Clinical trial results:
Proof of Concept study concerning efficacy of P03277 MR Imaging in HCC diagnosis
Phase IIa Clinical Study

Summary

EudraCT number	2016-002930-62
Trial protocol	FR
Global end of trial date	04 April 2019

Results information

Result version number	v1 (current)
This version publication date	28 October 2020
First version publication date	28 October 2020

Trial information

Trial identification

Sponsor protocol code	GDX-44-008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02973516
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GUERBET
Sponsor organisation address	BP 57400, Roissy CdG, France, 95943, Villepinte, France, 93420
Public contact	Jing HAO, Global Head of Medical Affairs & Clinical Development, GUERBET, 33 0145917626, jing.hao@guerbet.com
Scientific contact	Jing HAO, Global Head of Medical Affairs & Clinical Development, GUERBET, 33 0145915176, jing.hao@guerbet.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	04 April 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 April 2019
Global end of trial reached?	Yes
Global end of trial date	04 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the diagnostic value for hepatocellular carcinoma (HCC) of P03277 in patients with suspected small nodules and chronic liver disease.

Protection of trial subjects:

This trial has been conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, that are consistent with Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines and with the applicable regional/local regulations of the country in which the trial was conducted.
The safety data were monitored during the whole study period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 December 2016
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	France: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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	16
85 years and over	0

Subject disposition

Recruitment	
Recruitment details: -	
Pre-assignment	
Screening details: -	
Pre-assignment period milestones	
Number of subjects started	40
Number of subjects completed	40

Period 1	
Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Are arms mutually exclusive?	Yes
Arm title	P03277 - 0.1 mmol/kg

Arm description:

Subjects who have received P03277 (gadopiclenol) at the dose of 0.1 mmol/kg

Arm type	Experimental
Investigational medicinal product name	P03277
Investigational medicinal product code	
Other name	gadopiclenol
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

0.1 mmol/kg in a single injection

Arm title	P03277 - 0.05 mmol/kg

Arm description:

Subjects who have received P03277 (gadopiclenol) at the dose of 0.05 mmol/kg

Arm type	Experimental
Investigational medicinal product name	P03277
Investigational medicinal product code	
Other name	gadopiclenol
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

0.05 mmol/kg in a single injection

Number of subjects in period 1	P03277 - 0.1 mmol/kg	P03277 - 0.05 mmol/kg
Started	30	10
Completed	30	10

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	40	40	
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)	24	24	
From 65-84 years	16	16	
85 years and over	0	0	
Age continuous Units: years			
median	62		
full range (min-max)	21 to 78	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	32	32	
Weight Units: kilogram(s)			
median	78		
full range (min-max)	58 to 118	-	

End points

End points reporting groups

Reporting group title	P03277 - 0.1 mmol/kg
Reporting group description:	
Subjects who have received P03277 (gadopiclenol) at the dose of 0.1 mmol/kg	
Reporting group title	P03277 - 0.05 mmol/kg
Reporting group description:	
Subjects who have received P03277 (gadopiclenol) at the dose of 0.05 mmol/kg	

Primary: HCC diagnosis according to gadopiclenol MR imaging

End point title	HCC diagnosis according to gadopiclenol MR imaging[1]
End point description:	
End point type	Primary
End point timeframe:	
1 day procedure	

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: As a proof of concept study, no statistical analyses were performed.

End point values	P03277 - 0.1 mmol/kg	P03277 - 0.05 mmol/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	10		
Units: Nodules				
HCC	16	4		
Not HCC	27	9		

Statistical analyses

No statistical analyses for this end point

Primary: HCC diagnosis according to standard of reference

End point title	HCC diagnosis according to standard of reference[2]
End point description:	
The standard of reference is composed of histology analysis or two previous contrast-enhanced imaging (CT and/or MRI) and/or the most recent AFP results available.	
End point type	Primary
End point timeframe:	
Data collected before inclusion or at the optional visit 4 (up to 13 weeks after contrast administration)	

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: As a proof of concept study, no statistical analyses were performed.

End point values	P03277 - 0.1 mmol/kg	P03277 - 0.05 mmol/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	10		
Units: Nodules				
HCC	21	5		
Not HCC	22	8		

Statistical analyses

No statistical analyses for this end point

Primary: Diagnostic value evaluation for HCC

End point title	Diagnostic value evaluation for HCC[3]

End point description:

Sensitivity: number of nodules showing true positive HCC divided by all nodules considered HCC according to standard of reference.
Specificity: number of nodules showing true negative HCC divided by all nodules considered as not HCC or uncertain according to standard of reference.
Accuracy: number of nodules showing true positive HCC and true negative HCC over all nodules.
Positive predictive value: number of nodules showing true positive HCC divided by all nodules showing HCC according to gadopiclenol MR imaging.
Negative predictive value: number of nodules showing true negative HCC divided by all nodules not showing HCC according to gadopiclenol MR imaging.

End point type	Primary

End point timeframe:

Based on data collected before inclusion or at the optional visit 4 (up to 13 weeks after contrast administration) for the standard of reference and day 1 for gadopiclenol MR imaging.

Notes:

[3] - 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: As a proof of concept study, no statistical analyses were performed.

End point values	P03277 - 0.1 mmol/kg	P03277 - 0.05 mmol/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	10		
Units: Percent (%) lesions				
number (not applicable)				
Sensitivity	62	80		
Specificity	86	100		
Accuracy	74	92		
Positive predictive value	81	100		
Negative predictive value	70	89		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent signature to 1 day after contrast injection and at optional visit 4 (up to 13 weeks after contrast injection)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	P03277 all doses

Reporting group description: -

Serious adverse events	P03277 all doses		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 40 (2.50%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Procedural complication	Additional description: COMPLICATED BIOPSY		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastric perforation			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	P03277 all doses		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 40 (22.50%)		
Investigations			

Blood pressure increased	Additional description: Not related to contrast		
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
General disorders and administration site conditions			
Feeling hot			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Injection site coldness			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Injection site haematoma	Additional description: Not related to contrast		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Injection site pain			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscle tightness	Additional description: Not related to contrast		
subjects affected / exposed	1 / 40 (2.50%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2016	- Corrections within inclusion and non-inclusion criteria about duration of amenorrhea (>12 months amenorrhea) for post-menopausal criteria and accepted contraception methods. - Only one pregnancy test was required within 24h before gadopiclenol administration. - Only random glucose was required instead of glucose under fasting conditions. - Efficacy evaluation was reviewed and made consistent. - Race and ethnicity were needed to be collected. - The safety reporting section was modified according to new pharmacovigilance requirements in France and within Europe and for better management of new signal detection.
12 December 2017	- An additional 3D GRE T1 sequence with fat saturation was added at 15 ± 5 minutes in order to better see the kinetics of gadopiclenol. - A second cohort of 10 additional patients were recruited and received a dose of 0.05 mmol/kg. - It was acceptable to consider for standard of reference results of histology done within 2 months prior to gadopiclenol MR imaging.

Notes:

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.

Gadopiclenol at 0.05 mmol/kg seems sufficient for HCC diagnosis. Gadopiclenol at 0.1 mmol/kg prolonged wash-out time at portal/delayed phases due to its high relaxivity, leading to lower diagnostic accuracy as per EASL guidelines diagnostic criteria

Notes: