Clinical trial results:
A Pharmacokinetic Analysis of Posaconazole in the Plasma and Alveolar Compartment of Lung Transplant Recipients (PAPAL)

Summary

EudraCT number	2012-003140-68
Trial protocol	GB
Global end of trial date	16 January 2014

Results information

Result version number	v1 (current)
This version publication date	10 February 2016
First version publication date	13 June 2015

Trial information

Trial identification

Sponsor protocol code	MK-5592-105

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01667107
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

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	16 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 January 2014
Global end of trial reached?	Yes
Global end of trial date	16 January 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This single site study will examine plasma and alveolar compartment levels of posaconazole in cystic fibrosis and non-cystic fibrosis lung transplant recipients receiving routine post-operative anti-fungal prophylaxis. Invasive fungal infection rates will be assessed following transplantation.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 January 2013
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: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

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)	24
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All participants were scheduled to undergo lung transplantation. Participants with severe liver disease or receiving cytochrome P-450 (CYP)-3A4 inhibitors were excluded. Other inclusion and exclusion criteria applied.

Pre-assignment

Screening details:

There were no screening failures for cystic fibrosis participants and one for non-cystic fibrosis participants.

Period 1

Period 1 title	Posaconazole Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cystic Fibrosis Participants

Arm description:

Posaconazole 400 mg oral solution twice daily administered with Calogen® 30 mL oral emulsion (administered before the posaconazole to optimize absorption) for a total of 6 weeks starting within 12 hours of leaving surgery, thereafter administered in the hospital or as an outpatient; the dose could be changed to posaconazole 200 mg 4 times per day and Calogen® 15 mL if the participant was unable to meet the conditions for optimal absorption of posaconazole.

Arm type	Experimental
Investigational medicinal product name	Posaconazole
Investigational medicinal product code	
Other name	MK-5592, Noxafil®
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Posaconazole 400 mg oral solution twice daily administered with Calogen® 30 mL oral emulsion (administered before the posaconazole to optimize absorption) for a total of 6 weeks starting within 12 hours of leaving surgery, thereafter administered in the hospital or as an outpatient; the dose could be changed to posaconazole 200 mg 4 times per day and Calogen® 15 mL if the participant was unable to meet the conditions for optimal absorption of posaconazole.

Investigational medicinal product name	Calogen®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral emulsion
Routes of administration	Oral use

Dosage and administration details:

Posaconazole 400 mg oral solution twice daily administered with Calogen® 30 mL oral emulsion (administered before the posaconazole to optimize absorption) for a total of 6 weeks starting within 12 hours of leaving surgery, thereafter administered in the hospital or as an outpatient; the dose could be changed to posaconazole 200 mg 4 times per day and Calogen® 15 mL if the participant was unable to meet the conditions for optimal absorption of posaconazole.

Arm title	Non-cystic Fibrosis Participants

Arm description:

Posaconazole 400 mg oral solution twice daily administered with Calogen® 30 mL oral emulsion (administered before the posaconazole to optimize absorption) for a total of 6 weeks starting within 12 hours of leaving surgery, thereafter administered in the hospital or as an outpatient; the dose could be

changed to posaconazole 200 mg 4 times per day and Calogen® 15 mL if the participant was unable to meet the conditions for optimal absorption of posaconazole.

Arm type	Experimental
Investigational medicinal product name	Posaconazole
Investigational medicinal product code	
Other name	MK-5592, Noxafil®
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Posaconazole 400 mg oral solution twice daily administered with Calogen® 30 mL oral emulsion (administered before the posaconazole to optimize absorption) for a total of 6 weeks starting within 12 hours of leaving surgery, thereafter administered in the hospital or as an outpatient; the dose could be changed to posaconazole 200 mg 4 times per day and Calogen® 15 mL if the participant was unable to meet the conditions for optimal absorption of posaconazole.

Investigational medicinal product name	Calogen®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral emulsion
Routes of administration	Oral use

Dosage and administration details:

Posaconazole 400 mg oral solution twice daily administered with Calogen® 30 mL oral emulsion (administered before the posaconazole to optimize absorption) for a total of 6 weeks starting within 12 hours of leaving surgery, thereafter administered in the hospital or as an outpatient; the dose could be changed to posaconazole 200 mg 4 times per day and Calogen® 15 mL if the participant was unable to meet the conditions for optimal absorption of posaconazole.

Number of subjects in period 1	Cystic Fibrosis Participants	Non-cystic Fibrosis Participants
Started	8	18
Completed	4	11
Not completed	4	7
Adverse event, non-fatal	4	3
Tolerability issues	-	2
Protocol deviation	-	1
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cystic Fibrosis Participants
Reporting group description:	
Posaconazole 400 mg oral solution twice daily administered with Calogen® 30 mL oral emulsion (administered before the posaconazole to optimize absorption) for a total of 6 weeks starting within 12 hours of leaving surgery, thereafter administered in the hospital or as an outpatient; the dose could be changed to posaconazole 200 mg 4 times per day and Calogen® 15 mL if the participant was unable to meet the conditions for optimal absorption of posaconazole.	
Reporting group title	Non-cystic Fibrosis Participants
Reporting group description:	
Posaconazole 400 mg oral solution twice daily administered with Calogen® 30 mL oral emulsion (administered before the posaconazole to optimize absorption) for a total of 6 weeks starting within 12 hours of leaving surgery, thereafter administered in the hospital or as an outpatient; the dose could be changed to posaconazole 200 mg 4 times per day and Calogen® 15 mL if the participant was unable to meet the conditions for optimal absorption of posaconazole.	

Reporting group values	Cystic Fibrosis Participants	Non-cystic Fibrosis Participants	Total
Number of subjects	8	18	26
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	16	24
From 65-84 years	0	2	2
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	30	52.4	
standard deviation	± 7.82	± 10.39	-
Gender categorical Units: Subjects			
Female	5	7	12
Male	3	11	14

End points

End points reporting groups

Reporting group title	Cystic Fibrosis Participants

Reporting group description:

Posaconazole 400 mg oral solution twice daily administered with Calogen® 30 mL oral emulsion (administered before the posaconazole to optimize absorption) for a total of 6 weeks starting within 12 hours of leaving surgery, thereafter administered in the hospital or as an outpatient; the dose could be changed to posaconazole 200 mg 4 times per day and Calogen® 15 mL if the participant was unable to meet the conditions for optimal absorption of posaconazole.

Reporting group title	Non-cystic Fibrosis Participants

Reporting group description:

Posaconazole 400 mg oral solution twice daily administered with Calogen® 30 mL oral emulsion (administered before the posaconazole to optimize absorption) for a total of 6 weeks starting within 12 hours of leaving surgery, thereafter administered in the hospital or as an outpatient; the dose could be changed to posaconazole 200 mg 4 times per day and Calogen® 15 mL if the participant was unable to meet the conditions for optimal absorption of posaconazole.

Primary: Time to Reach 90% of the Steady State Serum Concentration of Posaconazole

End point title	Time to Reach 90% of the Steady State Serum Concentration of Posaconazole[1]

End point description:

Blood samples for measurement of serum posaconazole were collected approximately 4 hours after the first daily dose on Days 1-12 and every Monday and Thursday on Days 13-43. The time to reach 90% of the steady state serum posaconazole concentration was to be estimated from fitting a linear model to the concentration data over time. The data did not permit estimation of the endpoint from the modeling proposed in the protocol.

End point type	Primary

End point timeframe:

Four hours after the first daily dose on Days 1-12 and every Monday and Thursday on Days 13-43

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: The data did not permit estimation of the endpoint from the modeling proposed in the protocol

End point values	Cystic Fibrosis Participants	Non-cystic Fibrosis Participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Days				
number (not applicable)				

Notes:

[2] - The data did not permit estimation of the endpoint from the modeling proposed in the protocol

[3] - The data did not permit estimation of the endpoint from the modeling proposed in the protocol

Statistical analyses

No statistical analyses for this end point

Primary: Concentration of Posaconazole in Bronchoalveolar Lavage (BAL) and Serum

End point title	Concentration of Posaconazole in Bronchoalveolar Lavage (BAL) and Serum[4]

End point description:

Concurrent BAL and serum samples for measurement of posaconazole concentration were to be collected during any clinically-indicated bronchoscopy. A participant could have more than 1 bronchoscopy. Spearman rank correlation coefficients between BAL and serum posaconazole concentrations were 0.53 (P-value 0.139) for cystic fibrosis participants and 0.057 (P-value 0.59) for non-cystic fibrosis participants.

End point type	Primary

End point timeframe:

Up to Day 42

Notes:

[4] - 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: No between-group statistical analyses were planned for this endpoint

End point values	Cystic Fibrosis Participants	Non-cystic Fibrosis Participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[5]	7[6]		
Units: mg/L				
arithmetic mean (standard deviation)				
BAL	1.116 (± 1.1699)	0.764 (± 0.8)		
Serum	0.829 (± 0.3742)	0.7488 (± 0.3131)		

Notes:

[5] - The 5 participants had a total of 9 paired BAL and serum samples for analysis

[6] - The 7 participants had a total of 11 paired BAL and serum samples for analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Develop Invasive Fungal Infection

End point title	Percentage of Participants Who Develop Invasive Fungal Infection

End point description:

Invasive fungal infection was assessed using the Mycoses Study Group/European Organisation for Research and Treatment of Cancer (MSG/EORTC) criteria. Infections counted in the analysis were those classified as 'proven', 'probable', or 'possible' according to the criteria.

End point type	Secondary

End point timeframe:

Up to Day 84

End point values	Cystic Fibrosis Participants	Non-cystic Fibrosis Participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	18		
Units: Percentage of participants				
number (confidence interval 95%)	12.5 (2.2 to 47.1)	16.7 (5.8 to 39.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach a Serum Concentration of Posaconazole of >=0.5 mg/L

End point title	Time to Reach a Serum Concentration of Posaconazole of >=0.5 mg/L

End point description:

Blood samples for measurement of serum concentration of posaconazole were collected approximately 4 hours after the first daily dose on Days 1-12 and every Monday and Thursday on Days 13-43. A posaconazole concentration >=0.5 mg/L is the therapeutic level, the concentration thought to lead to antifungal efficacy. The time at which the serum posaconazole concentration reached >=0.5 mg/mL and remained at that level for all subsequent assessments was recorded.

End point type	Secondary

End point timeframe:

Four hours after the first daily dose on Days 1-12 and every Monday and Thursday on Days 13-43

End point values	Cystic Fibrosis Participants	Non-cystic Fibrosis Participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[7]	14[8]		
Units: Days				
arithmetic mean (standard deviation)	12.2 (± 8.82)	11.9 (± 9.86)		

Notes:

[7] - Participants who reached and maintained a posaconazole concentration >=0.5 mg/L

[8] - Participants who reached and maintained a posaconazole concentration >=0.5 mg/L

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration of Posaconazole (Cmax)

End point title	Maximum Serum Concentration of Posaconazole (Cmax)

End point description:

Blood samples for measurement of serum concentration of posaconazole were collected approximately 4 hours after the first daily dose on Days 1-12 and every Monday and Thursday on Days 13-43. The maximum serum concentration of posaconazole was recorded.

End point type	Secondary

End point timeframe:

Four hours after the first daily dose on Days 1-12 and every Monday and Thursday on Days 13-43

End point values	Cystic Fibrosis Participants	Non-cystic Fibrosis Participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	18		
Units: mg/L				
arithmetic mean (standard deviation)	1.481 (± 0.6014)	1.539 (± 0.8471)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximum Serum Concentration of Posaconazole (Tmax)

End point title	Time to Maximum Serum Concentration of Posaconazole (Tmax)

End point description:

Blood samples for measurement of serum concentration of posaconazole were collected approximately 4 hours after the first daily dose on Days 1-12 and every Monday and Thursday on Days 13-43. The time required to achieve the maximum serum concentration of posaconazole was recorded.

End point type	Secondary

End point timeframe:

Four hours after the first daily dose on Days 1-12 and every Monday and Thursday on Days 13-43

End point values	Cystic Fibrosis Participants	Non-cystic Fibrosis Participants		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	18		
Units: Days				
arithmetic mean (standard deviation)	19.5 (± 12.39)	23.1 (± 13.73)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to Day 88	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups	
Reporting group title	Cystic Fibrosis Participants
Reporting group description:	
Posaconazole 400 mg oral solution twice daily administered with Calogen® 30 mL oral emulsion (administered before the posaconazole to optimize absorption) for a total of 6 weeks starting within 12 hours of leaving surgery, thereafter administered in the hospital or as an outpatient; the dose could be changed to posaconazole 200 mg 4 times per day and Calogen® 15 mL if the participant was unable to meet the conditions for optimal absorption of posaconazole.	
Reporting group title	Non-cystic Fibrosis Participants
Reporting group description:	
Posaconazole 400 mg oral solution twice daily administered with Calogen® 30 mL oral emulsion (administered before the posaconazole to optimize absorption) for a total of 6 weeks starting within 12 hours of leaving surgery, thereafter administered in the hospital or as an outpatient; the dose could be changed to posaconazole 200 mg 4 times per day and Calogen® 15 mL if the participant was unable to meet the conditions for optimal absorption of posaconazole.	

Serious adverse events	Cystic Fibrosis Participants	Non-cystic Fibrosis Participants	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 8 (75.00%)	10 / 18 (55.56%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Investigations			
Immunosuppressant drug level decreased			
subjects affected / exposed	1 / 8 (12.50%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Supraventricular tachycardia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			

subjects affected / exposed	0 / 8 (0.00%)	2 / 18 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 8 (12.50%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Transplant rejection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver injury			
subjects affected / exposed	1 / 8 (12.50%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 8 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 8 (12.50%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	1 / 8 (12.50%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 8 (0.00%)	2 / 18 (11.11%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Fungal infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	2 / 18 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cystic Fibrosis Participants	Non-cystic Fibrosis Participants	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	2 / 18 (11.11%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Immunosuppressant drug level increased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

Eye disorders Vision blurred subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0	 1 / 18 (5.56%) 1	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1	 0 / 18 (0.00%) 0	
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all) Renal failure acute subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0	 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1	

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? Yes

Date	Interruption	Restart date
22 November 2013	The trial was terminated on 12-Dec-2013. Reason for early termination: A crude analysis of historic data gave the site concerns that there may have been an increased rate of renal failure requiring renal replacement therapy. Additionally, they found it difficult to titrate the tacrolimus level given the variability of posaconazole - which may have contributed in some cases to the perceived renal issue.	-

Notes:

Limitations and caveats

None reported