

# An adaptive pharmacological approach for the individualisation of voriconazole antifungal therapy

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| <b>Submission date</b><br>14/07/2014   | <b>Recruitment status</b><br>No longer recruiting        | <input type="checkbox"/> Prospectively registered<br><input type="checkbox"/> Protocol            |
| <b>Registration date</b><br>24/10/2014 | <b>Overall study status</b><br>Completed                 | <input type="checkbox"/> Statistical analysis plan<br><input checked="" type="checkbox"/> Results |
| <b>Last Edited</b><br>12/06/2019       | <b>Condition category</b><br>Infections and Infestations | <input type="checkbox"/> Individual participant data  |

## Plain English summary of protocol

### Background and study aims

Progressive (invasive) fungal infections are a major cause of many diseases and even death in patients with tumors affecting the blood and in those needing a treatment called haematopoietic stem cell transplantation. Invasive fungal infections often prevent the affected patient being able to have chemotherapy or transplantation. New ways to give an ideal antifungal therapy are urgently required. A drug called Voriconazole can be used for the prevention of invasive fungal infections. Research suggests that voriconazole exhibits clinically relevant drug exposure-response and drug-exposure toxicity relationships. Invasive fungal infections are deadly; therefore it is important to monitor the drug intake to ensure individual patients drug exposures are ideal. But there are no computer programs that can tell us how much drug should be given and at what intervals that enable the correct dosage in a timely and optimally precise manner. A computer program for this purpose has been developed. The software is used to individualise voriconazole regimens in patients to ensure they achieve desired levels and are deemed by that clinician to be safe and effective. The aim of this study is to find out how safe and effective this computer software is.

### Who can participate?

Patients requiring treatment for invasive fungal infections..

### What does the study involve?

Patients are required to stay in hospital and receive treatment every 12 hours for 5 days. In addition, patients have 13 blood samples taken during treatment. As part of the standard treatment patients are required to return to hospital on day 14, and day 35. During these visits patients have a medical examination, a blood sample taken, provide details of any other medications they are taking and on day 35 they may have a CT scan.

### What are the possible benefits and risks of participating?

It is hoped that the treatments will help patients. However, this cannot be guaranteed. The information from this study may help to improve the future treatment of patients with invasive fungal infections. Voriconazole is generally well tolerated. The most common side effects

experienced with voriconazole are liver disturbances, visual disturbances, skin rash, neurological disturbances, cardiovascular events, blood disorders, kidney disturbances, fever, vomiting, nausea, diarrhoea, headache, peripheral oedema, abdominal pain. Patients are required to have extra blood tests as part of the study. These may cause some bruising and soreness however this should be minor.

Where is the study run from?

Royal Liverpool University Hospital (UK)

When is the study starting and how long is it expected to run for?

August 2014 to August 2016

Who is funding the study?

National Institute for Health Research (NIHR) (UK)

Who is the main contact?

Prof. William Hope

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## Contact information

### Type(s)

Scientific

### Contact name

Prof William Hope

### Contact details

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United Kingdom  
L69 3GE

## Additional identifiers

### Clinical Trials Information System (CTIS)

2013-002578-34

### ClinicalTrials.gov (NCT)

NCT01887457

### Protocol serial number

UoL001025

## Study information

### Scientific Title

An adaptive Pharmacological approach for the Individualisation of VOriconazole Antifungal therapy (PIVOTAL): a Phase II registered single-centre medical device study

## **Acronym**

PIVOTAL

## **Study objectives**

Increasing evidence suggests that voriconazole exhibits clinically relevant drug exposure-response and drug-exposure toxicity relationships. Trough concentrations  $< 1$  mg/L are associated with a higher probability of clinical failure, while trough concentrations  $> 5.5$ - $6$  mg/L are associated with a higher probability of toxicity. Invasive fungal infections are rapidly lethal; therefore, there are strong grounds to offer therapeutic drug monitoring to ensure individual patients drug exposures are optimal.

## **Ethics approval required**

Old ethics approval format

## **Ethics approval(s)**

NRES Committee North West – Liverpool Central, 09/12/2014, ref: 14/NW/1323

## **Study design**

Phase II registered single-centre medical device study

## **Primary study design**

Interventional

## **Study type(s)**

Treatment

## **Health condition(s) or problem(s) studied**

Invasive fungal infection

## **Interventions**

Voriconazole is administered over 5 days. Treatment will be given every 12 hours, each treatment will be given over 2 hours via an intravenous drip, so there will be ten 2-hour treatments in total. After consenting initially through part 1 of the consent patients will receive three of these treatments, which are the same as standard treatment.

In addition, five blood samples will be taken, one 10 ml sample before the second treatment and then 5 ml samples taken 1, 3, 6 and 12 hours after the second infusion. Half of the first sample will be stored for future research, the other samples will be used to identify the best dose.

In addition, 5 ml blood samples will be taken before the fifth and tenth treatments, and further 5 ml blood samples taken at 1, 3, 6 and 12 hours after the fifth and tenth treatments. The samples taken before and after the fifth dose will be used to identify the best dose. The samples taken before and after the tenth dose will be used to assess whether the dose given was effective.

## **Intervention Type**

Drug

**Phase**

Phase II

**Drug/device/biological/vaccine name(s)**

Voriconazole

**Primary outcome(s)**

The safety and efficacy of computer software to attain pre-defined plasma concentrations of voriconazole for immunocompromised patients. Successful therapy is a trough concentration of 1-3 mg/L at the end of the 10th dosing interval on day 10.

**Key secondary outcome(s)**

1. Toxicity of patients receiving individualised voriconazole dosing at 35 days
2. Mortality of patients receiving individualised voriconazole dosing at 35 days

**Completion date**

31/08/2017

**Eligibility****Key inclusion criteria**

1. Patients  $\geq 18$  years old
2. Patients where a new course of voriconazole is indicated for prevention or treatment of an invasive fungal infection
3. Patients with sufficient venous access to enable repeated blood samples
4. Estimated creatinine clearance  $\geq 50$  mL/min
5. Able to give written informed consent
6. Able to remain in the hospital for at least 5 days
7. Willing to use adequate contraception if necessary

**Participant type(s)**

Patient

**Healthy volunteers allowed**

No

**Age group**

Adult

**Lower age limit**

18 years

**Sex**

All

**Total final enrolment**

19

**Key exclusion criteria**

1. Estimated creatinine clearance < 50 mL/minute
2. Use of haemodialysis or haemofiltration
3. Hepatic insufficiency (Childs B or C)
4. Hepatitis with LFTs > three-times upper limit of normal
5. Pregnancy, breastfeeding or planning pregnancy during the study
6. Past history of intolerance to voriconazole
7. Microbiological evidence of resistance to voriconazole
8. QT prolongation (see 20.6 page 68)
9. Use of other medications that contraindicate the use of voriconazole
10. Hypersensitivity to voriconazole, its excipients or other triazole antifungal agents

**Date of first enrolment**

01/08/2014

**Date of final enrolment**

01/08/2016

## Locations

**Countries of recruitment**

United Kingdom

England

**Study participating centre**

University of Liverpool

Liverpool

United Kingdom

L69 3GE

## Sponsor information

**Organisation**

University of Liverpool (UK)

**ROR**

<https://ror.org/04xs57h96>

## Funder(s)

**Funder type**

Government

**Funder Name**

National Institute for Health Research (NIHR) (UK)

**Alternative Name(s)**

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

**Funding Body Type**

Government organisation

**Funding Body Subtype**

National government

**Location**

United Kingdom

## Results and Publications

**Individual participant data (IPD) sharing plan****IPD sharing plan summary**

Not provided at time of registration

**Study outputs**

| Output type                                   | Details                       | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|-------------------------------|--------------|------------|----------------|-----------------|
| <a href="#">Results article</a>               | results                       | 27/03/2019   | 12/06/2019 | Yes            | No              |
| <a href="#">HRA research summary</a>          |                               |              | 28/06/2023 | No             | No              |
| <a href="#">Participant information sheet</a> | Participant information sheet | 11/11/2025   | 11/11/2025 | No             | Yes             |