Effect of inflammation on pharmacokinetics of posaconazole

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PROTOCOL TITLE

Effect of inflammation on pharmacokinetics of posaconazole

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Independent expert (s)	***Not applicable***
Laboratory sites	***UMCG***
Pharmacy	***UMCG***

PROTOCOL SIGNATURE SHEET

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
VCZ	**Voriconazole**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Posaconazole is indicated for prophylaxis of invasive aspergillosis and can also be used as treatment of several fungal infections. Therapeutic Drug Monitoring (TDM) of posaconazole can be performed to maintain efficacy, since exposure-respons relationships are described for posaconazole (ref Dolton AAC 2012: mail Marieke). Recently was shown that the plasma concentration of another antifungal agent, voriconazole, is influenced by inflammation, measured by C-reactive protein value [van Wanrooy *et al* AAC 2014, Encalada Ventura *et al* AAC 2015; manuscript in preparation of study with clinical trials.gov identifier NCT02074462]. During severe inflammation the metabolism of voriconazole is reduced via downregulation of cytochrome P450 enzymes, which results in high voriconazole plasma concentrations. Subsequently, dosages can be adjusted to avoid toxicity. However, if the degree of inflammation decreases again, the metabolism of the drug increases with as a result possible subtherapeutic drug concentrations. As posaconazole is only metabolized in limited extend by cytochrome P450 enzymes it is likely that posaconazole is not influenced by inflammation. However, no published data is available to support the hypothesis that exposure of posaconazole is not influenced by inflammation. Data on stable posaconazole exposure during treatment will result in a clinical benefit over voriconazole.

Objective: The objective of this study proposal is to determine if posaconazole drug exposure is influenced during different stages of inflammation.

Study design: A prospective observational study will be performed at the University Medical Center Groningen, the Netherlands to determine if posaconazole drug exposure is influenced by inflammation.

Study population: patients receiving posaconazole for treatment or (secondary) prophylaxis of fungal infections

Intervention (if applicable): none

Main study parameters/endpoints: Main study parameter is the posaconazole drug exposure during different stages of inflammation. Subsequently, a multiple linear regression model that describes the contribution of inflammation on posaconazole levels will be developed. At last, the relation between the change in CRP and change in drug plasma concentration from this study will be compared with the results of our earlier prospective voriconazole study [NCT02074462] based on matched patients.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: no risk or burden for the patients as samples from routine patient care

are used. Future patients may benefit from the results of this study, as more insight is given in the pharmacokinetics of posaconazole.

1. INTRODUCTION AND RATIONALE

Invasive aspergillosis (IA) is the leading cause of infection-related death in patients with acute leukemia and in hematopoietic stem cell transplant (HSCT) recipients. Various pathophysiological changes in severely ill patients, such as cancer patients, can affect the pharmacokinetics of antimicrobial agents. Adequate posaconazole drug exposure is associated with better treatment outcome. Until recently, posaconazole drug absorption was compromised by drug-drug interactions and insufficient food intake. This resulted in substantial intra- and interindividual patient variability in the pharmacokinetics of posaconazole [Dolton *et al* AAC 2014, Brüggemann *et al* CID 2009, Alffenaar *et al* CID 2009, Dolton *et al* AAC 2012, Vaes *et al* AAC 2012, Tonini *et al* AAC 2012]. The introduction of the new oral formulation and intravenous preparation improved drug exposure. [Maertens *et al* AAC 2014, Kraft *et al* AAC 2014].

For voriconazole it was recently shown by our group that metabolism of voriconazole was influenced by severe inflammation, measured by C-reactive protein value [van Wanrooy *et al* AAC 2014, Encalada Ventura *et al* AAC 2015; manuscript in preparation of study with clinical trials.gov identifier NCT02074462]. The underlying mechanism was cytokine induced down regulation of cytochrome P450 expression. The reduced metabolism resulted in voriconazole plasma concentrations exceeding the therapeutic window of voriconazole posing the patient at risk for toxicity. Subsequently, dosages were adjusted to remain the voriconazole plasma concentration within the therapeutic window. However, when the degree of inflammation decreased and thereby the metabolism of voriconazole increased, patients were at risk for subtherapeutic drug concentrations. Therefore, it was concluded that inflammation should be taken into account when therapeutic drug monitoring of voriconazole is performed.

As posaconazole is only metabolized in limited extend by cytochrome P450 enzymes it is likely that posaconazole is not influenced by inflammation. However, no published data is available to support the hypothesis that exposure of posaconazole is not influenced by inflammation. Data on stable posaconazole exposure during treatment will result in a clinical benefit over voriconazole.

2. OBJECTIVES

Primary Objective:
The objective of this study proposal is to explore the posaconazole drug exposure during treatment in different stages of inflammation.

Secondary Objective(s):

The secondary objective is to develop a multiple linear regression model to describe the contribution of inflammation to the variability in posaconazole concentration. Subsequently, the relation between change in CRP and change in drug plasma concentration from this

study will be compared with the results of our earlier prospective voriconazole study [NCT02074462] based on matched patients.

3. STUDY DESIGN

A prospective observational study will be performed at the University Medical Center Groningen, the Netherlands using longitudinal data collection to develop a dosing algorithm based on data of inflammatory markers and posaconazole concentrations.

4. STUDY POPULATION

4.1 Population (base)

Patients that receive posaconazole for treatment or (secondary) prophylaxis of fungal infections

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
-aged ≥ 18 yrs
-receive posaconazole
-written informed consent

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
-concomitantly using a strong inhibitor or inducer of CYP P450

4.4 Sample size calculation

To be able to develop and validate a model based on inflammatory markers and posaconazole multiple data points are mandatory. We estimate that it is feasible to collect 3-4 data points per treatment week.

Taken into account the non-invasive nature of this study, the routine sampling of critically ill patients we plan to recruit 30 patients for this study.

5. TREATMENT OF SUBJECTS

Subjects receive posaconazole as standard treatment or (secondary) prophylaxis for fungal infection. As the treatment with posaconazole and TDM are part of routine care they are neither initiated nor altered for study purposes (no intervention). Therefore this study is not being subjected to Medical Research Involving Human Subjects Act. Only data of standard care and TDM will be collected to develop the dosing algorithm for posaconazole during severe inflammation.

Attending physicians are allowed to request drug concentration measurement for patient care. If the posaconazole concentration is low the attending hospital pharmacist will provide the attending physician with a dosage advice. Dosages will be increased if levels are too low or decreased if levels are too high. The increase or decrease of the dosage will be based on the measured concentration, initial dosage and patient characteristics. Follow up will be performed to assure that the level reaches and remains in the therapeutic window.

5.1 Investigational product/treatment

Not applicable

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT

Not applicable; subject receive posaconazole as standard treatment or (secondary) prophylaxis for fungal infection

6.1 Name and description of investigational product(s)

Noxafil 100mg Tablet; Noxafil 300mg concentrate for solution for infusion; Noxafil 40 mg/mL oral suspension

6.2 Summary of findings from non-clinical studies

See SmPC of Noxafil

6.3 Summary of findings from clinical studies

See SmPC of Noxafil

6.4 Summary of known and potential risks and benefits

Non due to the nature of this study

6.5 Description and justification of route of administration and dosage

Depending on choice of attending physician; IV or PO

6.6 Dosages, dosage modifications and method of administration

Depending on choice of attending physician, dosage modifications based on measured posaconazole concentrations are part of routine care.

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable because Noxafil is not considered a study drug. Data on administration of the drug will be collected from the medical chart.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

7.1 Name and description of non-investigational product(s)

Not applicable

7.2 Summary of findings from non-clinical studies

Not applicable

7.3 Summary of findings from clinical studies

Not applicable

7.4 Summary of known and potential risks and benefits

Not applicable

7.5 Description and justification of route of administration and dosage

Not applicable

7.6 Dosages, dosage modifications and method of administration

Not applicable

7.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable

7.8 Drug accountability

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Explore the posaconazole drug exposure during treatment in different stages of inflammation.

