Clinical trial results:
Pharmacokinetics, safety and efficacy of a new gadolinium-based contrast agent, P03277, in pediatric patients from 2 to 17 years of age undergoing central nervous system contrast-enhanced MRI.

Summary

EudraCT number	2018-001516-30
Trial protocol	SK PL BG
Global end of trial date	10 August 2020

Results information

Result version number	v1 (current)
This version publication date	24 June 2021
First version publication date	24 June 2021

Trial information

Trial identification

Sponsor protocol code	GDX-44-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03749252
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 123673

Notes:

Sponsors

Sponsor organisation name	GUERBET
Sponsor organisation address	BP 57400, Roissy CdG, France, 95943, Villepinte, France,
Public contact	Global Head of Medical Affairs & Clinical Development, GUERBET, +33 0145915176, jing.hao@guerbet.com
Scientific contact	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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001949-PIP01-16, EMEA-001949-PIP02-18
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	16 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 August 2020
Global end of trial reached?	Yes
Global end of trial date	10 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetic profile of gadopiclenol (P03277) in plasma following single intravenous injection of 0.05 mmol/kg body weight in pediatric population aged from 2 to 17 years undergoing central nervous system (CNS) contrast-enhanced magnetic resonance imaging (MRI) (CNS cohort).

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	06 November 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Poland: 37
Country: Number of subjects enrolled	Slovakia: 16
Country: Number of subjects enrolled	Ukraine: 8
Worldwide total number of subjects	80
EEA total number of subjects	72

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)	49
Adolescents (12-17 years)	31
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

An age-down staggered approach was used. Patients were recruited into 3 predefined age groups. The inclusions started with Adolescents (12-17 years), followed by Preadolescents (7-11 years) and finally Young Children (2-6 years).

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	80
Number of subjects completed	80

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	CNS_2-6 years

Arm description:

Patients aged 2-6 years who underwent CNS contrast-enhanced MRI

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

Dosage and administration details:

0.05 mmol/kg in a single injection

Arm title	CNS_7-11 years

Arm description:

Patients aged 7-11 years who underwent CNS contrast-enhanced MRI

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

Dosage and administration details:

0.05 mmol/kg in a single injection

Arm title	CNS_12-17 years

Arm description:

Patients aged 12-17 years who underwent CNS contrast-enhanced MRI

Arm type	Experimental

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

Dosage and administration details:
0.05 mmol/kg in a single injection

Arm title	Body_2-17 years

Arm description:
Patients aged 2-17 years who underwent Body contrast-enhanced MRI

Arm type	Experimental
Investigational medicinal product name	gadopiclenol
Investigational medicinal product code	
Other name	
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	CNS_2-6 years	CNS_7-11 years	CNS_12-17 years
Started	20	20	20
Completed	20	20	20

Number of subjects in period 1	Body_2-17 years
Started	20
Completed	20

Baseline characteristics

Reporting groups	
Reporting group title	Period 1

Reporting group description: -

Reporting group values	Period 1	Total	
Number of subjects	80	80	
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)	49	49	
Adolescents (12-17 years)	31	31	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	9.3		
standard deviation	± 4.7	-	
Gender categorical Units: Subjects			
Female	39	39	
Male	41	41	
Weight Units: kilogram(s)			
arithmetic mean	39.61		
standard deviation	± 21.02	-	

End points

End points reporting groups

Reporting group title	CNS_2-6 years
Reporting group description:	
Patients aged 2-6 years who underwent CNS contrast-enhanced MRI	
Reporting group title	CNS_7-11 years
Reporting group description:	
Patients aged 7-11 years who underwent CNS contrast-enhanced MRI	
Reporting group title	CNS_12-17 years
Reporting group description:	
Patients aged 12-17 years who underwent CNS contrast-enhanced MRI	
Reporting group title	Body_2-17 years
Reporting group description:	
Patients aged 2-17 years who underwent Body contrast-enhanced MRI	

Primary: Clearance

End point title	Clearance[1][2]
End point description:	
End point derived from a PopPK model and assessed only in the CNS cohort	
End point type	Primary
End point timeframe:	
Four blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (1-20 min, 30-45 min, 2-3 h, 7-8 h).	

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

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point assessed only in the CNS cohort

End point values	CNS_2-6 years	CNS_7-11 years	CNS_12-17 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	19	
Units: L/h/kg				
median (full range (min-max))	0.12 (0.05 to 0.28)	0.10 (0.04 to 0.24)	0.08 (0.04 to 0.20)	

Statistical analyses

No statistical analyses for this end point

Primary: Central volume of distribution (V1)

End point title	Central volume of distribution (V1)[3][4]

End point description:

End point derived from a PopPK model and assessed only in the CNS cohort

End point type	Primary

End point timeframe:

Four blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (1-20 min, 30-45 min, 2-3 h, 7-8 h).

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

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point assessed only in the CNS cohort

End point values	CNS_2-6 years	CNS_7-11 years	CNS_12-17 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	19	
Units: L/kg				
median (full range (min-max))	0.12 (0.06 to 0.26)	0.12 (0.06 to 0.24)	0.11 (0.05 to 0.24)	

Statistical analyses

No statistical analyses for this end point

Primary: Peripheral volume of distribution (V2)

End point title	Peripheral volume of distribution (V2)[5][6]

End point description:

End point derived from a PopPK model and assessed only in the CNS cohort

End point type	Primary

End point timeframe:

Four blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (1-20 min, 30-45 min, 2-3 h, 7-8 h).

Notes:

[5] - 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

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point assessed only in the CNS cohort

End point values	CNS_2-6 years	CNS_7-11 years	CNS_12-17 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	19	
Units: L/kg				
median (full range (min-max))	0.06 (0.06 to 0.06)	0.06 (0.06 to 0.06)	0.06 (0.06 to 0.06)	

Statistical analyses

No statistical analyses for this end point

Primary: Terminal elimination half-life

End point title	Terminal elimination half-life[7][8]

End point description:

End point derived from a PopPK model and assessed only in the CNS cohort

End point type	Primary

End point timeframe:

Four blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (1-20 min, 30-45 min, 2-3 h, 7-8 h).

Notes:

[7] - 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

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point assessed only in the CNS cohort

End point values	CNS_2-6 years	CNS_7-11 years	CNS_12-17 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	19	
Units: hour				
median (full range (min-max))	1.29 (0.69 to 3.38)	1.48 (0.83 to 3.20)	1.77 (1.00 to 3.57)	

Statistical analyses

No statistical analyses for this end point

Primary: Simulated gadopiclenol concentrations 10 min post-injection

End point title	Simulated gadopiclenol concentrations 10 min post-

End point description:

End point derived from a PopPK model and assessed only in the CNS cohort

End point type	Primary

End point timeframe:

Four blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (1-20 min, 30-45 min, 2-3 h, 7-8 h).

Notes:

[9] - 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

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point assessed only in the CNS cohort

End point values	CNS_2-6 years	CNS_7-11 years	CNS_12-17 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	19	
Units: mg/L				
arithmetic mean (standard deviation)	302.11 (± 44.68)	327.20 (± 47.95)	349.15 (± 52.59)	

Statistical analyses

No statistical analyses for this end point

Primary: Simulated gadopiclenol concentrations 20 min post-injection

End point title	Simulated gadopiclenol concentrations 20 min post-

End point description:

End point derived from a PopPK model and assessed only in the CNS cohort

End point type	Primary

End point timeframe:

Four blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (1-20 min, 30-45 min, 2-3 h, 7-8 h).

Notes:

[11] - 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

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point assessed only in the CNS cohort

End point values	CNS_2-6 years	CNS_7-11 years	CNS_12-17 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	19	
Units: mg/L				
arithmetic mean (standard deviation)	234.88 (± 30.18)	259.67 (± 32.02)	285.16 (± 35.35)	

Statistical analyses

No statistical analyses for this end point

Primary: Simulated gadopiclenol concentrations 30 min post-injection

End point title	Simulated gadopiclenol concentrations 30 min post-

End point description:

End point derived from a PopPK model and assessed only in the CNS cohort

End point type	Primary

End point timeframe:

Four blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (1-20 min, 30-45 min, 2-3 h, 7-8 h).

Notes:

[13] - 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

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point assessed only in the CNS cohort

End point values	CNS_2-6 years	CNS_7-11 years	CNS_12-17 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	19	
Units: mg/L				
arithmetic mean (standard error)	188.26 (± 25.10)	211.20 (± 25.82)	237.25 (± 26.97)	

Statistical analyses

No statistical analyses for this end point

Primary: Simulated area under the curve (AUCinf)

End point title	Simulated area under the curve (AUCinf)[15][16]

End point description:

End point derived from a PopPK model and assessed only in the CNS cohort

End point type	Primary

End point timeframe:

Four blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (1-20 min, 30-45 min, 2-3 h, 7-8 h).

Notes:

[15] - 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

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: End point assessed only in the CNS cohort

End point values	CNS_2-6 years	CNS_7-11 years	CNS_12-17 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	20	20	19	
Units: mg.h/L				
arithmetic mean (standard deviation)	403.16 (± 93.35)	477.25 (± 105.71)	582.30 (± 122.08)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent signature untill the end of the study (up to 120 days after gadopiclenol administration).

Adverse event reporting additional description:

Adverse events occuring during or after gadopiclenol administration are listed below.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Safety Set

Reporting group description:

All patients administered gadopiclenol

Serious adverse events	Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 80 (3.75%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Head injury	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Epilepsy	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coma	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Condition aggravated	Additional description: Not related to contrast		
subjects affected / exposed	2 / 80 (2.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hydronephrosis	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Tonsillitis	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
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 / 80 (16.25%)		
Investigations			
Blood pressure increased	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Electrocardiogram QT prolonged	Additional description: Related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Eosinophil count increased	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Neutrophil count decreased	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Cardiac disorders			
Long QT syndrome	Additional description: Not related to contrast		

subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	2		
Nervous system disorders			
Epilepsy	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
General disorders and administration site conditions			
Condition aggravated	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Application site erythema	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Nausea	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Vomiting	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Rhinorrhoea	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Pruritus	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Rash maculo-papular	Additional description: Related to contrast		

subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Infections and infestations			
Herpes virus infection	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Nasopharyngitis	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Pharyngitis	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Respiratory tract infection viral	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Tracheobronchitis mycoplasmal	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Upper respiratory tract infection	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		
Urinary tract infection	Additional description: Not related to contrast		
subjects affected / exposed	1 / 80 (1.25%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2018	Total urine collection from 0 to 8 hours for PK assessment in patients capable to control urination was added in appropriate sections, while the spot urine sample at 1 day after the injection was finally not collected. In addition, the collection of serious AEs was prolonged up to the last follow-up visit at day 90.
19 March 2019	An additional cohort of 20 patients, receiving 0.05 mmol/kg of gadopiclenol, was included in order to assess the safety and urinary excretion of gadopiclenol and efficacy of gadopiclenol-enhanced MRI in children with pathologies of various body organs. This amendment was approved in Ukraine under the condition that no patients would be enrolled in the Body cohort in this country.
24 April 2020	The main changes implemented in this amendment were the possibility to perform visits V3 and V4 remotely and additional on-site visits were scheduled at the latest 30 days and 120 days after gadopiclenol administration. Regarding the Body cohort, it was possible to shorten the 8-hour confinement period if it could not be respected and it was possible to perform the day 2 visit at patient's home and remotely at the very least. This amendment was not submitted in Ukraine.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported