Clinical trial results:
Gastrointestinal behavior of posaconazol in healthy human volunteers

Summary

EudraCT number	2013-002836-26
Trial protocol	BE
Global end of trial date	10 September 2015

Results information

Result version number	v1 (current)
This version publication date	29 December 2019
First version publication date	29 December 2019
Summary attachment (see zip file)	Hens et al. - Supersaturation and precipitation of posaconazole in the human GI tract (2015 - Hens - Supersaturation & Precipitation Posaconazole - JPhaSci.pdf)

Trial information

Trial identification

Sponsor protocol code	DDD13POSA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Clinical Trial Center UZ Leuven: S

Notes:

Sponsors

Sponsor organisation name	KU Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Drug Delivery & Disposition, KU Leuven, 32 16330302, bart.hens@pharm.kuleuven.be
Scientific contact	Drug Delivery & Disposition, KU Leuven, 32 16330302, bart.hens@pharm.kuleuven.be

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	27 June 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 June 2014
Global end of trial reached?	Yes
Global end of trial date	10 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Study of the gastrointestinal behavior of posaconazol in healthy volunteers by using a suspension of the drug and a solution. This will learn us more about the behaviour of the drug in the GI tract (supersaturation/ precipitation/ dissolution/ ...)

Protection of trial subjects:

NA.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2014
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	Belgium: 5
Worldwide total number of subjects	5
EEA total number of subjects	5

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)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited by email based on an existing database.

Pre-assignment

Screening details:

Exclusion criteria were checked during a medical examination and included gastrointestinal disorders, infection with hepatitis B, hepatitis C or HIV, use of medication, pregnancy and frequent X-ray exposure. All volunteers provided informed consent to participate in the clinical study.

Period 1

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

Blinding implementation details:

NA

Arms

Are arms mutually exclusive?	No
Arm title	Suspension pH 1.6 40 mg

Arm description:

For the acidified suspension, 1 mL of Noxafil® (40 mg posaconazole as such, which corresponds to 10% of the typical therapeutic dose) was dispersed in 240 mL of tap water acidified to pH 1.6 with HCl (70% of posaconazole in solution). This suspension was intragastrically administered to healthy subjects.

Arm type	Experimental
Investigational medicinal product name	Posaconazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

For the acidified suspension, 1 mL of Noxafil® (40 mg posaconazole as such, which corresponds to 10% of the typical therapeutic dose) was dispersed in 240 mL of tap water acidified to pH 1.6 with HCl (70% of posaconazole in solution). This suspension was intragastrically administered to healthy subjects.

Arm title	Suspension pH 7.1 40 mg

Arm description:

For the neutral suspension, 1 mL of Noxafil® (40 mg posaconazole) was dispersed in 240 mL of tap water (pH 7.1; 2.3% of posaconazole in solution). After intragastric administration, antral and duodenal fluids were aspirated for 3 h; samples were taken at 2, 7, 15, 25, 35, 45, 55, and 60 min during the first hour and every 15 min for the next 2 h. The sampling volumewas kept as small as possible (<4mL per time point). Immediately after aspiration of fluids, pH was measured (Hamilton Knick Portamess®, Bonaduz, Switzerland) and the determination of dissolved and total posaconazole was initiated. Blood samples were collected in heparinized tubes (BD Vacutainer systems, Plymouth, UK) at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, and 24 h after intragastric administration. Blood samples were centrifuged (2880g, 10 min, 4°C) and the obtained plasma was stored at -26°C until analysis.

Arm type	Experimental
Investigational medicinal product name	Posaconazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

For the neutral suspension, 1 mL of Noxafil® (40 mg posaconazole) was dispersed in 240 mL of tap water (pH 7.1; 2.3% of posaconazole in solution). After intragastric administration, antral and duodenal fluids were aspirated for 3 h; samples were taken at 2, 7, 15, 25, 35, 45, 55, and 60 min during the first hour and every 15 min for the next 2 h. The sampling volumewas kept as small as possible (<4mL per time point). Immediately after aspiration of fluids, pH was measured (Hamilton Knick Portamess®, Bonaduz, Switzerland) and the determination of dissolved and total posaconazole was initiated. Blood samples were collected in heparinized tubes (BD Vacutainer systems, Plymouth, UK) at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, and 24 h after intragastric administration. Blood samples were centrifuged (2880g, 10 min, 4°C) and the obtained plasma was stored at -26°C until analysis.

Arm title	Solution pH 1.6 20 mg

Arm description:

In an additional condition (no blood sampling involved), posaconazole as such was intragastrically administered as a solution in order to assess intestinal posaconazole precipitation without the potential impact of accelerated nucleation due to the presence of
solid particles from the suspensions. The solution was prepared by dissolving 0.5 mL of Noxafil® (20 mg posaconazole) in 240 mL of tap water acidified to pH 1.6. Analogous to previous test conditions, antral and duodenal fluids were aspirated for 3 h, followed by pH measurement (Hamilton Knick Portamess®) and determination of dissolved and total posaconazole concentrations. Blood
samples were not collected.

Arm type	Experimental
Investigational medicinal product name	Posaconazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

In an additional condition (no blood sampling involved), posaconazole as such was intragastrically administered as a solution in order to assess intestinal posaconazole precipitation without the potential impact of accelerated nucleation due to the presence of
solid particles from the suspensions. The solution was prepared by dissolving 0.5 mL of Noxafil® (20 mg posaconazole) in 240 mL of tap water acidified to pH 1.6. Analogous to previous test conditions, antral and duodenal fluids were aspirated for 3 h, followed by pH measurement (Hamilton Knick Portamess®) and determination of dissolved and total posaconazole concentrations. Blood
samples were not collected.

Number of subjects in period 1	Suspension pH 1.6 40 mg	Suspension pH 7.1 40 mg	Solution pH 1.6 20 mg
Started	5	5	5
Completed	5	5	5

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	5	5	
Age categorical			
A cross-over study with three experimental conditions was performed in five healthy volunteers (HVs; three women and two men, aged between 23 and 25 years).			
Units: Subjects			
adults (0-65 years old)	5	5	
Gender categorical Units: Subjects			
Female	3	3	
Male	2	2	

End points

End points reporting groups

Reporting group title	Suspension pH 1.6 40 mg

Reporting group description:

For the acidified suspension, 1 mL of Noxafil® (40 mg posaconazole as such, which corresponds to 10% of the typical therapeutic dose) was dispersed in 240 mL of tap water acidified to pH 1.6 with HCl (70% of posaconazole in solution). This suspension was intragastrically administered to healthy subjects.

Reporting group title	Suspension pH 7.1 40 mg

Reporting group description:

For the neutral suspension, 1 mL of Noxafil® (40 mg posaconazole) was dispersed in 240 mL of tap water (pH 7.1; 2.3% of posaconazole in solution). After intragastric administration, antral and duodenal fluids were aspirated for 3 h; samples were taken at 2, 7, 15, 25, 35, 45, 55, and 60 min during the first hour and every 15 min for the next 2 h. The sampling volumewas kept as small as possible (<4mL per time point). Immediately after aspiration of fluids, pH was measured (Hamilton Knick Portamess®, Bonaduz, Switzerland) and the determination of dissolved and total posaconazole was initiated. Blood samples were collected in heparinized tubes (BD Vacutainer systems, Plymouth, UK) at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, and 24 h after intragastric administration. Blood samples were centrifuged (2880g, 10 min, 4°C) and the obtained plasma was stored at -26°C until analysis.

Reporting group title	Solution pH 1.6 20 mg

Reporting group description:

In an additional condition (no blood sampling involved), posaconazole as such was intragastrically administered as a solution in order to assess intestinal posaconazole precipitation without the potential impact of accelerated nucleation due to the presence of
solid particles from the suspensions. The solution was prepared by dissolving 0.5 mL of Noxafil® (20 mg posaconazole) in 240 mL of tap water acidified to pH 1.6. Analogous to previous test conditions, antral and duodenal fluids were aspirated for 3 h, followed by pH measurement (Hamilton Knick Portamess®) and determination of dissolved and total posaconazole concentrations. Blood
samples were not collected.

Primary: Gastrointestinal and plasma AUC, Cmax and Tmax

End point title	Gastrointestinal and plasma AUC, Cmax and Tmax

End point description:

End point type	Primary

End point timeframe:

GI samples were taken at 2, 7, 15, 25, 35, 45, 55, and 60 min during the first hour and every 15 min for the next 2 h. Blood samples were collected at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, and 24 h after intragastric administration.

End point values	Suspension pH 1.6 40 mg	Suspension pH 7.1 40 mg	Solution pH 1.6 20 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	5	5	
Units: luminal and systemic Concentrations				
number (not applicable)	5	5	5	

Statistical analyses

Statistical analysis title	Data Presentation and Statistical Analysis

Statistical analysis description:

Intraluminal concentration-time profiles are presented as mean ± standard error of the mean (SEM) for five subjects. Pharmacokinetic parameters (plasma and duodenal Cmax tmax, and area under the curve [AUC]) are reported as mean ± SD. Test conditions were compared using a paired t-test (after logarithmic transformation of Cmax and AUC); differences were considered statistically significant at $p < 0.05$.

Comparison groups	Suspension pH 1.6 40 mg v Suspension pH 7.1 40 mg v Solution pH 1.6 20 mg
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 1-sided

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

After each test condition, questions were asked to the subject about adverse events. No adverse events were reported.

Assessment type	Non-systematic

Dictionary used

Dictionary name	Excel file
Dictionary version	office 365

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

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: There were nor serious nor non-serious events that occurred during this clinical study.

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

None reported