8.1.2 Secondary study parameters/endpoints (if applicable)

Develop a multiple linear regression model that describes the contribution of inflammation on posaconazole levels. Compare the relation between change in CRP

and change in drug plasma concentration from this study with the results of our earlier prospective voriconazole study [NCT02074462] based on matched patients drug plasma concentration from this study will be compared with the results of our earlier prospective voriconazole study [NCT02074462] based on matched patients.

8.1.3 Other study parameters (if applicable)

Not applicable

8.2 Randomisation, blinding and treatment allocation

Not applicable

8.3 Study procedures

-Patients starting on posaconazole treatment will be evaluated for inclusion.
-After informed consent is obtained medical data will be collected from the medical chart and plasma samples from routine analysis will be obtained.
-Samples for posaconazole and inflammatory analysis will be collected 3-4 times weekly during treatment. Inflammatory markers like CRP will be determined by the department of Clinical Chemistry of the UMCG. Other inflammatory markers of IL-6, IL-8 and procalcitonin will not be determined, since these markers are not routinely measured. Posaconazole plasma concentrations (trough levels) will be measured with a validated and externally tested LC-MS/MS method of analysis [Alffenaar *et al* J Chrom B 2009].

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

Any subject leaving the study will be replaced

8.6 Follow-up of subjects withdrawn from treatment

Not applicable

8.7 Premature termination of the study

Not applicable

9. SAFETY REPORTING

Because this study proposal does not consider an investigational drug and the use of posaconazole and TDM are part of routine care, safety reporting is not subjected to the procedures described in the Medical Research Involving Human Subjects Act.

Because the posaconazole is part of routine care safety reporting will be performed according to Dutch Law ('Geneesmiddelenwet' in English: Medication Act) to the The Netherlands Pharmacovigilance Centre Lareb.

9.1 Section 10 WMO event

Not applicable

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Reporting according to Dutch Law.

9.2.2 Serious adverse events (SAEs)

Reporting according to Dutch Law.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Reporting according to Dutch Law.

9.3 Annual safety report

Not applicable, only for investigational drugs

9.4 Follow-up of adverse events

Will be performed in routine patient care

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

Not applicable

10. STATISTICAL ANALYSIS

Descriptive analysis
The Mann-Whitney U test (continuous data) and the Fisher's exact test (binominal data) were used to assess possible differences between the patients, in terms of demographics, underlying disease, VCZ treatment, laboratory parameters and co-medication.

10.1 Descriptive statistics

Demographic characteristics of the patients will be described. Numerical variables will be summarized with medians and interquartile range and categorical variables as frequencies and percentages.

10.2 Longitudinal data analysis

The longitudinal data of the posaconazole concentration will be analyzed with a linear mixed model. A log transformation will be performed if the data are not normally distributed. A random additive effect will be selected for patients to address different concentrations between patients. A first-order autoregressive correlation between posaconazole trough concentrations over time will also be selected to correct for differences in intervals between observations. To investigate the effect of inflammation on posaconazole concentration, the Wald type III test will be conducted after correcting for gender, age, posaconazole dose and route of administration, liver enzymes (ALP, ALAT, ASAT, γ-GT and total bilirubin) and the use of interacting co-medication. The analysis will be performed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). A p value < 0,05 is considered statistically significant.

10.3 Other study parameters

Not applicable

10.4 Interim analysis (if applicable)

Not applicable

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki.

No approval by the local ethical committee will be required, in accordance with Dutch Law (Medical Research Involving Human Subjects Act) due to the nature of this study

11.2 Recruitment and consent

After treatment with posaconazole is started by the attending physician, he or she informs the patient or representative of the patient, if the patient is not capable of giving informed consent, according to article 6 paragraph 1c of the WMO about the study. The patient or representative is allowed 48 hours for consideration of participation to the study. Written informed consent is obtained from the patient or the representative by the research nurse, study physician or investigator. The patient information letter and the informed consent form are attached.

11.3 Objection by minors or incapacitated subjects (if applicable)

In case of impaired consciousness or sedation, the patient is not able to object. The representative of the patient, according to article 6 paragraph 1c of the WMO, is then asked for informed consent. The representative of the patient is the legal representative, or (if no legal representative has been appointed) the person authorized in writing by the subject to act on his or her behalf, or (if no such person is available) the subject's spouse,

registered partner or other companion in life, thereafter the subjects parents, thereafter the subjects adult children and thereafter the adult siblings of the subject.

11.4 Benefits and risks assessment, group relatedness

No risks are related to this study as neither investigational drug is administered or intervention or invasive is performed. No benefit is expected for the participants.

11.5 Compensation for injury

As there is no additional risk for participation in this study, the METC of the UMCG granted exemption from liability insurance (art. 4 lid 1 Besluit verplichte verzekering bij medischwetenschappelijk onderzoek met mensen).

11.6 Incentives (if applicable)

None

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data and documents are handled confidentially. A subject identification code list is used to link the data to the subject. The key to the code is safeguarded by the investigator. The investigator and the project leader have access to the source data via a secured data folder. The handling of personal data meets the criteria of the dutch Personal Data Protection Act (Wbp).

12.2 Monitoring and Quality Assurance

Monitoring will be preformed by a QA officer of the department. Written informed consent, inclusion & exclusion criteria will be checked for every patient. Data collection will be checked for every 5^{th} patient.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The results of the study will be published without any restrictions to its content.

13. STRUCTURED RISK ANALYSIS

Not applicable

14. REFERENCES

1. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: Clinical practice guidelines of the infectious diseases society of america. Clin Infect Dis, **2008**; 46(3): 327-60.

2. Dolton MJ, Ray JE, Chen SC, Ng K, Pont LG, McLachlan AJ. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. Antimicrob Agents Chemother, **2012**; 56(9): 4793-9.

3. Park WB, Kim NH, Kim KH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: A randomized controlled trial. Clin Infect Dis, **2012**; 55(8): 1080-7.

4. Smith J, Safdar N, Knasinski V, et al. Voriconazole therapeutic drug monitoring. Antimicrob Agents Chemother, **2006**; 50(4): 1570-2.

5. Miyakis S, van Hal SJ, Ray J, Marriott D. Voriconazole concentrations and outcome of invasive fungal infections. Clin Microbiol Infect, **2010**; 16(7): 927-33.

6. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis, **2008**; 46(2): 201-11.

7. Pascual A, Csajka C, Buclin T, et al. Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: Population pharmacokinetics-based analysis of adult patients with invasive fungal infections. Clin Infect Dis, **2012**; 55(3): 381-90.

8. Trifilio S, Ortiz R, Pennick G, et al. Voriconazole therapeutic drug monitoring in allogeneic hematopoietic stem cell transplant recipients. Bone Marrow Transplant, **2005**; 35(5): 509-13.

9. Trifilio SM, Yarnold PR, Scheetz MH, Pi J, Pennick G, Mehta J. Serial plasma voriconazole concentrations after allogeneic hematopoietic stem cell transplantation. Antimicrob Agents Chemother, **2009**; 53(5): 1793-6.

10. Weiss J, Ten Hoevel MM, Burhenne J, et al. CYP2C19 genotype is a major factor contributing to the highly variable pharmacokinetics of voriconazole. J Clin Pharmacol, **2009**; 49(2): 196-204.

11. Jeu L, Piacenti FJ, Lyakhovetskiy AG, Fung HB. Voriconazole. Clin Ther, **2003**; 25(5): 1321-81.

12. Bruggemann RJ, Alffenaar JW, Blijlevens NM, et al. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. Clin Infect Dis, **2009**; 48(10): 1441-58.

13. Morgan ET. Regulation of cytochromes P450 during inflammation and infection. Drug Metab Rev, **1997**; 29(4): 1129-88.

14. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/pharmacodynamic profile of voriconazole. Clin Pharmacokinet, **2006**; 45(7): 649-63.

15. Alffenaar JW, Wessels AM, van Hateren K, Greijdanus B, Kosterink JG, Uges DR. Method for therapeutic drug monitoring of azole antifungal drugs in human serum using LC/MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci, **2010**; 878(1): 39-44.

16. Roffey SJ, Cole S, Comby P, et al. The disposition of voriconazole in mouse, rat, rabbit, guinea pig, dog, and human. Drug Metab Dispos, **2003**; 31(6): 731-41.