Clinical trial results:
Phase 2 Proof-of-Activity Study of Oral Posaconazole in the Treatment of Asymptomatic Chronic Chagas Disease (Phase 2, Protocol No. P05267)

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2013-000161-36
Trial protocol	ES
Global end of trial date	12 January 2015

Results information

Result version number	v1 (current)
This version publication date	18 February 2016
First version publication date	18 February 2016

Trial information

Trial identification

Sponsor protocol code	MK-5592-055

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01377480
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Code: P05267

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, +1 800-672-6372, ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp, +1 800-672-6372, 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	12 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 July 2014
Global end of trial reached?	Yes
Global end of trial date	12 January 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a study to compare the efficacy of oral posaconazole to placebo for the treatment of asymptomatic Chagas disease. The primary hypothesis of the study is that posaconazole 400 mg twice daily improves therapeutic response compared to placebo in participants with a diagnosis of asymptomatic chronic Chagas disease.

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	06 July 2011
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	Argentina: 93
Country: Number of subjects enrolled	Chile: 11
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Guatemala: 2
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Spain: 10
Worldwide total number of subjects	120
EEA total number of subjects	10

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)	120
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 393 participants were screened, 123 were eligible for enrollment, and 120 were randomized.

Period 1

Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Posaconazole

Arm description:

Posaconazole (POS) 400 mg (10 mL) oral suspension twice daily for 60 days

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

Dosage and administration details:

400 mg (10 mL) oral suspension twice daily for 60 days

Arm title	Placebo

Arm description:

POS placebo (10 mL) oral suspension twice daily for 60 days

Arm type	Placebo
Investigational medicinal product name	Placebo to posaconazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

POS placebo (10 mL) oral suspension twice daily for 60 days

Arm title	Posaconazole + Benznidazole

Arm description:

POS 400 mg (10 mL) oral suspension twice daily for 60 days and benznidazole (BNZ) 100 mg oral tablet twice daily (200-mg daily dose) for 60 days

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

Dosage and administration details: 400 mg (10 mL) oral suspension twice daily for 60 days	
Investigational medicinal product name	Benznidazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: BNZ 100 mg oral tablet twice daily (200-mg daily dose) for 60 days	
Arm title	Benznidazole + Placebo
Arm description: BNZ 100 mg oral tablet twice daily (200-mg daily dose) for 60 days and POS placebo (10 mL) oral suspension twice daily for 60 days	
Arm type	Active comparator
Investigational medicinal product name	Placebo to posaconazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use
Dosage and administration details: POS placebo (10 mL) oral suspension twice daily for 60 days	
Investigational medicinal product name	Benznidazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: BNZ 100 mg oral tablet twice daily (200-mg daily dose) for 60 days	

Number of subjects in period 1	Posaconazole	Placebo	Posaconazole + Benznidazole
Started	32	30	28
Completed	32	29	18
Not completed	0	1	10
Consent withdrawn by subject	-	-	1
Evidence of drug-induced hepatotoxicity	-	1	1
Not specified	-	-	7
Serious adverse event	-	-	1
Protocol deviation	-	-	-

Number of subjects in period 1	Benznidazole + Placebo
Started	30
Completed	19
Not completed	11
Consent withdrawn by subject	-

Evidence of drug-induced hepatotoxicity	-
Not specified	6
Serious adverse event	1
Protocol deviation	4

Baseline characteristics

Reporting groups	
Reporting group title	Posaconazole
Reporting group description:	
Posaconazole (POS) 400 mg (10 mL) oral suspension twice daily for 60 days	
Reporting group title	Placebo
Reporting group description:	
POS placebo (10 mL) oral suspension twice daily for 60 days	
Reporting group title	Posaconazole + Benznidazole
Reporting group description:	
POS 400 mg (10 mL) oral suspension twice daily for 60 days and benznidazole (BNZ) 100 mg oral tablet twice daily (200-mg daily dose) for 60 days	
Reporting group title	Benznidazole + Placebo
Reporting group description:	
BNZ 100 mg oral tablet twice daily (200-mg daily dose) for 60 days and POS placebo (10 mL) oral suspension twice daily for 60 days	

Reporting group values	Posaconazole	Placebo	Posaconazole + Benznidazole
Number of subjects	32	30	28
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	40.3	42.2	40.2
standard deviation	± 8.6	± 7.8	± 8.4
Gender Categorical Units: Subjects			
Female	16	7	13
Male	16	23	15

Reporting group values	Benznidazole + Placebo	Total	
Number of subjects	30	120	
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	40.4		
standard deviation	± 7.7	-	
Gender Categorical Units: Subjects			
Female	17	53	
Male	13	67	

End points

End points reporting groups

Reporting group title	Posaconazole
Reporting group description:	
Posaconazole (POS) 400 mg (10 mL) oral suspension twice daily for 60 days	
Reporting group title	Placebo
Reporting group description:	
POS placebo (10 mL) oral suspension twice daily for 60 days	
Reporting group title	Posaconazole + Benznidazole
Reporting group description:	
POS 400 mg (10 mL) oral suspension twice daily for 60 days and benznidazole (BNZ) 100 mg oral tablet twice daily (200-mg daily dose) for 60 days	
Reporting group title	Benznidazole + Placebo
Reporting group description:	
BNZ 100 mg oral tablet twice daily (200-mg daily dose) for 60 days and POS placebo (10 mL) oral suspension twice daily for 60 days	

Primary: Percentage of Participants with a Successful Response as Measured by Qualitative Polymerase Chain Reaction

End point title	Percentage of Participants with a Successful Response as Measured by Qualitative Polymerase Chain Reaction
End point description:	
Blood samples were collected for qualitative polymerase chain reaction (PCR) assay for Trypanosoma cruzi deoxyribonucleic acid (DNA). Successful response was defined as a negative qualitative PCR value at the Day 180 follow up visit. The Full Analysis Population included all randomized participants who received at least one dose of study drug.	
End point type	Primary
End point timeframe:	
Day 180	

End point values	Posaconazole	Placebo	Posaconazole + Benznidazole	Benznidazole + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	30	28	30
Units: Percentage of participants				
number (confidence interval 95%)	15.6 (6.9 to 31.8)	10 (3.5 to 25.6)	82.1 (64.4 to 92.1)	86.7 (70.3 to 94.7)

Statistical analyses

Statistical analysis title	Difference in Successful Response
Comparison groups	Placebo v Posaconazole

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5125261
Method	Miettinen & Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.6
upper limit	23.7

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
All adverse events: up to Day 90 (30 days post treatment); procedure-related serious adverse events: up to Day 360 (300 days post treatment)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups	
Reporting group title	Posaconazole
Reporting group description:	
Posaconazole (POS) 400 mg (10 mL) oral suspension twice daily for 60 days	
Reporting group title	Posaconazole + Benznidazole
Reporting group description:	
POS 400 mg (10 mL) oral suspension twice daily for 60 days and benznidazole (BNZ) 100 mg oral tablet twice daily (200-mg daily dose) for 60 days	
Reporting group title	Benznidazole + Placebo
Reporting group description:	
BNZ 100 mg oral tablet twice daily (200-mg daily dose) for 60 days and POS placebo (10 mL) oral suspension twice daily for 60 days	
Reporting group title	Placebo
Reporting group description:	
POS placebo (10 mL) oral suspension twice daily for 60 days Placebo	

Serious adverse events	Posaconazole	Posaconazole + Benznidazole	Benznidazole + Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 32 (3.13%)	2 / 28 (7.14%)	3 / 30 (10.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 32 (0.00%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	0 / 32 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 32 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 32 (3.13%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Photodermatosis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 28 (3.57%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 32 (0.00%)	0 / 28 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 30 (3.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Photodermatosis			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Posaconazole	Posaconazole + Benznidazole	Benznidazole + Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 32 (37.50%)	18 / 28 (64.29%)	21 / 30 (70.00%)
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 32 (3.13%)	2 / 28 (7.14%)	0 / 30 (0.00%)
occurrences (all)	1	2	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 32 (0.00%)	3 / 28 (10.71%)	2 / 30 (6.67%)
occurrences (all)	0	3	2
Headache			
subjects affected / exposed	3 / 32 (9.38%)	8 / 28 (28.57%)	4 / 30 (13.33%)
occurrences (all)	4	14	5
Paraesthesia			
subjects affected / exposed	0 / 32 (0.00%)	1 / 28 (3.57%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
Somnolence			
subjects affected / exposed	0 / 32 (0.00%)	1 / 28 (3.57%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 28 (3.57%)	1 / 30 (3.33%)
occurrences (all)	2	1	1
Pyrexia			
subjects affected / exposed	0 / 32 (0.00%)	0 / 28 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 32 (0.00%)	1 / 28 (3.57%)	3 / 30 (10.00%)
occurrences (all)	0	1	3
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 32 (0.00%)	3 / 28 (10.71%)	2 / 30 (6.67%)
occurrences (all)	0	3	2
Diarrhoea			

subjects affected / exposed	0 / 32 (0.00%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	3 / 32 (9.38%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Nausea			
subjects affected / exposed	3 / 32 (9.38%)	5 / 28 (17.86%)	3 / 30 (10.00%)
occurrences (all)	3	7	4
Vomiting			
subjects affected / exposed	1 / 32 (3.13%)	2 / 28 (7.14%)	2 / 30 (6.67%)
occurrences (all)	1	3	3
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 32 (0.00%)	2 / 28 (7.14%)	2 / 30 (6.67%)
occurrences (all)	0	2	2
Pruritus			
subjects affected / exposed	0 / 32 (0.00%)	3 / 28 (10.71%)	4 / 30 (13.33%)
occurrences (all)	0	3	4
Rash			
subjects affected / exposed	1 / 32 (3.13%)	4 / 28 (14.29%)	6 / 30 (20.00%)
occurrences (all)	1	5	8
Rash pruritic			
subjects affected / exposed	0 / 32 (0.00%)	0 / 28 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Urticaria			
subjects affected / exposed	0 / 32 (0.00%)	0 / 28 (0.00%)	3 / 30 (10.00%)
occurrences (all)	0	0	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 32 (0.00%)	2 / 28 (7.14%)	1 / 30 (3.33%)
occurrences (all)	0	2	1
Back pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 28 (0.00%)	0 / 30 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			

subjects affected / exposed	0 / 32 (0.00%)	2 / 28 (7.14%)	0 / 30 (0.00%)
occurrences (all)	0	3	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 32 (6.25%)	3 / 28 (10.71%)	0 / 30 (0.00%)
occurrences (all)	2	3	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 30 (26.67%)		
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Paraesthesia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypersensitivity			

subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Gastritis			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Rash pruritic			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 30 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0 2 / 30 (6.67%) 2 0 / 30 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 May 2011	Changes in Amendment 1: Number of centers was changed from 8 to 10; text in the Inclusion/Exclusion criteria was changed to specify that 12-lead electrocardiogram and 2-D echocardiogram results, if not normal, must be determined to be clinically significant.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported