Clinical trial results:
DOTAREM® Pharmacokinetics, Safety and Efficacy Study in Pediatric Subjects Aged <2 Years (Term Newborn Infants to Toddlers 23 Months of Age Inclusive)

Summary

EudraCT number	2013-003215-21
Trial protocol	FR HU AT
Global end of trial date	19 October 2015

Results information

Result version number	v1 (current)
This version publication date	16 July 2016
First version publication date	16 July 2016

Trial information

Trial identification

Sponsor protocol code	DGD-44-063

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02411201
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 65.041

Notes:

Sponsors

Sponsor organisation name	GUERBET
Sponsor organisation address	BP 57400, ROISSY CDG Cedex, France, 95943
Public contact	Corinne DUBOURDIEU, Head of Clinical Projects , GUERBET, 0033 145915000, corinne.dubourdieu@guerbet-group.com
Scientific contact	Corinne DUBOURDIEU, Head of Clinical Projects , GUERBET, 0033 145915000, corinne.dubourdieu@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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2015
Global end of trial reached?	Yes
Global end of trial date	19 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate pharmacokinetics profile in plasma of DOTAREM following single intravenous injection in pediatric subjects aged up to 23 months (inclusive)

Protection of trial subjects:

A PK population approach with sparse blood sampling was used to minimize the clinical burden to children.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 March 2015
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	Poland: 32
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Hungary: 11
Worldwide total number of subjects	51
EEA total number of subjects	51

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	5
Infants and toddlers (28 days-23 months)	46
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	51
Number of subjects completed	45

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	Adverse event, non-fatal: 2
Reason: Number of subjects	Age group completed: 2

Period 1

Period 1 title	overall period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	DOTAREM

Arm description: -

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

Dosage and administration details:

0.1 mmol/kg BW (0.2 ml/kg BW) in a single intravenous injection at 1-2 ml/s

Number of subjects in period 1[1]	DOTAREM
Started	45
Completed	45

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 51 subjects were enrolled. Among them 45 subjects received IMP. 6 subjects did not reach the baseline period due to non-completion of the pre-assignment period; reasons are reported. Baseline period includes subjects who received IMP only.

Baseline characteristics

Reporting groups	
Reporting group title	overall period

Reporting group description: -

Reporting group values	overall period	Total	
Number of subjects	45	45	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	5	5	
Infants and toddlers (28 days-23 months)	40	40	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: months			
arithmetic mean	9.88		
standard deviation	± 7.36	-	
Gender categorical Units: Subjects			
Female	23	23	
Male	22	22	
Body weight Units: kg			
arithmetic mean	8.1		
standard deviation	± 3.1	-	

End points

End points reporting groups

Reporting group title	DOTAREM

Reporting group description: -

Primary: Terminal elimination half life

End point title	Terminal elimination half life[1]

End point description:

End point type	Primary

End point timeframe:

Blood sampling done 3 times: between 10 min to 60 min, between 2h to 4h and between 6h to 8h post-injection

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: No statistical analysis for this endpoint. Descriptive statistics only for PK endpoints

End point values	DOTAREM			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: hour				
median (full range (min-max))	1.3545 (0.8859 to 3.0291)			

Statistical analyses

No statistical analyses for this end point

Primary: Area under the curve

End point title	Area under the curve[2]

End point description:

End point type	Primary

End point timeframe:

Blood sampling done 3 times: between 10 min to 60 min, between 2h to 4h and between 6h to 8h post-injection

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: No statistical analysis for this endpoint. Descriptive statistics only for PK endpoints

End point values	DOTAREM			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: hour.µmol/L				
median (full range (min-max))	1591.1 (981.43 to 2841)			

Statistical analyses

No statistical analyses for this end point

Primary: Clearance

End point title	Clearance[3]

End point description:

End point type	Primary

End point timeframe:

Blood sampling done 3 times: between 10 min to 60 min, between 2h to 4h and between 6h to 8h post-injection

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: No statistical analysis for this endpoint. Descriptive statistics only for PK endpoints

End point values	DOTAREM			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: litre/h per kg				
median (full range (min-max))	0.0602 (0.0352 to 0.1019)			

Statistical analyses

No statistical analyses for this end point

Primary: Volume of distribution at steady state

End point title	Volume of distribution at steady state[4]

End point description:

End point type	Primary

End point timeframe:

Blood sampling done 3 times: between 10 min to 60 min, between 2h to 4h and between 6h to 8h post-injection

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 statistical analysis for this endpoint. Descriptive statistics only for PK endpoints

End point values	DOTAREM			
Subject group type	Reporting group			
Number of subjects analysed	45			
Units: litre/kg				
median (full range (min-max))	0.0473 (0.0273 to 0.1597)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent signature untill end of study (7+/- 1 days after IMP administration)

Adverse event reporting additional description:

Adverse events occuring after IMP administration are listed below.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Safety set

Reporting group description: -

Serious adverse events	Safety set		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 45 (2.22%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	1 / 45 (2.22%)		
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	Safety set		
Total subjects affected by non-serious adverse events subjects affected / exposed	13 / 45 (28.89%)		
Nervous system disorders Tremor subjects affected / exposed occurrences (all)	1 / 45 (2.22%) 1		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) Device difficult to use subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	5 / 45 (11.11%) 5 1 / 45 (2.22%) 1 1 / 45 (2.22%) 1		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 45 (4.44%) 2 1 / 45 (2.22%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting	1 / 45 (2.22%) 1 1 / 45 (2.22%) 1 1 / 45 (2.22%) 1		

subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 45 (2.22%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2014	Change the study phase from phase I to phase IV: the Investigational Medicinal Product (DOTAREM®) was used in the study in indications and population approved in the countries where the study was conducted. The reference document was the local Summary of Product Characteristics. Add clarification on the collection of blood for PK
24 March 2015	Removal of coordinating investigator due to the death of Pr Guy Sebag. Recruitment period extended to Q4 2015 and enlarged to 20 sites worldwide. Inclusion criterion related to the normal renal function was clarified. Non-inclusion criterion related to severe liver disease was clarified. Non-inclusion criterion related to the previous participation to a clinical study was reduced to 7 days. Non-inclusion criteria related to the concomitant participation to a clinical study was clarified. The group of age was collected instead of date of birth according to local regulations in some countries. The definition of overdose was added to follow an update in Good Vigilance Practice. Rules for rounding the dose administered were then removed. Adverse event definition, including overdose, was updated. The “safety follow-up phone call” at visit 4 was changed in a “safety follow-up contact” which allowed different ways to monitor the subject’s safety at day 7 +/- 1. Clarifications were made on the use of local laboratory data to validate the normal renal function at inclusion time.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported