Clinical trial results:
Open label study of the efficacy and safety of isavuconazole for the treatment of Chronic Pulmonary Aspergillosis

Summary

EudraCT number	2016-003921-40
Trial protocol	GB
Global end of trial date	22 May 2015

Results information

Result version number	v1 (current)
This version publication date	09 February 2020
First version publication date	09 February 2020
Summary attachment (see zip file)	2016IF002 statement (2016IF002 early termination statement.docx)

Trial information

Trial identification

Sponsor protocol code	2016IF002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC reference: 17/NW/0298

Notes:

Sponsors

Sponsor organisation name	Manchester University NHS Foundation Trust
Sponsor organisation address	29 Grafton Street, Manchester, United Kingdom, M13 9WU
Public contact	Dr Lynne Webster, Manchester University NHS Foundation Trust, +44 161276 4125, research.sponsor@mft.nhs.uk
Scientific contact	Dr Lynne Webster, Manchester University NHS Foundation Trust, +44 161276 4125, research.sponsor@mft.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 May 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Isavuconazole is an antifungal agent that was recently approved for the treatment of invasive aspergillosis on the basis of non-inferior outcomes compared to the standard of care, voriconazole. Isavuconazole is associated with a lower incidence of side effects than current standard treatment with antifungal drugs. There are no data on the use of isavuconazole in chronic pulmonary aspergillosis (CPA). The trial hypothesis is that isavuconazole will be at least as effective and safe as current available therapy for CPA.

The primary objective of the study is to assess the efficacy and safety of isavuconazole in the treatment of CPA.

Protection of trial subjects:

The most common treatment-related adverse reactions are elevated liver chemistry (7.9%). These changes are not related to liver failure and rarely requires stopping of treatment. Monitoring of liver enzymes during treatment will be considered during study scheduled visits. Isavuconazole has a moderate effect on the ability of patients to drive and use machines. Patients will be advised to avoid driving or operating machinery if symptoms of confusional state, somnolence, fainting and/or dizziness are experienced. Patients on treatment will be seen in the clinic at regular intervals to check for the signs and symptoms of adverse reactions. Patients will be provided with supportive care to reduce the burden of the side effects. Female patients of childbearing age are advised to use effective methods of contraception to prevent pregnancy. Patients are screened for pregnancy at regular intervals during the scheduled visits. In case of overdose, there is no specific treatment but patients will be treated with supportive care and appropriate medical support will be provided . As a preventative measure and to check compliance, the patient diary and number of capsules taken and returned will be checked during each visit to ensure overdose has not occured and also to check if the patient is receiving adequate level of treatment.

Background therapy:

None.

Evidence for comparator:

N/A

Actual start date of recruitment	01 January 1900
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 99999
Worldwide total number of subjects	99999
EEA total number of subjects	99999

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	99999
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Potential participants will be identified through screening of the patients referred to the National Aspergillosis Centre by their local GP or consultant with suspected diagnosis of CPA. Potential participants who are deemed to be eligible or meeting the inclusion criteria will be provided with a participant information sheet.

Pre-assignment

Screening details:

Inclusion criteria:
1. Willing to give informed consent
2. Male or female aged 18 years plus
3. Diagnosed with CPA with azoles treatment indicated
4. Participants must not have received antifungals for treatment of CPA in the last 6 months and not for longer than 3 months
5. Sexually active females must agree to effective contraception

Period 1

Period 1 title	Isavuconazole (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This was an open label study with no active comparator or placebo so no blinding was to take place.

Arms

Arm title	Isavuconazole treatment

Arm description:

Eligible patients will be treated with isavuconazole (200mg) three times daily for 6 doses, followed by 200mg once daily. Patients will attend scheduled visits at 1, 2, 4, 6, 9, , 12, 16, 20, 24, 30, 36, 44 and 52 weeks of treatment and followed up for 6 months with two scheduled visits at 12 and 24 week after the end of treatment.

Arm type	Experimental
Investigational medicinal product name	Cresemba 100 mg hard capsules
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Eligible patients will be treated with isavuconazole (200mg) three times daily for 6 doses, followed by 200mg once daily. Patients will attend scheduled visits at 1, 2, 4, 6, 9, , 12, 16, 20, 24, 30, 36, 44 and 52 weeks of treatment and followed up for 6 months with two scheduled visits at 12 and 24 week after the end of treatment.

Number of subjects in period 1	Isavuconazole treatment
Started	99999
Completed	99999

Baseline characteristics

End points

End points reporting groups

Reporting group title	Isavuconazole treatment

Reporting group description:

Eligible patients will be treated with isavuconazole (200mg) three times daily for 6 doses, followed by 200mg once daily. Patients will attend scheduled visits at 1, 2, 4, 6, 9, , 12, 16, 20, 24, 30, 36, 44 and 52 weeks of treatment and followed up for 6 months with two scheduled visits at 12 and 24 week after the end of treatment.

Primary: Monitoring of clinical and biochemical evidence of toxicity throughout treatment period

End point title	Monitoring of clinical and biochemical evidence of toxicity throughout treatment period[1]

End point description:

End point type	Primary

End point timeframe:

Within treatment period

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This trial was terminated prior to opening at the trust.

End point values	Isavuconazole treatment			
Subject group type	Reporting group			
Number of subjects analysed	99999			
Units: 99999	99999			

Statistical analyses

No statistical analyses for this end point

Primary: Clinical and radiological evidence of response to treatment after 12 months of therapy , as assessed by response on chest CT scan and clinical response (assessed using the SGRQ) and classified as improvement, stability and deterioration

End point title	Clinical and radiological evidence of response to treatment after 12 months of therapy , as assessed by response on chest CT scan and clinical response (assessed using the SGRQ) and classified as improvement, stability and deterioration[2]

End point description:

End point type	Primary

End point timeframe:

After 12 months of treatment

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This trial was terminated prior to opening at the trust.

End point values	Isavuconazole treatment			
Subject group type	Reporting group			
Number of subjects analysed	99999			
Units: 99999	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: Serological response (improvement in Aspergillus IgG by 20% or to <40mg/L after 6 and 12 months of treatment)

End point title	Serological response (improvement in Aspergillus IgG by 20% or to <40mg/L after 6 and 12 months of treatment)

End point description:

End point type	Secondary

End point timeframe:

After 6 and 12 months of treatment

End point values	Isavuconazole treatment			
Subject group type	Reporting group			
Number of subjects analysed	99999			
Units: 99999	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: Discontinuation of study drug before 12 months

End point title	Discontinuation of study drug before 12 months

End point description:

End point type	Secondary

End point timeframe:

Before 12 months

End point values	Isavuconazole treatment			
Subject group type	Reporting group			
Number of subjects analysed	99999			
Units: 99999	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: Symptomatic improvement (any 2 key symptoms other than weight gain)

End point title	Symptomatic improvement (any 2 key symptoms other than weight gain)

End point description:

End point type	Secondary

End point timeframe:

After follow up complete

End point values	Isavuconazole treatment			
Subject group type	Reporting group			
Number of subjects analysed	99999			
Units: 99999	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients showing improvement in SGRQ by >8 points at 6 and 12 months

End point title	Proportion of patients showing improvement in SGRQ by >8 points at 6 and 12 months

End point description:

End point type	Secondary

End point timeframe:

At 6 and 12 months

End point values	Isavuconazole treatment			
Subject group type	Reporting group			
Number of subjects analysed	99999			
Units: 99999	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients showing deterioration SGRQ by >4 points at 6 and 12 months

End point title	Proportion of patients showing deterioration SGRQ by >4 points at 6 and 12 months

End point description:

End point type	Secondary

End point timeframe:

At 6 and 12 months

End point values	Isavuconazole treatment			
Subject group type	Reporting group			
Number of subjects analysed	99999			
Units: 99999	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: Weight gain or loss of >3Kg at 6 and 12 months

End point title	Weight gain or loss of >3Kg at 6 and 12 months

End point description:

End point type	Secondary

End point timeframe:

At 6 and 12 months

End point values	Isavuconazole treatment			
Subject group type	Reporting group			
Number of subjects analysed	99999			
Units: 99999	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: Recurrence 6 months after therapy discontinuation, assessed by deterioration in SGRQ by ≥8 points.

End point title	Recurrence 6 months after therapy discontinuation, assessed by deterioration in SGRQ by ≥8 points.

End point description:

End point type	Secondary

End point timeframe:

After 6 months of treatment

End point values	Isavuconazole treatment			
Subject group type	Reporting group			
Number of subjects analysed	99999			
Units: 99999	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: Positive respiratory culture for Aspergillus fumigatus with emergence of isavuconazole resistance

End point title	Positive respiratory culture for Aspergillus fumigatus with emergence of isavuconazole resistance

End point description:

End point type	Secondary

End point timeframe:

After follow up end

End point values	Isavuconazole treatment			
Subject group type	Reporting group			
Number of subjects analysed	99999			
Units: 99999	99999			

Statistical analyses

No statistical analyses for this end point

Secondary: PK analysis of Isavuconazole in patients on treatment

End point title	PK analysis of Isavuconazole in patients on treatment

End point description:

End point type	Secondary

End point timeframe:

After follow up completion

End point values	Isavuconazole treatment			
Subject group type	Reporting group			
Number of subjects analysed	99999			
Units: 99999	99999			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Inflammatory markers during treatment; C Reactive Protein and Plasma Viscosity

End point title	Inflammatory markers during treatment; C Reactive Protein and Plasma Viscosity

End point description:

End point type	Other pre-specified

End point timeframe:

Exploratory endpoint. After follow up complete.

End point values	Isavuconazole treatment			
Subject group type	Reporting group			
Number of subjects analysed	99999			
Units: 99999	99999			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All SAEs that occur between day 1 of treatment and 30 days post the last trial treatment dose administration (or after this date if the site investigator considers the event to be related to the trial treatment) must be submitted to the Sponsor.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	0

Reporting groups

Reporting group title	Isavuconazole treatment

Reporting group description:

Eligible patients will be treated with isavuconazole (200mg) three times daily for 6 doses, followed by 200mg once daily.

Serious adverse events	Isavuconazole treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 99999 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Isavuconazole treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 99999 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: This trial was terminated prior to opening at the trust. As such, no adverse events occurred.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This trial was cancelled as the company supplying the Investigational Medicinal Product (IMP) was brought out by another company who did not want to continue with the trial concept. No R&D confirmation of capacity and capability was given or contract

Notes: