Clinical trial results:
Diagnostic contribution of XENETIX® CT PERFUSION in pre-therapeutical assessment of hepatocellular carcinoma.

Summary

EudraCT number	2011-002609-31
Trial protocol	DE AT
Global end of trial date	18 December 2015

Results information

Result version number	v1 (current)
This version publication date	01 January 2017
First version publication date	01 January 2017

Trial information

Trial identification

Sponsor protocol code	ISO-44-013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01639703
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Guerbet
Sponsor organisation address	BP57400, Roissy CDG Cedex, France, 95943
Public contact	Clinical Project Manager, Guerbet, 33 145915019, camille.pitrou@guerbet-group.com
Scientific contact	Clinical Project Manager, Guerbet, 33 145915019, camille.pitrou@guerbet-group.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	18 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2015
Global end of trial reached?	Yes
Global end of trial date	18 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To prospectively determine the diagnostic value of Xenetix®-CT perfusion for the discrimination between well-differentiated HCC and moderately/poorly differentiated HCC (off-site assessment). Histopathology will be used as the gold standard for the evaluation of HCC grading

Protection of trial subjects:

A patent IV line should be established and maintained throughout the examination. Subjects who might have a particular reaction (e.g., allergic reaction) during the iodine injection should receive added surveillance (e.g., carefully monitored pulse and blood pressure).
Examination of the subject will be discontinued if a serious adverse event occurs during or just after injection of Xenetix® (preventing post contrast imaging sequence).
In any case, a delay of fourty-eight hours is recommended between two contrast medium examinations (MR or X-Ray).
Oxygen equipment, emergency case and antihistaminic medications should be available for immediate treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 April 2012
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	Germany: 2
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Korea, Republic of: 85
Country: Number of subjects enrolled	Switzerland: 6
Worldwide total number of subjects	96
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)	77
From 65 to 84 years	18
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	96
Number of subjects completed	96

Period 1

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

Arms

Arm title	Xenetix CT-perfusion

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Xenetix
Investigational medicinal product code	
Other name	iobitridol
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

For CT-perfusion procedure, 50 mL of Xenetix 350 was administered at a flow rate of 5 mL/sec.

Number of subjects in period 1	Xenetix CT-perfusion
Started	96
Completed	84
Not completed	12
Consent withdrawn by subject	5
Other reason	7

Baseline characteristics

Reporting groups	
Reporting group title	Xenetix CT-perfusion

Reporting group description: -

Reporting group values	Xenetix CT-perfusion	Total	
Number of subjects	96	96	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	77	77	
From 65-84 years	18	18	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	56.2		
standard deviation	± 11.2	-	
Gender categorical			
For one patient, gender was missing.			
Units: Subjects			
Female	22	22	
Male	73	73	
Missing	1	1	
Severity of cirrhosis (Child-Pugh score) Units: Subjects			
Class A	79	79	
Class B	8	8	
Class C	2	2	
Missing	7	7	

End points

End points reporting groups

Reporting group title	Xenetix CT-perfusion
Reporting group description: -	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients with at least one available histopathology assessment regarding hepatocellular carcinoma WHO classification off-site	
Subject analysis set title	Patients with well-differentiated lesions
Subject analysis set type	Full analysis
Subject analysis set description:	
Among the 38 patients analyzed, 47 lesions were graded as well-differentiated according to the WHO classification.	
Subject analysis set title	Patients with moderately/poorly-differentiated lesions
Subject analysis set type	Full analysis
Subject analysis set description:	
Among the 42 patients analyzed, 43 lesions were graded as moderately/poorly-differentiated according to the WHO classification.	

Primary: Blood Volume (BV) according to degree of lesions differentiation

End point title	Blood Volume (BV) according to degree of lesions differentiation
End point description:	
The mean level of each CT perfusion parameter was compared between well differentiated and moderately/poorly differentiated lesions according to WHO classification evaluated off-site.	
End point type	Primary
End point timeframe:	
Within a week from CT perfusion to surgery	

End point values	Patients with well-differentiated lesions	Patients with moderately/poorly-differentiated lesions		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	42		
Units: millilitre(s)/100 grams				
arithmetic mean (standard deviation)	15.93 (± 6.663)	13.958 (± 5.315)		

Statistical analyses

Statistical analysis title	Difference of means
Statistical analysis description:	
Student t-test, corresponding to superiority of group of well differentiated versus moderately/poorly differentiated. Each of the 3 p-value must be compared to 0.025/3=0.0083	
Comparison groups	Patients with well-differentiated lesions v Patients with

	moderately/poorly-differentiated lesions
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0763
Method	t-test, 2-sided

Primary: Blood Flow (BF) according to degree of lesions differentiation

End point title	Blood Flow (BF) according to degree of lesions differentiation

End point description:

The mean level of each CT perfusion parameter was compared between well differentiated and moderately/poorly differentiated lesions according to WHO classification evaluated off-site.

End point type	Primary

End point timeframe:

Within a week from CT perfusion to surgery

End point values	Patients with well-differentiated lesions	Patients with moderately/poorly-differentiated lesions		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	42		
Units: millilitre(s)/100 grams/min				
arithmetic mean (standard deviation)	73.042 (± 21.551)	72.051 (± 31.792)		

Statistical analyses

Statistical analysis title	Difference of means

Statistical analysis description:

Student t-test, corresponding to superiority of group of well differentiated versus moderately/poorly differentiated. Each of the 3 p-value must be compared to 0.025/3=0.0083

Comparison groups	Patients with moderately/poorly-differentiated lesions v Patients with well-differentiated lesions
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4362
Method	t-test, 2-sided

Primary: Permeability Surface (PS) according to degree of lesions differentiation

End point title	Permeability Surface (PS) according to degree of lesions differentiation

End point description:

The mean level of each CT perfusion parameter was compared between well differentiated and moderately/poorly differentiated lesions according to WHO classification evaluated off-site.

End point type	Primary

End point timeframe:

Within a week from CT perfusion to surgery

End point values	Patients with well-differentiated lesions	Patients with moderately/poorly-differentiated lesions		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	42		
Units: millilitre(s)/100 grams/min				
arithmetic mean (standard deviation)	26.421 (± 10.014)	27.75 (± 9.425)		

Statistical analyses

Statistical analysis title	Difference of means

Statistical analysis description:

Student t-test, corresponding to superiority of group of well differentiated versus moderately/poorly differentiated. Each of the 3 p-value must be compared to 0.025/3=0.0083

Comparison groups	Patients with well-differentiated lesions v Patients with moderately/poorly-differentiated lesions
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7261
Method	t-test, 2-sided

Secondary: Arterial Liver Perfusion (ALP) according to degree of lesions differentiation

End point title	Arterial Liver Perfusion (ALP) according to degree of lesions differentiation

End point description:

The mean level of each CT perfusion parameter was compared between well differentiated and moderately/poorly differentiated lesions according to WHO classification evaluated off-site.

End point type	Secondary

End point timeframe:

Within a week from CT perfusion to surgery

End point values	Patients with well-differentiated lesions	Patients with moderately/poorly-differentiated lesions		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	42		
Units: millilitre(s)/min/100 millilitres				
arithmetic mean (standard deviation)	43.234 (± 16.989)	42.967 (± 16.678)		

Statistical analyses

No statistical analyses for this end point

Secondary: Portal Venous Liver Perfusion (PVP) according to degree of lesions differentiation

End point title	Portal Venous Liver Perfusion (PVP) according to degree of lesions differentiation

End point description:

The mean level of each CT perfusion parameter was compared between well differentiated and moderately/poorly differentiated lesions according to WHO classification evaluated off-site.

End point type	Secondary

End point timeframe:

Within a week from CT perfusion to surgery

End point values	Patients with well-differentiated lesions	Patients with moderately/poorly-differentiated lesions		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	42		
Units: millilitre(s)/min/100 millilitres				
arithmetic mean (standard deviation)	19.492 (± 14.586)	13.708 (± 13.207)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Liver Perfusion (TLP) according to degree of lesions differentiation

End point title	Total Liver Perfusion (TLP) according to degree of lesions differentiation

End point description:

The mean level of each CT perfusion parameter was compared between well differentiated and moderately/poorly differentiated lesions according to WHO classification evaluated off-site.
TLP = ALP + PVP

End point type	Secondary

End point timeframe:

Within a week from CT perfusion to surgery

End point values	Patients with well-differentiated lesions	Patients with moderately/poorly-differentiated lesions		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	42		
Units: millilitre(s)/min/100 millitres				
arithmetic mean (standard deviation)	62.725 (± 15.62)	56.674 (± 20.494)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hepatic Perfusion Index (HPI) according to degree of lesions differentiation

End point title	Hepatic Perfusion Index (HPI) according to degree of lesions differentiation

End point description:

The mean level of each CT perfusion parameter was compared between well differentiated and moderately/poorly differentiated lesions according to WHO classification evaluated off-site.

End point type	Secondary

End point timeframe:

Within a week from CT perfusion to surgery

End point values	Patients with well-differentiated lesions	Patients with moderately/poorly-differentiated lesions		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	38	42		
Units: percentage				
arithmetic mean (standard deviation)	75.232 (± 18.458)	80.834 (± 14.503)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were recorded during and immediately after the CT perfusion examination over a 30 min follow up period.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Safety Set
Reporting group description:	
All included patients receiving at least one injection of Xenetix, regardless of the quantity. This set was used for safety analyses.	

Serious adverse events	Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 84 (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	Safety Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 84 (4.76%)		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 84 (2.38%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 84 (1.19%)		
occurrences (all)	1		
Infections and infestations			

Pneumonia subjects affected / exposed occurrences (all)	1 / 84 (1.19%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 April 2012	Modifying the time of surgery, specifying the first non-inclusion criteria, and need of body weight.
27 September 2012	Modifying inclusion criteria with additional types of surgery, the administration of product and imaging protocol for morphologic CT were clarified, treatment for surgery and anaesthesia's preparation were excluded from reported concomitant treatment.
16 July 2013	Adjusting the number of patients to be enrolled, adjusting the acquisition parameters and process for scanning the pathology slides.
05 November 2015	Modifying the protocol of the central reading of pathology material and the date of study end

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported