Cycle 5/6. Similarly, no differences were observed for two metabolites. It was concluded that neither the mother compound nor those metabolites showed any signs of accumulation.

In the opinion of this assessor, no firm conclusions on the risk of accumulation can be drawn with the information provided. Data are limited. Furthermore, taking into account the short T1/2 (1.5 h) of gusperimus and the duration of the washout period (i.e. at least 7 days, mean 14 days), accumulation of gusperimus was not expected anyway.

Due to the lack of PK data after IV administration, the CHMP concern on the possible impact of differences in the PK between the subcutaneous and intravenous administration on efficacy and safety has not been solved. However, since according to the proposed SPC the IV administration will not be finally recommended this issue does not deserve further discussion.

The applicant's conclusion that renal impairment does not significantly affect the pharmacokinetics of gusperimus as there is no hint that the drug accumulates in these patients was criticized during previous assessment and PK data in the target population were demanded to get more information on patients with different degrees of renal impairment.

PK data in 13 patients with WG were provided by study 102 but the study report states that within-study comparison in terms of e.g. clearance as related to renal function is not possible due to the limited number of patients. However, e.g. mean maximum concentrations of the parent compound are approximately doubled compared to those reported for healthy volunteers (dose 0.5 mg/kg) while total clearance is reduced (see doc 2) page 71 of 99 and doc 1) page 8).The applicant states that the reason of the higher plasma pharmacokinetic profile in WG patients is at present not clear with the data available and concludes from only two patients with moderate renal dysfunction in comparison to 11 patients with normal renal function that renal function showed no effect on the pharmacokinetic

profile of gusperimus. This is doubted for two reasons. Firstly, in renal transplant patients with allograft rejection and thus impaired renal function a prolonged half-life of gusperimus in plasma and a reduced excretion rate was observed. Secondly, the number of 2 patients is simply too small to exclude any influence of impaired renal function on the pharmacokinetic profile of gusperimus and more data are needed. “Classic” WG is a form of systemic vasculitis which primarily involves the upper and lower respiratory tract and the kidneys. It is questioned whether the study population really represented classical WG patients and the fact that a possible dose adjustment recommendation in patients with different levels of renal impairment cannot be made from available data (see SPC Section 4.2) remains a concern.

Considering that bone marrow toxicity associated with gusperimus is dose dependent and since an increase in gusperimus exposure in WG patients with renal impairment might be expected, unpredictable effects on bone marrow reserve, especially if renal function is unstable, cannot be completely ruled out. Therefore, a closer myelosuppression monitoring, possibly through more frequent WBC count, would be prudent in patients with mild to moderate renal impairment, until such time as additional data in this patient population are available.

Additionally, no specific data on patients with severe renal impairment (Creat/pl > 3 mg/dl) have been provided. In this case the use of gusperimus in patients with severe renal impairment is not recommended until further data on the pharmacokinetics, and safety monitoring of these patients become available.

The pharmacokinetics of gusperimus in patients with liver impairment has not been assessed. For hepatic dysfunction an effect on gusperimus metabolism is considered unlikely due to the fact that it is scarcely metabolized in the liver.

Accordingly, it may be advisable to combine available scarce datasets attempting to build up a PopPK analysis in order to at least find a reasonable explanation for the observed PK differences. Data generated in the framework of possibly required additional clinical studies may be used also to explain the in vivo disposition of the drug compound.

No specific data on elderly and children patients have been provided.

Pharmacokinetic interactions have not been investigated in clinical trials. The Applicant has provided bibliographical references of in vitro and in vivo non-clinical studies describing the absence of PK interactions due to gusperimus induction or inhibition of human liver CYP isoforms.

Moreover, the Applicant justifies the absence of specific drug-drug interaction clinical studies with the results obtained in study 101 and 102 in which gusperimus was concomitantly administered with a number of agents commonly used in the treatment of this pathology, as well as the fact that according to literature, these co-administrate drugs seem not to inhibit/activate the amine oxidase activity (enzymes responsible for gusperimus metabolism).

**Pharmacodynamics**

The Applicant has provided data from 6 studies on the pharmacodynamics of gusperimus (5 bibliographic references). Of these, one was carried out in patients undergoing renal transplant, 3 were carried out in cancer patients and 2 in various forms of glomerulonephritis. In addition, one article in press was provided on in vivo effects of cyclic administration of gusperimus on leukocyte function in patients with refractory WG (Kälsch et al).

Several pharmacodynamic effects contribute to the combined immunosuppressive efficacy of gusperimus. The mechanism of action of gusperimus seems to be associated with a specific binding to member(s) of the heat shock protein (hsp) 70 family interfering with both the translocation of NF-κB from cytoplasm into the nucleus of cells and peptide loading of MHC class I and II molecules. In addition, induction of apoptosis in lymphocytes is postulated to contribute to the effects exerted by gusperimus. Gusperimus appears to affect the cellular immune response via inhibition of cytotoxic

T-cell generation, and the humoral immune response via impairment of specific B-cell activation resulting in inhibition of antibody secretion. Furthermore, both parts of a specific immune response may be influenced by interference of gusperimus with antigen processing and presentation. In general, gusperimus can be considered as an inhibitor of proliferation and/or differentiation.

In humans, evidence of the immunosuppressive effects of gusperimus is provided by the clinical outcome in renal transplant patients; treatment with gusperimus inhibits allograft rejection and results in improvement of renal function. Evidently, treatment with the drug results in effective immunosuppression of an anti-allograft response, which is predominantly, caused by activation of alloreactive T-lymphocytes and antigen-presenting cells (APC). Furthermore, in cancer patients the humoral immune response resulting in anti-murine antibodies was effectively suppressed suggesting a probable inhibitory and thus beneficial effect of gusperimus on auto-antibody generation in autoimmune diseases. In one cancer study however, no specific conclusions could be drawn about the immunologic properties of gusperimus (Havlin et al.) since increased cytotoxic activity was not related to the dose of gusperimus or alterations in the pattern of cell surface antigens or leukocyte phenotypes.

The efficacy of gusperimus on the leukocyte functions was examined in patients with refractory WG. In the responses of $CD4^+$ T-lymphocytes stimulated with anti-CD3 and anti-CD28 antibodies, the proliferation and the production of INFγ and IL-10 was markedly suppressed after the gusperimus treatment. The production of TNFα mediated by lipopolysaccharide activation was also impaired after gusperimus treatment. These effects were reversible. It seems that the suppression of T-lymphocyte and monocyte functions by gusperimus treatment contributes to the efficacy of gusperimus in patients with refractory WG (Kälsch et al. in press).

These pharmacodynamic findings in patients with WG are new and provide a rationale for the clinical outcome of the two studies performed in patients with refractory WG.

Apart from that gusperimus treatment seems to be related to a significant decrease in proteinuria which could be related to immunosuppressive activity of the drug. Data of urinary protein excretion were scarce in study 102.

**Clinical efficacy**

*Dose-response studies and main clinical studies*
Two phase II studies have been provided to support the MA of gusperimus in the treatment of patients with WG.

The major clinical concerns of previous assessment of **study 101** were the inhomogeneous study population and the uncontrolled design.

Although the product claimed an indication in refractory patients, the studied cohort included several patients that were not refractory and that might well have been treated with available therapies. Included patients were heterogeneous and the lack of knowledge on the response that those patients could have been obtained with other therapies precluded the acceptance of the observed response in some patients as a proof of efficacy enough to recommend the use of gusperimus as an alternative to those products.

Observed response was not considered outstanding and relayed on an unnecessarily low number of patients, followed in a non-controlled study and where responses were judged by a subjective assessment by the responsible physician. There was no consistent support to the subjective response by available scales to assess efficacy. In addition, the role that the increase of the corticosteroids dose previous to gusperimus treatment may have played in the observed response in some patients was unclear.

It was considered that there was no scientific justification to limiting the clinical development of this new immunosuppressant only to the last choice treatment in patients with difficult to treat WG. This

led to an unnecessary situation with lack of data to properly assess the benefit risk of the product, even in the claimed very restrictive indication.

Finally, no dose-finding studies were performed and therefore the optimal dose regimen of gusperimus in the proposed indication was not determined. It was deemed that data to support either a daily dose of 0.5 mg/kg day or a recommended length of treatment of 28 or 21 days were insufficient.

Therefore, taking into account the methodological limitations of the study, it was considered very difficult to properly assess the efficacy profile of gusperimus in WG based on the available data and considering the safety concerns raised, mainly related to bone marrow toxicity, a negative opinion on the benefit/risk balance of gusperimus was concluded at D150 that led to the MA withdrawal.

In the new pivotal **study 102** the applicant tried to resolve these problems as far as the inclusion criteria are concerned. The study, however, is again uncontrolled.

The question whether such a controlled study e.g. against best supportive care is feasible and should be mandatory for MA was extensively discussed during previous assessment and scientific advice. From a clinical point of view refractory WG patients are those10 % of patients which failed on standard treatment and are severely ill and suffering from dramatic symptoms such as progressing retroorbital granulomas leading to enucleation, progressive sinusitis with osseous destruction, severe subglottic stenosis with severe dyspnoea, renal failure, pulmonary insufficiency to enumerate only some of the complications that can be found in spite of standard therapeutic regimen (Aries et al. 2006). The applicant argued that the inclusion of a control arm as best supportive care as suggested during previous advice was highly theoretical since it should be considered unethical to put refractory, severely ill patients on a therapeutic regimen that failed before. For these patients best supportive care is not defined and a clear and urgent unmet medical need is identified. However, as a conditional study post-approval the applicant now proposes a randomized trial of gusperimus versus cyclophosphamide or methotrexate in patients with refractory WG. The outlined study protocol disproves the applicant's original argumentation that a controlled study in the intended indication is not feasible. From an ethical point of view, it is quite questionable that refractory patients (really refractory) to CYC and MTX should be exposed to these treatments during a clinical relapse.

Whether study 102 can be accepted for conditional approval of gusperimus in refractory WG is crucially dependent on whether or not a truly refractory population was included in the trial and the demonstration of a favourable risk-benefit in these patients.

The applicant made an effort to include a more homogeneous truly refractory study population as this population was defined to have a total BVAS score $\geq 4$ with disease activity in one major organ or at least three minor organs at screening and pre treatment assessment. Patients had to have received $\geq 3$ months CYC therapy and/or $\geq 6$ months MTX treatment. With this patient population the following indication should be supported: Therapy in refractory WG, unresolved by standard treatment, where:

- patients have an active unresponsive disease and their condition is otherwise not brought under control by the course of treatment already administered
- patients have an active and constant grumbling disease with frequent relapses (history of intractable course)
- patients are intolerant to current standard immunosuppression treatment, i.e. have received a high cumulative dose of cyclophosphamide (CYC)."

Unfortunately, after study 102 was finalised the recently published EULAR/EUVAS recommendations (Hellmich et al.) introduced a revised definition of "refractory disease" for ANCA-associated vasculitis, as either i) unchanged or increased disease activity after four weeks treatment with daily oral CYC (2-3 mg/kg) and GC or pulse intermittent high dose CYC (15 mg/kg) with GC or ii) lack of response, defined as <50% reduction in disease activity score and/or lack of improvement of at least one major item, after 4-6 weeks of treatment or iii) chronic persistent disease, defined as presence of at least one major or three minor items on the disease activity score

list, despite 8 weeks of treatment. In addition, patients, who are intolerant to the above therapy or have contraindications against the use of CYC (e.g. haemorrhagic cystitis), should not be included but assessed in a subgroup analysis. Patients intolerant to CYC should have received the best available alternative standard therapy and be considered for escalation with experimental therapy.

Primary objective was to determine the response rate to treatment with gusperimus in patients suffering from refractory WG. The primary efficacy variable was the rate of clinical response, determined using the Birmingham Vasculitis Activity Score (BVAS) criteria, which was considered acceptable. Complete remission (CR) was defined as a score of 0, which was maintained for at least 2 months. Partial remission (PR) was defined as BVAS ≤ 50% of the initial score for at least 2 months. Stable disease was defined as maintenance of BVAS score, less than or equal to the baseline BVAS, where the BVAS score could not be classified as either CR or PR. A patient who experienced worsening of the disease (i.e. BVAS> baseline) was defined as disease progression.

Secondary objectives were duration of response, defined as time from CR or PR to relapse; assessment of anti-inflammatory activity of gusperimus using surrogate markers including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and urinalysis (haematuria); assessment of the degree of irreversible damage due to the vasculitis using the vasculitis Damage Index (VDI) scoring system; impact of gusperimus on general health using the SF-36 questionnaire; PK information after repeated administration as well as assessment of ANCA. Safety and tolerability were also measured.

In study 102 the remission rate is 46% (CR) and the response rate is 92% (PR plus CR) which exceeds the efficacy data of study 101 that had a response rate of only 65%. Taking the new definition into account the response rate is still 88 % (42/ CR and 46 % PR). However, only 27 (60%) of patients in study 102 can be considered refractory according to the new EUVAS definition.

Since there were still concerns regarding the true refractoriness of the patient population and several doubts existed whether patients included were real candidates to treatment for induction of remission the applicant was requested to do a detailed work-up of the patient population (see also Tables C1.1-1 and C 1.2-5 and Fig. C1.2-1 in the appendix of the applicant's response document).

Patients of Study 102 were allocated according to newly defined EUVAS/EULAR recommendations and clinical symptoms were correlated with the respective BVAS scores. Apart from that individual information on glucocorticoid and other immunosuppressive treatment was given for each patient. Unfortunately the BVAS scores graded as zero were not provided in Table C1.2-5 of the appendix, although requested during meeting at BfARM on August 14$^{th}$ 2007, so complete remission and its duration cannot be easily evaluated.

Nevertheless, the data are now presented in a way that allows an assessment of case by case which is necessary to determine whether included patients were candidates for induction of remission therapy and whether they could be considered refractory to standard therapy.

According to EUVAS "refractory disease" should not include patients who are intolerant to or have contraindications against the use of CYC since these patients are probably distinct in terms of complication of treatment, probability of response or damage. So in 10 patients a subgroup analysis should be performed among which 4 were classified as non-refractory, 2 not assessable due to protocol violation and 3 cases received more than 25 mg corticosteroid /day at end of cycle1 (1 overlapping with non-refractoriness) thus leaving only 2 patients in this subgroup.

Of the 21 patients initially considered to have "grumbling disease" 18 were, according to the applicant, refractory as defined by the new EUVAS criteria. This number is however questioned, since at least 5 of these patients (01-04, 01-03, 06-02, 06-03, 06-17, 06-15) had rather mild clinical symptoms and might not have needed the induction of remission therapy with a new immunosuppressant drug but rather maintenance therapy. "The presence of a constant grumbling disease who tended to relapse during maintenance treatment with CYC, MTX, MMF or other immunosuppressant therapy", simply describes the natural course of the disease in the overall WG population but, by itself, not necessarily means that these patients should be considered as refractory.

Even though some of them could have been refractory, likely they would be refractory to the maintenance treatment which does not necessarily mean that they are also refractory to an induction regimen with the standard treatment.

Apart from that according to Table C15-1, three patients had no relapse and seven patients only one relapse on standard available therapies prior to study entry which indeed raises doubts on the refractory condition of the enrolled patient population and consequently on the necessity of treatment with a new immunosuppressant. Of note, the number of relapses in Table C 15-1 does not exactly correspond to the number of relapses described in table C 1.1 1 of the appendix. Here it is not entirely possible to disentangle the provided information.

However, if the applicant's allocation is accepted, 28 patients remain for primary efficacy analysis. Of these 24 achieved the primary endpoint of partial or complete remission. The applicant states that of the 28 refractory patients 43% had a complete remission and 46% partial remission. Complete remission was defined as a BVAS score of 0 $\geq$ 2 months duration. According to the information contained in Fig. C1-2-1 at least 2 patients had a BVAS score of 0 for less than 2 months duration (06-02 and 06-15, exact data are missing in table C1.2-5, see above) which ends up in a complete remission rate of 35% (10/28).

Ten of these 24 patients had a possible influence of corticosteroids on the clinical outcome (see assessment of question 1.2) which leaves a data base of only 14 patients.

The shortened new dose regimen, i.e. 6 cycles of 0.5mg/kg/d during 3 weeks with at least 7-day rest before the next cycle in study 102 was based on the results of Study 101, where most patients did not tolerate more than 3-week of treatment due to leucopenia. The appropriateness of this dose regimen is still questioned since more than half of the cycles initiated were not completed due safety issues.
The proportion of the non-completed cycles of at least 21 days within the total number of cycles initiated was 54% (135/248) The proportion of patients who completed the pre-established treatment (6 cycles of 21 days treatment) was not provided.

Up to 11 (24.4%) of the patients in the safety population increased the dose of CS at any time point between baseline until last day of best response of BVAS, which might have had a contribution to the achievement of remission. To further assess the possible impact of CS in the observed effect the Applicant was asked to provide detailed data on the immunosuppressant treatment used, included CS, at the start of treatment. Cases where high doses of corticosteroid started at the same time or just before gusperimus was started were provided.

According to the EULAR recommendations for conducting clinical studies in systemic vasculitis, glucocorticoid dosage should be stable and should not be changed at least two weeks before the study. A clearly defined protocol for GC taper should be described in the study protocol and criteria for delaying the taper or increasing the dosage should be provided. To determine whether or not the absence of clinical symptoms is actually related to the effects of the experimental drug under study and not simply a result of high dose GC therapy, it is recommended for clinical studies that "remission" should only be defined as occurring when a patient has attained a stable low dose of prednisolone or prednisone of $\leq$ 7.5 mg/day for a defined period. (EULAR recommendations for conducting clinical studies and /or clinical trials in systemic vasculitis, Hellmich et al, Ann Rheum Dis 2007, 66 605-617).

For Study 102, a corticosteroid treatment was permitted as it was in line with consensus practice: "at inclusion into the study, the allowed window of steroid dosage is 7.5 mg/day to 60 mg/day. By the end of treatment Cycle 1 at Day 22, the maximum steroid dosage should be $\leq$ 25 mg/day". No further specification for GC taper is given. Success of gusperimus was post-hoc defined as achievement of the primary end-point of partial or complete remission without interference from a sustained steroid dose >15 mg/day after 3 months of the treatment period. It is agreed that this cut-off is more stringent than the one of 25 mg which was initially used in the protocol of study 102. Only 24 patients of the refractory population met these criteria.

Among this already restricted population for 10 patients a possible influence of corticosteroids cannot be excluded:

- Patient 01-04 had an increase in steroid dose to around 20 mg/day from days 56 to day 80.
- Patient 06-05 received 1 week around 20 mg/day GC at day 142.
- Patient 06-10 had 1 week around 20 mg/day GC at day 84.

The applicant states that this short term increase in GC had no influence on efficacy. This is difficult to verify in the absence of a control group. Apart from that allowed increase and duration of GC treatment during the study was not predefined in the protocol.

- Patient 06-12 should be definitely excluded since shots of GC above the predefined threshold were given prior to study entry and at the beginning to cycle 1. In addition there was a treatment with 3 doses of 30 mg/day of corticosteroids during cycle 2.

- Patient 02-02 had steroid >15 until day 42 (according to Fig. C1.2-1 in cycle 1 around 60 mg around mid-cycle then slowly tapering). At the end of the study when BVAS increased again a steroid shot of around 600 mg was provided with complete remission afterwards.
- Patient 02-04 had high steroids until day 112 (cycle 4).
- Patient 06-02 had steroid increases up till 30 during the first 3 cycles.
- Patient 06-14 had increases of steroids after cycle 1 up till 30 in cycle 3 with subsequent BVAS reduction which was maintained afterwards.
- Patient 14-01 had high steroid doses throughout cycle 2 and additional immunosuppressant (cyclosporin) due to renal transplant, the latter representing an exclusion criterion in itself according to study protocol.
- Patient 14-03 (graph is missing) received a steroid dose of 22.5 mg/day from screening throughout the entire study course.

Among these patients, when the dose of GC was increased a confounding effect cannot be excluded. This could have been solved, at least partially, with a controlled arm. On the other hand, there are some patients for whom the dose of GC was not increased during the first weeks, as it is usually done in clinical practice to control disease activity, which suggest that patients included had a mild disease activity and thus, would have been controlled merely by increasing the dose of GC or, most probably, by increasing the dose of the baseline/maintenance immunosuppressant. The role of gusperimus in this situation is more than questionable.

No data on long-term efficacy or safety are available and therefore only its use as short-term therapy for the induction of remission up to 6 months can be recommended.

Mean duration of response was 231.5 days ranging from 28 to 368 days. Duration of remission is considered a key secondary endpoint in the assessment of the overall effect of gusperimus. However, the duration of the follow up period and the number of visits were too limited to properly and accurately assess the length of the treatment effect. Notwithstanding these limitations, in order to facilitate the interpretation of the available results, the Applicant was requested to provide the proportion of patients with different durations of response, e.g. ≤ 3months, > 3 to 6 months, > 6 to 9 months, > 9 to 12 months. These data show that in 16 out of 39 patients (41% ) the clinical response was maintained for up to 9-12 months and that in only 2/39 (5%) of patients the response was maintained for a longer duration. The duration of the treatment response is limited, as expected in a heavily treated and long-lasting disease population.

It is noted that according to the study protocol, remission was defined as patients with > 50% improvement in BVAS score that was maintained for at least 2 months. According to the information contained in Fig.C1-2-1 at least 2 patients had a BVAS score of 0 for less than 2 months duration (06-02 and 06-15, exact data are missing in table C1.2-5, see 1.2) which according to the definition of the primary end-point is not the pre-specified criterion. This ends up in a complete remission rate of 35% (10/28).

Duration of best response in patients with complete remission ranged from 28 to 340 days.

The overall relapse rate is 35.6 % and quite high as expected in a chronic disease population.

The anti-inflammatory activity of NKT-01 was assessed using surrogate markers including C reactive protein (CRP), erythrocyte sedimentation rate (ESR) and urinalysis (haematuria). Minor non-clinically relevant changes were observed for these three parameters. More than half of patients had baseline ESR values within the normal range and total mean change does not show any significant benefit. Similar conclusions do apply for CRP. In the case of haematuria, although there was a reduction in the proportion of patients with 3+ and 4+, the proportion of patients with no haematuria at the end of study (following cycle 6) was not modified. The proportion of patients with abnormal values at baseline (defining the method of assessment) who normalised their values at the end of treatment might be helpful to assess any possible effect/co-relation with inflammatory biomarkers. Only 18 patients of the entire study population showed haematuria and / or proteinuria as signs of renal involvement at baseline (Cycle 1, Day 1). Table C13-1 summarizes the creatinine clearance of the safety population at screening with a mean of 94.5 Only 9 patients had a CTC grading of I (1.2 – 1.8 mg/dl) or II (1.8 – 3.6 mg/dl) during the study. GFR was not provided. 5 patients (01-01, 01-02, 04-05, 08-04 and 08-05) with decreased renal function (less than 50 ml/min of creatinine clearance) are presented in Figure C13-1. In 3 patients (01-01, 01-02, 04-05) the creatinine clearance was improved during gusperimus treatment, but its efficacy was transient. The other 2 patients (08-04, 08-05) had no improvement of creatinine clearance. However, no worsening of creatinine clearance during the gusperimus treatment occurred.

“Classic” WG is a form of systemic vasculitis that primarily involves the upper and lower respiratory tracts and the kidneys. The data on renal involvement in the study population are scarce. No information for classic WG with renal involvement is provided and no dose recommendations can be given (see also pharmacokinetics Question 5) for different grades of renal impairment which remains a concern.

Similarly, minor improvement in some sub-indices of the SF-36 health questionnaire was observed.

An assessment of the degree of irreversible damage due to the vasculitis using the VDI scoring system, was made at baseline, cycle 3 Day 22, End of Study, and during the follow-up period. For the overall efficacy population, there were minor changes in the VDI following participation in the study of undoubtful but probably nil relevance. However, to assess any possible deleterious impact on organ damage, the description of those patients with a worsening in the VDI during the whole study duration should be provided. Nevertheless, considering the limited study duration it is quite unlikely to detect changes in the VDI.

A summary of the ANCA test results for the safety/efficacy populations is presented. The number of patients who switched from positive to negative during treatment was rather small. The clinical relevance of the observed effect appears poor and no conclusions can be derived from these results since there is a weak correlation between the presence of ANCA and response to treatment.

The outstanding results seen for the primary endpoint (BVAS) are only partially substantiated by minor and probably non-clinically relevant changes in inflammatory parameters, quality of life assessment and ANCA evaluations.

The steroid sparing effects was additionally analysed. When comparing the steroid dose from end of cycle 1 to last day of best BVAS response, a decrease could be obtained in 34 patients of the safety population and 30 patients of the efficacy population. The steroid dose decreased from (mean ± SD [median]) 19.44 ± 11.94 (20.00) mg to 11.39 ± 12.33 (8.00) mg in the safety population and from 18.71 ± 10.87 (20.00) mg to 9.97 ± 6.70 (8.50) mg in the efficacy population. An increase of steroid dose at any timepoint between baseline until last day of best response in BVAS was observed in 11 (24.4%) patients in the safety population and in 9 (23.1%) patients in the efficacy population.

Overall, in study 102 patients with a clear relapse and those with some activity (formerly assigned to "grumbling disease") are mixed up in the same pool, which is not acceptable. Some patients of the "grumbling disease" group with rather mild clinical symptoms and some patients with one or zero prior relapses might not have needed an induction therapy with a new immunosuppressant.

So the open questions regarding the true refractoriness of this population were not resolved and are still considered as major.

There are clear EUVAS recommendations for GC use before and during clinical trials and as a threshold for remission. The pre-specified threshold of 25 mg GC at the end of cycle 1 is quite high and was post hoc reduced to 15 mg/day after 3 months of the treatment period. It was reached by only 24 patients of the study population and among these 10 had a possible influence of GC treatment (shots or longer increases in dosage) during the study course which is difficult to exclude in the absence of a control group. This represents a serious shortcoming of the data and the point is considered as unresolved. Apart from that some of the studied patients were not shown to have a highly active disease with the need for induction of remission and therefore the proposed indication is questioned. In the light of these deficiencies the proposed dose regimen which was followed in only 46% of cycles is not really substantiated. There are insufficient data to recommend dosage in various degrees of renal impairment which remains a concern since classic WG often affects the kidneys.

**Clinical safety**

The number of patients that has been exposed to the drug as it is intended to be used in the applied indication (study 101 and 102) is limited with a total of 37 patients with a dose of 0.5 mg/kg with a duration of 21 days for 6 cycles and 15 patients with a duration of 28 days for 6 cycles.

Since the safety data from studies performed in other indications with other therapeutic doses and dose schedules are distinctly different from the intended administration an extrapolation is questionable. In addition, the specific characteristics of WG do not allow an extrapolation from another patient population either.

100% of patients in study 101 and 94% of patients included in study 102 reported adverse events. Altogether, the main safety profile in study 101 and 102 corresponds with that known for the immunosuppressive effect of gusperimus. The AEs documented in both studies are comparable. Despite an adjusted study design (in study 102 the duration of each cycle was shortened to reduce the AEs) a relevantly improved risk could not be identified. Anyway, the average cycle length in both studies was at the end of the studies de facto similar. In so far this result is not surprising. But in total the number of patients assessed is too small for a reliable evaluation. The numbers of AEs in study 102 are not presented so that a comparison with study 101 could not be done to better detect numerical differences.

The patients (study 101 and 102) mainly experienced haematological toxicities (65%, Table C19-C1) during treatment and consecutively infections (82%, Table C19-B3).

Any cumulative AE over time of treatment cannot be identified; however the small number of patients and the number of possible parameters which may have an additional impact and the lacking control group don't allow a valid evaluation. In some patients infections, especially candidiasis or respiratory tract infections occurred several times during treatment and/or were prolonged.

Serious infections occurred in 16% of patients, one case in study 102 possibly fatal. Most documented infections concerned the respiratory tract. Furthermore, skin infections are documented as very common in study 102.

The proportion of affected patients with haematological toxicities in both studies is comparable (study 101: 65%; study 102: 64.4%). The detailed numerical comparison shows leucopenia to be increased in study 101 whereas no case of neutropenia is documented in this study. Red blood cells

are found to be decreased already at day 22 of cycle 2, data for red blood cells over time of treatment (days) are not presented.

Other AEs reported in study 102 are: 22% of patients reported diarrhoea, 20% anaemia, 20% nausea, 20% alopecia, 16% dysgeusia, 16% fissures, 16% fatigue and 13% anorexia. Hypertension (5 cases) was reported as very common; 64% of patients reported injection site disorders. In study 101 the AEs were as follows: 25% diarrhoea, 20% parageusia, 20% hyperemesis or nauseas, 15% paraesthesia, rhagades, flushing and fatigue. In addition, dysmenorrhoea was identified in studies with other patient populations.

On the base of the submitted data it is not possible to identify a dose related impact of gusperimus on patients with existing liver enzyme elevations. No difference in frequency or severity of hepatic function disorder in relation to duration of study or between the studies can be identified. The number of patients assessed is too small. Thus, valid recommendations for patients with liver impairment cannot be given.

On the base of the submitted data it is not possible to identify a dose related impact of gusperimus (e.g. decrease in WBC count) on patients with existing renal impairment. No difference in frequency or severity of renal function disorder in relation to duration of study or between the studies can be identified. However, the number of patients assessed is too small. Furthermore, it is not entirely clear why the proportion of patients with renal impairment enrolled in the studies is that small although normally WG is a disease with a high percentage of renal exposure especially in patients with a progressed disease status. Valid recommendations for patients with renal impairment cannot be given.

Data for long-term exposure or repeated treatment are scarce but the disease is a recurrent disease that may require longer or further treatment. A dose titration was not performed, thus a proven rationale for the current dose regimen does not exist.

**Pharmacovigilance System**

The missing SOPs have been finalised and their content is summarized in the revised detailed description of the pharmacovigilance system dated 16 November 2007. All aspects of the Volume 9 A of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Human Use - are adequately addressed now.

## IV. ORPHAN MEDICINAL PRODUCTS

An Orphan Medicinal Product Designation for gusperimus for the treatment of WG was granted in EU on 29th March 2001 and it was entered into the Community Register of Orphan Medicinal Products for Human Use with number EU/3/01/034.
The prevalence of WG is between 42 and 63 per million inhabitants in the EU.

## V. BENEFIT RISK ASSESSMENT

### V.1. Benefits

The evidence to support the MAA relies on two open-label phase II studies performed in a limited number of patients.

Even though the study design has been improved and despite efficacy results show a relevant effect on disease activity, as measured by changes in BVAS, uncertainties concerning the population included as well as the possible contribution of corticosteroids to the observed effect remain and do not allow concluding on the possible value of gusperimus in the treatment of WG.

This could have been solved at least partially with a control group.

The lack of data on the effect of gusperimus in some relevant clinical endpoints such as proteinuria and creatinine clearance and the minor, and probably non-clinically relevant changes observed in haematuria, CRP and ESR add further uncertainty to the observed effect. No dose recommendations can be given to patients with various degrees of impaired renal function which remains a concern especially in the light of a dose regimen which was followed in less than half of the cycles.

## V.2 Risks

Overall, the treatment with gusperimus is related with clinically relevant AEs (leucopenia, anaemia, thrombocytopenia, infections (to a large extent continuous or severe)) which are consistent with the action of an immunosuppressive agent. Additionally, it seems to be not well tolerated by a great proportion of patients (nausea, vomiting, paraesthesia, hypertension, application site disorders). Any cumulative AEs over time of treatment cannot be identified.

A clinically relevant difference in frequency or severity of AEs between study 101 and 102 cannot be identified; in so far the changed dose regimen shows no advantage and could be further improved.

Special populations are not sufficiently assessed; this concerns especially patients with renal impairment which is common in WG.

In general, the database with the proposed dose regimen is too small for a reliable evaluation.

## V.3 Balance

In summary the data do not allow defining a WG population for treatment with gusperimus satisfactorily since:

- only a small portion of patients can be allocated to the refractory group according to the new EUVAS criteria
- refractory patients and patients with grumbling disease are mixed up in the same pool
- a possible influence of steroids on efficacy cannot be excluded due to the lack of a control group.

Some of the studied patients were not shown to have a highly active disease with the need for induction of remission but with a possible need for alternative treatments of more maintenance character and the role of gusperimus in this situation is more than questionable.

Therefore, even though gusperimus might have a possible role in the treatment of WG for the induction of remission the evidence provided is too weak to draw any conclusions.

## V.4. Conclusions

The overall benefit/risk balance of gusperimus in the treatment of WG is negative. The minimum requirements for a conditional approval are not fulfilled.

The proposed study 103 disproves the applicant's original argumentation that a controlled study is not feasible in the intended indication. The refractory status of the enrolled patient population has to be properly defined and the study should be conducted prior to marketing authorisation.

If gusperimus is intended to be an alternative to CYC to induce remission, it would be preferable to investigate it in a controlled trial versus CYC, rather than limiting from the beginning its place to those "refractory or intolerant" selected patients and then decide that the controlled clinical trial is not feasible. Alternatively, if gusperimus aims to focus on those existing more infrequent cases refractory or intolerant to "standard treatment", it should be ensured that no other options are left, which is highly questionable for the vast majority of the patients included in study 102.

The applicant will be invited to provide an oral explanation to the CHMP at the time the Committee will discuss the responses to the List of Outstanding Issues.