

Pharmacologic optimization of voriconazole -
a prospective clustered group-randomized
cross-over trial of therapeutic drug monitoring
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PROTOCOL TITLE

Pharmacologic optimization of voriconazole - a prospective clustered group-randomized cross-over trial of therapeutic drug monitoring

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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 (ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EORTC	European Organisation for Research and Treatment of Cancer
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 productinformatie 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
TDM	Therapeutic Drug Monitoring
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)
WMO	Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen)

SUMMARY

Rationale: Patients with haematological malignancies and chemotherapy induced prolonged neutropenia are at risk for severe bacterial and fungal infections. These opportunistic infections can result in prolonged hospital stay, increases costs and greater mortality. Voriconazole has now been recommended as the first line agent for invasive pulmonary aspergillosis (IA). Retrospective observational studies of voriconazole serum concentration suggest that serum concentration correlate with toxicity and clinical response. These observations were however made in small series of patients and data were collected retrospectively. These inherent methodological flaws make it impossible to draw definite conclusions about the effect of voriconazole serum concentration monitoring on the outcome of IA, and therefore considered insufficient proof to recommend voriconazole concentration determination in blood as standard of care. The impact that so-called serum concentration guided dosing of voriconazole will have on treatment success can only be evaluated through a prospective randomized clinical trial.

Objective: The objective of this study proposal is to determine whether pharmacologic optimization of voriconazole by means of therapeutic drug monitoring (TDM) results in improved patient outcomes (efficacy and safety) and is more cost-effective compared to the current standard of care.

Study design: we designed a prospective stratified cluster randomized cross-over trial of therapeutic drug monitoring in patients with haematological disease who have developed IA. The order of periods (TDM or standard of care, each 12 months) will be randomized per centre.

Study population: Patients with haematological malignancies and possible, probable or proven IA according to EORTC criteria.

Intervention (if applicable): In the intervention group the voriconazole dosage will be adjusted to achieve trough blood concentrations in a predefined window of 2-5 mg/L. In the control group voriconazole will be dosed according to product leaflet.

Main study parameters/endpoints: The primary clinical endpoint will be a global response consisting of a combined endpoint of toxicity and response to therapy (clinical, microbiologic and radiologic responses) 28 days after starting treatment with voriconazole. A sample size of n=192 is needed to detect a 20% absolute reduction in the number of

treatment failures (40% to 20 %) compared to control. It total 200 patients will be included to compensate a loss during follow up. A cost-effectiveness analysis will be performed from a hospital and societal perspective. The cost effectiveness ratio will depict the extra amount of money, which has to be invested to prevent the therapeutic failure for a single patient, with TDM guided voriconazole treatment compared to standard of care.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There is no additional risk compared to standard of care. The study is designed to optimize standard of care by dosing on serum concentration and therefore possibly preventing side effects and increasing efficacy. The extra sample needed for TDM are no extra burden as these patients are often monitored for clinical or pharmacological parameters. The sample is taken during regular sampling for routine laboratory parameters like electrolyte, hepatic function etc. The advantage of choosing this sampling moment (early morning) is that no extra vena puncture has to be performed.

1. INTRODUCTION AND RATIONALE

Patients with prolonged and severe neutropenia (neutrophils $<0.5 \times 10^9/L$ for >10 days), are at risk for life-threatening infections especially invasive pulmonary aspergillosis. The risk of invasive Aspergillosis (IA) increases with the severity and duration of neutropenia. Patients treated for haematologic malignancies with intensive chemotherapy and hematopoietic stem cell transplant recipients are at particularly high risk [6-10]. Other risk factors for IA include Graft-Versus-Host Disease and its treatment with corticosteroids, previous invasive mould infection and high environmental exposure to fungal spores in ambient air [11-14]. As the reported response to antifungal therapy is low (50%) and mortality high (30-50%) there is still an urgent need to improve treatment [23-25].

Every year, about 200 patients in the Netherlands with haematological malignancies, are treated with voriconazole for invasive fungal infection. This translates into 15-25 patients per centre annually. When patients encounter an invasive fungal infection the chemotherapy for the haematological malignancy is often interrupted or sometimes continued in a reduced intensity. This results in a suboptimal treatment of the underlying malignancy. The results of antifungal therapy are far from optimal with response rates for voriconazole and lipid amphotericin B being approximately 50%. The overall mortality at 12 weeks is still 30-50%. Clearly, there is a dire need to improve treatment outcome for IA. Haematologists, in consultation with an infectious diseases specialists, medical microbiologists and hospital pharmacists put effort in optimizing treatment in this critically ill patient population.

Voriconazole is the first line treatment of IA among patients with haematological malignancies and hematopoietic stem cell transplant recipients according to recent international guidelines [43] as reported in a large randomised trial [16]. Recent observational studies suggest that voriconazole serum concentrations of at least 1 to 2.0 mg/L are associated with improved clinical outcome [18, 19, 42]. This clinical finding is supported by the in-vitro susceptibility of *Aspergillus fumigatus* to voriconazole [20]. On the other hand high trough concentrations exceeding 5 mg/L are associated with toxicity, mainly neurological and hepatotoxicity [40, 42,46]. It has also been shown that the inter-individual variation of voriconazole plasma levels is significant due to hereditary factors that influence the rate of clearance of the drug. Consequently, the guidelines for the treatment of IA published recently by the Infectious Diseases Society of America (IDSA) recommend monitoring of voriconazole concentration levels and adjusting dosage accordingly as an option for patients not responding to the standard weight-based dosing of voriconazole. This may be caused by sub-therapeutic serum concentrations or treatment discontinuation due to side effects that might be caused by toxic serum concentrations. Monitoring of serum

concentrations and adjusting the dose will be an alternative to switching to other antifungal agents such as a lipid formulation of amphotericin B, caspofungin or posaconazole [43].

Furthermore, voriconazole treatment is relatively expensive itself (€400/day for parenteral treatment) and suboptimal use can be expected to result in therapeutic failure, and additional costs incurred by the need for more expensive salvage antifungal therapy and prolonged hospital stay. We hypothesize that dosing of voriconazole based on serum concentration (so-called therapeutic drug monitoring) will result in improved clinical outcome of patients with IA, by reducing the risk of therapeutic failure and toxicity and that this will be cost-effective [39, 41, 43]. A multi-center randomized controlled clinical trial was designed to test this hypothesis [21, 22, 41].

As too low (< 2 mg/L) or too high (> 5 mg/L) voriconazole serum concentrations are observed in 25-60% and 10-25% of patients respectively TDM has the potential to improve treatment outcome. Optimizing antifungal therapy through concentration based dosing of voriconazole fits within the theme of pharmacotherapy as it is likely to optimize efficacy of treatment in the individual patient. This approach could be cost-effective through the prevention of toxicity and treatment failure that requires the use of more expensive antifungal agents for salvage therapy. At present, no randomized trials have addressed the question whether the use of TDM improves the outcome of voriconazole therapy. We hypothesize that therapeutic failure, now estimated around 40% can be reduced by half - i.e., to 20% using TDM. Failure is defined clinically. In a previous randomised trial with voriconazole in a dosage according to product leaflet the response to therapy was: complete in 20%, partial in 30%, stable infection in 10% and progressive infection (failure) in 40% [16]. As TDM is most likely to benefit patients with low voriconazole trough levels who are not responding or in patients with high trough levels who stopped because of side effects a reduction of failure from 40% to 20% can be anticipated to occur with TDM.

At present, there is a paucity of well-conducted studies on the added value and cost-effectiveness of TDM in general [26,27], and no data exists on the costs-effectiveness of TDM in patients with IA in particular. The costs of TDM in the present study proposal are estimated to be between €315 and €790 per patient per treatment episode, depending on the time elapsed until an adequate voriconazole serum level is reached. The costs of voriconazole may be higher in the early phase of therapy compared to the standard dosing scheme, due to an increase in dosage. However, in the latter phase of therapy these costs could be reduced by a switch from intravenous to oral therapy, or a shorter duration of treatment as a consequence of a better response to treatment. Furthermore, an increase in

treatment response will obviate the use of more expensive alternative antifungal drugs as salvage therapy. The costs of oral voriconazole are about €70 a day (200mg bid), compared to €540 a day for intravenous therapy (4 mg/kg bid). In a retrospective study management costs of 80 IA cases among 269 patients with AML-MDS patients undergoing intensive chemotherapy were assessed. IA was categorized according to revised EORTC-MSG definitions. Costs were documented from a hospital and societal perspective. Treatment with voriconazole was given orally from day 1 onwards whenever oral intake was possible. Total IA-related management costs were €10765 and €26182 respectively for possible and probable/proven IA. Based on these findings and the available literature [16,17], we hypothesize that treatment based on TDM will reduce the mean length of hospital stay by 3 days per patient, saving about € 1500 per patient per treatment course. Earlier transfer from the intensive care unit to the hospital ward will save an additional €1250 per patient per day. In addition, we expect fewer drug related adverse events and therapeutic failure in the TDM episode, which will lead to less additional diagnostic testing and additional therapy. Preventing the switch to more expensive antifungal therapy can save €200-500 per day of treatment. This will have a positive effect on the balance between costs and benefits.

2. OBJECTIVES

Primary objective

The aim of this study is to demonstrate a 20% absolute reduction in the number of treatment failures (40% to 20%) with the use of voriconazole therapeutic drug monitoring in patients with haematological malignancies suffering from invasive Aspergillosis.

Secondary objective

In addition we want to study the balance between costs from hospital and societal perspective and effects.

3. STUDY DESIGN

As the number of patients treated for invasive aspergillosis in each hospital is limited, a multi centre set up is required to have a study powered to detect a clinically relevant difference in outcome between the intervention group and the control group. For this study a cluster randomized design - instead of a randomisation at patient level - was chosen to minimize logistic problems, optimize inclusion of patients and limit bias during the study. Blinding the intervention would increase the costs of the study considerably without providing better results. The cross-over design was chosen to diminish influences by centre, as the inter-centre variability in facility and treatment can influence outcome of treatment. Differences which are found can now be attributed solely to the intervention as the centre serves as its own control. As this study will be performed in several centres with random start with standard care or with TDM-tailored treatment, we anticipate that the time-based biases will be negligible. To diminish the carry-over effect from one period to the next a wash-out period of 28 days is established, which equals the time of start of treatment until evaluation on the primary endpoint. This prevents that two treatment protocols, intervention and control are operational at the same time. For these reasons we choose a cluster randomized cross-over design in which every cluster receives both interventions during two consecutive periods (TDM and standard care, 12 months each). This longitudinal design was previously successfully used in the Netherlands [32]. Randomization by a computer-generated randomization system determines the sequence within in each cluster. In this way the variability between clusters is taken into account, this results in an improved power. The randomization will be stratified to obtain equally balanced clusters with respect to experience and size. At six months, inclusion will be evaluated and it will be estimated whether duration per period has to be increased or decreased and whether the clusters are still balanced. The intervention (TDM) consists of taking serum samples at day three of treatment, measuring the voriconazole serum levels and adjusting the dosage to reach the therapeutic window. Dosing of voriconazole will be done during the control period according to the product brochure.

Response to treatment will be evaluated at day 7 (fever), day 28 (primary endpoint) and at 12 weeks after start of therapy (mortality). Assessment of quality of life will be performed after release from the hospital at different time points (2 weeks, 3 months, 6 months and 1 year). Cost effectiveness from hospital perspective will be evaluated after release from the hospital. Cost effectiveness from societal perspective will be evaluated after 1 year after start of the treatment.

An expert panel (EPHO) of three specialists in the field of haemato-oncology, radiology, and mycology, and who are unaware of allocation to either of the two arms of the study (intervention or control), will classify all documented aspergillosis according to the EORTC/MSG criteria [33,45] and will report the likelihood whether fever was caused by: drug fever (e.g. cytarabine), mucositis, malignancy, Graft –Versus-Host Disease, or infection and a likelihood whether mortality was caused by fungal infection or progression of malignancy or any other cause, using protocol-defined criteria. Likelihood will be presented on a scale of 0/3 till 3/3. The evaluation of endpoints by an independent expert panel excludes investigators' bias [34, 35]. At the end of the study the EPHO, unaware of allocation to either of the two arms of the study (intervention or control), will review each patient on the primary and the following secondary endpoints 1, 2, 5 and 6. After the review of the independent expert panel the multi disciplinary study team, consisting of haematologists, infectious diseases specialists, radiologists, pharmacists, medical microbiologists, a biostatistician and a MTA expert will analyze the data on all endpoints using the outcome of the pre-screening of the expert panel.

4. STUDY POPULATION

4.1 Population (base)

There is a considerable variability in host-specific factors in the targeted population of this study resulting in a heterogeneous population. Reducing the heterogeneity of the population or stratification for all key variables [28] will result in an inadequately powered study due to a lack of sufficient numbers of eligible subjects. However, due to participation of 13 centre's we are able to reduce variability in patients by narrowing the inclusion criteria, (i.e. exclusion of the group *other patients* (non-hematological malignancies and solid organ transplant recipient)) compared to the study conducted by Herbrecht et al [16]. In previously conducted randomized controlled trials, stratification was performed for risk of infection and antifungal prophylaxis [17]. As diagnosing invasive fungal disease is difficult, the EORTC/MSG, defined three levels of probability of invasive fungal disease: possible, probable or proven invasive fungal disease. These definitions will be used in this study at baseline and again at the end of treatment.

In the Netherlands each year 100 patients are classified as possible, 70 patients as probable and 30 as proven IA. Most of these patients are treated in University Medical Centres, but larger peripheral centres also treat these patients. Due to competing studies from the pharmaceutical industry a part of these potentially eligible subjects will not be included. Due to the more strict in- and exclusion criteria, and refusal to consent, the number of subjects included in these studies will be relatively small. However, some of the eligible study participants will not participate as they refuse informed consent. If these two combined count for half of the patients that are potentially eligible to participate in this study, the number of study participants left to participate in this trial will be sufficient, as by virtue of the trial design of this study proposal, very few patients are expected to drop out.

4.2 Inclusion criteria

- 1) are at least 18 years of age
- 2) have received chemotherapy for haematological malignancies or have received a hematopoietic stem cell transplant
- 3) proven, probable or possible invasive fungal disease according to the EORTC/MSG criteria
- 4) treatment with voriconazole

4.3 Exclusion criteria

- 1) allergic to voriconazole or its excipients
- 2) age below 18 years

4.4 Sample size calculation

In a previous randomized trial with voriconazole in a dosage according to product leaflet with similar inclusion criteria the response was: complete in 20%, partial in 30%, stable in 10% and failure in 40% [16]. As TDM will probably result in the largest benefit in patient with low voriconazole trough levels, who are not responding, or in patients with high trough levels, who stopped because of side effects, the sample size calculation of this study is based on the reduction of patients failing on voriconazole therapy. For control patients (treated without TDM) a failure rate of 40% is expected [16], while for patients during the experimental TDM episode, a failure of 20% is expected. Under the most unfavourable assumption that the intra cluster correlation coefficient equals the intra period correlation coefficient varying between 0.002 and 0.02, and knowing that at least 12 centres are participating in this study, each cluster must include 16 patients to obtain a power of about 80% with an unreliability of 5% (two-sided) to detect a clinically relevant improvement of 20% of reduction of patients failing on voriconazole at day 28 of treatment compared to control. This means that in total 192 patients are necessary for performing this study. To compensate for loss during follow-up in total 200 patients will be included. Loss during follow-up is defined as patients not willing to continue participation because of personal reasons. Patient stopping because of voriconazole adverse effects are noted as "failure".

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The intervention (TDM) consists of taking serum samples at day three of treatment, measuring the voriconazole serum levels and adjusting the dosage to reach the therapeutic window. Dosing of voriconazole will be done during the control period according to the product brochure.

Voriconazole is registered for treatment of invasive Aspergillosis. Product leaflet is added as attachment,

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Name and description of investigational medicinal product

Vfend® (voriconazole); ampul 200mg; tablet 200mg; suspension 40mg/ml.

6.2 Summary of findings from non-clinical studies

See attached 1B brochure

6.3 Summary of findings from clinical studies

See attached 1B brochure

6.4 Summary of known and potential risks and benefits

See attached 1B brochure

6.5 Description and justification of route of administration and dosage

See attached 1B brochure for route of administration for both groups and for starting dosage in both group (6mg/kg IV bid; 400mg PO bid) and for maintenance dose in control group (4mg/kg IV bid; 200mg PO bid)

As in daily practice serum concentration levels are measured for toxicity or therapeutic failure, the attending physician may request a concentration level. This request is subjected to a protocol: toxicity (rise in liver enzymes > 5 times upper level of normal values, after starting voriconazole), failure (no clinical, microbiological or radiological response after 7 days of treatment with voriconazole).

6.6 Dosages, dosage modifications and method of administration

Dosage modification in intervention group:

In a previous randomised trial with voriconazole in a dosage according to product brochure the response to therapy was: complete in 20%, partial in 30%, stable infection in 10% and progressive infection (failure) in 40% [16]. As too high (occurring in 10-25% of cases) or too low (25-60%) voriconazole serum concentrations can potentially be avoided by TDM guided dosing the percentage of subtherapeutic and toxic voriconazole concentrations can be reduced from 25-60% and 10-25% respectively to < 10%. As TDM is most likely to benefit patients with low voriconazole trough levels who are not responding or in patients with high trough levels who stopped because of side effects a reduction of failure from 40% to 20% can be anticipated to occur with TDM. During the TDM episode, the voriconazole dosage will be adjusted to achieve trough serum concentrations in a predefined window of 2-5 mg/L. Voriconazole serum concentrations after the 5th dosage (IV 6mg/kg for the first 24 hours followed by 4mg/kg bid, PO 400mg for the first 24 hours followed by 200mg bid) will be measured in all patients during

treatment with voriconazole during the TDM period. Two blood samples will be drawn, one immediately before the dose ($t=0$) and one 2h after the dosage ($t=2$) when administered orally or 1h after the end of infusion when administered intravenously. If the serum trough level is < 2.0 mg/L the dosage will be increased. If the serum trough level is > 5 mg/L the dosage will be reduced. Dosage adjustment will be performed according to a standard algorithm. Three days after dosage adjustment a control sample series is drawn, followed by the same dose adjustment algorithm. After reaching the therapeutic window trough levels, surveillance samples will be drawn twice a week while the patient is in the hospital. For outpatient treatment trough levels will be drawn at regular visits of the patients to the outpatient clinic (about once every two weeks). Since outpatients are clinically more stable, fluctuations are expected to be less frequent, moreover patients are often put on voriconazole during hospital stay and have a stable level when leaving the hospital.

6.7 Preparation and labelling of Investigational Medicinal Product

Not applicable

6.8 Drug accountability

Not applicable

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

Defining the primary endpoints in a heterogeneous study population is difficult. A combined endpoint (global response) consisting of clinical, microbiological and radiological response to therapy has been previously used previously and is well accepted in clinical trials investigating the efficacy of antifungal agents [17, 29-31]. The global response, consisting of a combination of clinical, microbiological and radiological responses on day 28 of treatment, will be categorized as one of the following four possible outcomes:

- 1) Complete Response: resolution of all clinical signs and symptoms and more than 90 percent of the IA related lesions that were visible on radiographic studies at baseline;
- 2) Partial Response: Clinical improvement and greater than 50 percent improvement in radiological findings present at baseline;
- 3) Stable: No change from baseline, or an improvement of less than 50 percent in radiological findings;
- 4) Failure: Worsening disease and death

The primary endpoint is a reduction in risk of failure on voriconazole therapy. This failure is based on the categorized global response.

7.1.2 Secondary study parameters/endpoints (if applicable)

- 1) mortality at day 28 and week 12 of therapy due to fungal infection, overall mortality at 28 days and 12 weeks.
- 2) resolution of neutropenic fever, defined as percentage of patients with a oral temperature of $<38\text{ }^{\circ}\text{C}$ at day 7 of voriconazole treatment [17]; time (in days) to resolve fever is also noted.
- 3) percentage of voriconazole serum concentrations within the targeted window of 2-5mg/L during therapy based on repeated measurements in time.
- 4) percentage switched to salvage therapy (i.e. amphotericin B or one of its lipid or liposomal formulations; or echinocandin (e.g., caspofungin/anidulafungin) or other triazole (e.g., posaconazole); or measured concentration level in control arm during treatment for toxicity or failure)

- 5) side effects (visual disturbance and liver enzymes) Side effects leading to drug discontinuation.
- 6) time (in days) of to global response as defined under the primary endpoint definition after the start of voriconazole
- 7) The evaluation of cost-effectiveness (hospital and societal per perspective) of voriconazole TDM in patients with invasive aspergillosis will be an integral part of this project.

7.1.3 Other study parameters (if applicable)

A set of patient characteristics and clinical parameters is used for baseline characteristics of the control and intervention group:

- age, gender, weight, BMI
- parameters for EORTC/MSG classification
- underlying medical condition and previous/ongoing treatment for haematological malignancies
- co-medication: agents which influences pharmacokinetics of voriconazole, immunosuppressive agents (corticosteroids, ciclosporin, MMF)
- Pharmacogenetics (CYP450 2C9 and 2C19)
- For the economical evaluation (cost effectiveness if TDM) of this study the costs of both treatment arms are evaluated. The costs of hospital and ICU stay, diagnostic procedures, used medication and blood product are evaluated, Also quality of life and production loss is evaluated after release from the hospital.
- for detailed information see CRF.

7.2 Randomisation, blinding and treatment allocation

Randomization by a computer-generated randomization system determines the sequence within in each cluster (TDM of standard of care).

7.3 Study procedures

- 1) At day two of fever the patients is informed about the study and a 24 hour period is given to think of participation.
- 2) The haematologist, in consultation with a medical microbiologist or infectious diseases specialist, will decide to start voriconazole therapy in a patient with suspected IA based on EORTC/MSG criteria. A HRCT scan is crucial part of the procedure for diagnosing the invasive fungal disease. Triggers for ordering an HRCT include detection of galactomannan in serum or plasma, pulmonary complaints or abnormalities seen on X-ray and unexplained fever of > 4 days despite broad-spectrum antibiotic therapy. A HRCT is performed at start of voriconazole treatment +/- 3 days.
- 3) Voriconazole serum concentrations after the 5th dosage (IV 6mg/kg for the first 24 hours followed by 4mg/kg bid, PO 400mg for the first 24 hours followed by 200mg bid) will be measured in all patients during treatment with voriconazole during the TDM period. Two blood samples will be drawn, one immediately before the dose (t= 0) and one 2h after the dosage (t=2) when administered orally or 1h after the end of infusion

when administered intravenously. If the serum trough level is < 2.0 mg/L the dosage will be increased. If the serum trough level is > 5mg/L the dosage will be reduced. Dosage adjustment will be performed according to a standard algorithm. Also a sample (5ml) will be drawn to assess CYP450 2C9 and 2C19 polymorphisms.

- 4) Three days after dosage adjustment a control sample series is drawn, followed by the same dose adjustment algorithm.
- 5) After reaching the therapeutic window trough levels, surveillance samples will be drawn twice a week while the patient is in the hospital. For outpatient treatment trough levels will be drawn at regular visits of the patients to the outpatient clinic (about once every two weeks). Since outpatients are clinically more stable, fluctuations are expected to be less frequent, moreover patients are often put on voriconazole during hospital stay and have a stable level when leaving the hospital. In the period without TDM, serum samples will be stored and used later to evaluate serum trough levels during the standard care episode. During this period, no additional vena punctures will have to be performed for the purpose of the study as the blood samples will be taken during regular sampling on the morning round. In total 16-54ml will be drawn depending on the duration of treatment.
- 6) After release from the hospital the patient receives at 2 weeks, 3 months, 6 months and 1 year after release a questionnaire to assess the quality of life and production loss.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. Withdrawal from the study means that the patient does not allow the investigator to use the medical data for study purposes (intervention group) or does not allow the investigator to use the medical data for study purposes and taking control samples (control period).

7.4.1 Specific criteria for withdrawal (if applicable)

7.5 Replacement of individual subjects after withdrawal

7.6 Follow-up of subjects withdrawn from treatment

7.7 Premature termination of the study

If evidence from this study or from other studies (grade A1) becomes available that therapeutic drug monitoring of voriconazole is better or worse than dosing according to dosing according to product leaflet the proceeding of the study will be discussed and the METc will be informed.

8. SAFETY REPORTING

8.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

8.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational drug. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose results in death;

- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported to the accredited METC that approved the protocol, according to the requirements of that METC.

8.2.1 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or

severity, is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product).

The sponsor will report expedited the following SUSARs to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trial of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The sponsor will report expedited all SUSARs to the competent authority, the Medicine Evaluation Board and the competent authorities in other Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

8.2.2 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

8.4 Data Safety Monitoring Board (DSMB)

An independent expert panel (EPHO) of three specialists in the field of haemato-oncology, radiology, and mycology, and who are unaware of allocation to either of the two arms of the study (intervention or control), will classify all documented aspergillosis according to the EORTC/MSG criteria. This independent expert panel will also be involved in safety follow up (toxicity differences between the two arms) and premature termination of the study (grade A1 evidence that TDM of voriconazole improves outcome).

9. STATISTICAL ANALYSIS

The endpoints with respect to percentages at day 7, day 28 (including the primary endpoint) and at 12 weeks will be analyzed using hierarchical models where intervention effects, (random) cluster effects, and random cluster-period effects will be analyzed. Time to events (for example response or death) will be analyzed using Kaplan Maier curves with log rank tests and Cox regression models.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version, date, see for the most recent version: www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts

10.2 Recruitment and consent

For this study a cluster randomized design - instead of a randomisation at patient level - was chosen to minimize logistic problems, optimize inclusion of patients and limit bias during the study. The cross-over design was chosen to prevent influences by center, as the inter-center variability in facility and treatment can influence outcome of treatment. Differences which are found can now be attributed solely to the intervention as the center serves as its own control. As this study will be performed in several centres with random start with standard care or with TDM-tailored treatment, we anticipate that the time-based biases will be negligible. This design was previously successfully used in the Netherlands [32]. Following the design of this study a patient does not have to specially recruited for start of the treatment. So no informed consent has to be asked for starting the treatment. The physician asks the patients at day two of fever via regular procedures, commonly used for EORTC/HOVON studies whether clinical data can be used for study purposes and additional in the control group whether control samples can be drawn. If the patient agrees the data is used, if not data are not used. For this decision a regular time of 1 day is given to the patient to think of participation.

10.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

10.4 Benefits and risks assessment, group relatedness

Retrospective observational studies of voriconazole serum concentration suggest that serum concentration correlate with toxicity and clinical response. The objective of this study proposal is to determine whether pharmacologic optimization of voriconazole by means of therapeutic drug monitoring (TDM) results in improved patient outcomes (efficacy and safety) and is more cost-effective compared to the current standard of care. The patients in the intervention population possibly benefit from the intervention, as toxicity and sub therapeutic concentration could be prevented. In the control group

patients receive standard of care. The latter group will also probably benefit from this trial as patients in trials tend to get more attention from medical staff.

10.5 Compensation for injury

As there is no additional risk for participation in this study the Medical Ethics committee of the UMCG granted exemption from liability insurance (art. 4 lid 1 Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen).

10.6 Incentives (if applicable)

Not applicable

11. ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents

Data is handled confidentially. A subject identification code list is used to link the data to the subject. The code is based on a clusternumber, abbreviation of the center and number of inclusion (e.g. 1-UMCG-12). The key to the code should be safeguarded by the investigator. The handling of personal data complies with the Dutch Personal Data Protection Act.

11.2 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

11.3 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.

11.4 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and

the competent authority 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 and the Competent Authority.

11.5 Public disclosure and publication policy

The CCMO statement regarding publication policy of the study results is subscribed.

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Appendix 1

Dosage algorithm UMCG

voriconazole trough level	dosage each 12 hrs (oral)				voriconazole trough level	dosage each 12 hrs (intravenous)			
	200mg*	250mg*	300mg*	400mg*		4mg/kg*	5mg/kg*	6mg/kg*	7mg/kg*
<0,1mg/L	400mg	400mg	400mg	500mg	<0,1mg/L	6mg/kg	7mg/kg	8mg/kg	8,5mg/kg
0.1-0.4mg/L	400mg	400mg	400mg	500mg	0.1-0.4mg/L	6mg/kg	7mg/kg	8mg/kg	8,5mg/kg
0.5-1mg/L	300mg	300mg	400mg	450mg	0.5-1mg/L	5mg/kg	6mg/kg	7mg/kg	8mg/kg
1-1,5mg/L	250mg	300mg	450mg	450mg	1-1,5mg/L	5mg/kg	6mg/kg	7mg/kg	8mg/kg
1.5-2mg/L	250mg	300mg	350mg	450mg	1.5-2mg/L	4,5mg/kg	5,5mg/kg	6,5mg/kg	7,5mg/kg
2-3.5mg/L	200mg	250mg	300mg	400mg	2-3.5mg/L	4mg/kg	5mg/kg	5mg/kg	6mg/kg
3.5-5mg/L	150mg	200mg	250mg	300mg	3.5-5mg/L	3mg/kg	4mg/kg	4mg/kg	5mg/kg
> 5mg/L	100mg	150mg	150mg	200mg	> 5mg/L	2mg/kg	3mg/kg	3mg/kg	4mg/kg

* = dosage given to patient at time of concentration measurement