Clinical trial results:
Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI

Summary

EudraCT number	2021-003825-31
Trial protocol	HU PL BG
Global end of trial date	30 September 2024

Results information

Result version number	v1 (current)
This version publication date	16 April 2025
First version publication date	16 April 2025

Trial information

Trial identification

Sponsor protocol code	GDX-44-015

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05590884
WHO universal trial number (UTN)	-
Other trial identifiers	IND No.: : 123673

Notes:

Sponsors

Sponsor organisation name	Guerbet
Sponsor organisation address	15, rue des Vanesses, Villepinte, France, 93420
Public contact	Frantz Hebert, Global Head of Clinical Development, Guerbet, +33 680249334, frantz.hebert@guerbet.com
Scientific contact	Frantz Hebert, Global Head of Clinical Development, Guerbet, +33 680249334, frantz.hebert@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	19 December 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2024
Global end of trial reached?	Yes
Global end of trial date	30 September 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the pharmacokinetic profile of gadopiclenol in plasma following single intravenous injection of 0.05 mmol/kg body weight (BW) in pediatric population aged up to 23 months (inclusive) scheduled for a contrast-enhanced MRI examination of any body region including central nervous system (CNS).

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.
A Trial Safety Review Board (TSRB) was set up to ensure the participants' safety, appraise the trial conduct and progress and make a decision on providing green light for next age group (when applicable).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 September 2022
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	Poland: 19
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	36
EEA total number of subjects	31

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	1

Infants and toddlers (28 days-23 months)	35
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:

The inclusions started with the oldest patients (3 to 23 months). The aged-down staggered approach was discontinued to allow the inclusions of patients aged from birth to 27 days, simultaneously to inclusions of other 2 age groups (3-23 months group and 28- 89 days group). The inclusions in the 3 age groups were therefore completed in parallel.

Pre-assignment

Screening details:

A total of 41 patients were enrolled. Among them, five patients were screen failed. Therefore, 36 patients received an injection of gadopiclenol for MRI: 33 aged 3-23 months, 2 aged 28-89 days and 1 aged 0-27 days. One patient aged 3-23 months prematurely discontinued the study before the 1-day safety follow-up due to withdrawal of consent.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group1: 3-23 months

Arm description:

Patients aged 3-23 months who underwent a contrast-enhanced MRI examination of any body region including central nervous system (CNS cohort), vessels (Blood vessel cohort) and pool of others region (Body cohort)

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

Dosage and administration details:

gadopiclenol administered at a dose of 0.05 mmol/kg body weight (0.1 mL/kg body weight) in a single injection

Arm title	Group 2: 28-89 days

Arm description:

Patients aged 28-89 days who underwent a contrast-enhanced MRI examination of any body region including central nervous system (CNS cohort), vessels (Blood vessel cohort) and pool of others region (Body cohort)

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

Dosage and administration details:

gadopiclenol administered at a dose of 0.05 mmol/kg body weight (0.1 mL/kg body weight) in a single injection

Arm title	Group 3: 0-27 days

Arm description:

Patients aged 0-27 days who underwent a contrast-enhanced MRI examination of any body region

including central nervous system (CNS cohort), vessels (Blood vessel cohort) and pool of others region (Body cohort)

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

Dosage and administration details:

gadopiclenol administered at a dose of 0.05 mmol/kg body weight (0.1 mL/kg body weight) in a single injection

Number of subjects in period 1	Group1: 3-23 months	Group 2: 28-89 days	Group 3: 0-27 days
Started	33	2	1
Completed	33	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Group1: 3-23 months
Reporting group description:	
Patients aged 3-23 months who underwent a contrast-enhanced MRI examination of any body region including central nervous system (CNS cohort), vessels (Blood vessel cohort) and pool of others region (Body cohort)	
Reporting group title	Group 2: 28-89 days
Reporting group description:	
Patients aged 28-89 days who underwent a contrast-enhanced MRI examination of any body region including central nervous system (CNS cohort), vessels (Blood vessel cohort) and pool of others region (Body cohort)	
Reporting group title	Group 3: 0-27 days
Reporting group description:	
Patients aged 0-27 days who underwent a contrast-enhanced MRI examination of any body region including central nervous system (CNS cohort), vessels (Blood vessel cohort) and pool of others region (Body cohort)	

Reporting group values	Group1: 3-23 months	Group 2: 28-89 days	Group 3: 0-27 days
Number of subjects	33	2	1
Age categorical Units: Subjects			
Newborns (0-27 days)	0	0	1
3-23 months	33	0	0
28-89 days	0	2	0
Age continuous Units: months			
arithmetic mean	13.11	1.94	0.8
standard deviation	± 6.22	± 0.14	± 0
Gender categorical Units: Subjects			
Female	17	1	0
Male	16	1	1
Weight Units: kilogram(s)			
arithmetic mean	9.40	5.10	4.50
standard deviation	± 2.18	± 0.28	±

Reporting group values	Total		
Number of subjects	36		
Age categorical Units: Subjects			
Newborns (0-27 days)	1		
3-23 months	33		
28-89 days	2		
Age continuous Units: months			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female	18		
Male	18		
Weight Units: kilogram(s) arithmetic mean standard deviation	 -		

Subject analysis sets

Subject analysis set title	Pharmacokinetics Analyses
Subject analysis set type	Per protocol

Subject analysis set description:

Patients from the GDX-44-015 Per Protocol Set (PPS) population including all patients in the Safety Set without major deviations likely to impact the population PK model was used for the population PK analysis (35 patients). The reference population including 134 participants from studies GDX-44-003 (adult participants with normal renal function), GDX-44-005 (including adult participants with renal impairment [mild, moderate or severe]) and GDX-44-007 pediatric patients (2-17 years old) was used to set up gadopiclenol popPK model. Due to incomplete recruitment in study GDX-44-015, with only 2 patients aged 28-89 days and none aged less than 28 days who could be included in the popPK analysis, exposure in these groups was only obtained by simulation using the final model.

Reporting group values	Pharmacokinetics Analyses		
Number of subjects	35		
Age categorical Units: Subjects			
Newborns (0-27 days)	1		
3-23 months	32		
28-89 days	2		
Age continuous Units: months arithmetic mean standard deviation	 12.1 ± 6.6		
Gender categorical Units: Subjects			
Female	18		
Male	17		
Weight Units: kilogram(s) arithmetic mean standard deviation	 9.16 ± 2.35		

End points

End points reporting groups

Reporting group title	Group1: 3-23 months

Reporting group description:

Patients aged 3-23 months who underwent a contrast-enhanced MRI examination of any body region including central nervous system (CNS cohort), vessels (Blood vessel cohort) and pool of others region (Body cohort)

Reporting group title	Group 2: 28-89 days

Reporting group description:

Patients aged 28-89 days who underwent a contrast-enhanced MRI examination of any body region including central nervous system (CNS cohort), vessels (Blood vessel cohort) and pool of others region (Body cohort)

Reporting group title	Group 3: 0-27 days

Reporting group description:

Patients aged 0-27 days who underwent a contrast-enhanced MRI examination of any body region including central nervous system (CNS cohort), vessels (Blood vessel cohort) and pool of others region (Body cohort)

Subject analysis set title	Pharmacokinetics Analyses
Subject analysis set type	Per protocol

Subject analysis set description:

Patients from the GDX-44-015 Per Protocol Set (PPS) population including all patients in the Safety Set without major deviations likely to impact the population PK model was used for the population PK analysis (35 patients). The reference population including 134 participants from studies GDX-44-003 (adult participants with normal renal function), GDX-44-005 (including adult participants with renal impairment [mild, moderate or severe]) and GDX-44-007 pediatric patients (2-17 years old) was used to set up gadopiclenol popPK model. Due to incomplete recruitment in study GDX-44-015, with only 2 patients aged 28-89 days and none aged less than 28 days who could be included in the popPK analysis, exposure in these groups was only obtained by simulation using the final model.

Primary: Area under the curve (AUCinf)

End point title	Area under the curve (AUCinf)[1]

End point description:

Exposure parameter by age group predicted from the final model in participants with normal renal function receiving gadopiclenol 0.05 mmol/kg

End point type	Primary

End point timeframe:

Three blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (10-60 min, 2-4 hours, 6-8 h). Each time window contained 4 time points for blood collection.

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: The primary criteria was pharmacokinetics in plasma for pediatric patients aged up to 23 months
(inclusive) assessed based on the following pharmacokinetic parameters determined from the population PK (popPK) model: simulated concentrations at 10, 20, and 30 minutes post injection (C10 min, C20 min, C30 min); Area Under the Curve (AUC); Elimination half-life; Total clearance (CL); Volume of distribution. Descriptive statistical analysis was performed for pharmacokinetic profile in plasma.

End point values	Group1: 3-23 months	Group 2: 28-89 days	Group 3: 0-27 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	2	0[2]	
Units: h.mg/L				
geometric mean (geometric coefficient of variation)	392.3 (± 27.6)	493.3 (± 9.9)	()	

Notes:

[2] - The patient aged 0-27 days was excluded from the Per Protocol Set due to a major deviation.

Statistical analyses

No statistical analyses for this end point

Primary: Terminal half-life (t1/2α)

End point title	Terminal half-life (t1/2α)[3]

End point description:

Exposure parameter by age group predicted from the final model in participants with normal renal function receiving gadopiclenol 0.05 mmol/kg

End point type	Primary

End point timeframe:

Three blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (10-60 min, 2-4 hours, 6-8 h). Each time window contained 4 time points for blood collection.

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: The primary criteria was pharmacokinetics in plasma for pediatric patients aged up to 23 months
(inclusive) assessed based on the following pharmacokinetic parameters determined from the population PK (popPK) model: simulated concentrations at 10, 20, and 30 minutes post injection (C10 min, C20 min, C30 min); Area Under the Curve (AUC); Elimination half-life; Total clearance (CL); Volume of distribution. Descriptive statistical analysis was performed for pharmacokinetic profile in plasma.

End point values	Group1: 3-23 months	Group 2: 28-89 days	Group 3: 0-27 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	2	0[4]	
Units: h				
geometric mean (geometric coefficient of variation)	0.3 (± 30.3)	0.3 (± 30.3)	()	

Notes:

[4] - The patient aged 0-27 days was excluded from the Per Protocol Set, due to a major deviation.

Statistical analyses

No statistical analyses for this end point

Primary: Terminal half-life (t1/2β)

End point title	Terminal half-life (t1/2β)[5]

End point description:

Exposure parameter by age group predicted from the final model in participants with normal renal function receiving gadopiclenol 0.05 mmol/kg

End point type	Primary

End point timeframe:

Three blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (10-60 min, 2-4 hours, 6-8 h). Each time window contained 4 time points for blood collection.

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: The primary criteria was pharmacokinetics in plasma for pediatric patients aged up to 23 months
(inclusive) assessed based on the following pharmacokinetic parameters determined from the population PK (popPK) model: simulated concentrations at 10, 20, and 30 minutes post injection (C10 min, C20 min, C30 min); Area Under the Curve (AUC); Elimination half-life; Total clearance (CL); Volume of distribution. Descriptive statistical analysis was performed for pharmacokinetic profile in plasma.

End point values	Group1: 3-23 months	Group 2: 28-89 days	Group 3: 0-27 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	2	0[6]	
Units: h				
geometric mean (geometric coefficient of variation)	1.5 (± 21.4)	2.1 (± 8.4)	()	

Notes:

[6] - The patient aged 0-27 days was excluded from the Per Protocol Set, due to a major deviation.

Statistical analyses

No statistical analyses for this end point

Primary: Gadopiclenol concentrations 10 min post-injection (C10 min)

End point title	Gadopiclenol concentrations 10 min post-injection (C10 min)[7]

End point description:

Exposure parameter by age group predicted from the final model in participants with normal renal function receiving gadopiclenol 0.05 mmol/kg

End point type	Primary

End point timeframe:

Three blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (10-60 min, 2-4 hours, 6-8 h). Each time window contained 4 time points for blood collection.

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: The primary criteria was pharmacokinetics in plasma for pediatric patients aged up to 23 months
(inclusive) assessed based on the following pharmacokinetic parameters determined from the population PK (popPK) model: simulated concentrations at 10, 20, and 30 minutes post injection (C10 min, C20 min, C30 min); Area Under the Curve (AUC); Elimination half-life; Total clearance (CL); Volume of distribution. Descriptive statistical analysis was performed for pharmacokinetic profile in plasma.

End point values	Group1: 3-23 months	Group 2: 28-89 days	Group 3: 0-27 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	2	0[8]	
Units: mg/L				
geometric mean (geometric coefficient of variation)	226.8 (± 15.8)	190.4 (± 16.2)	()	

Notes:

[8] - The patient aged 0-27 days was excluded from the Per Protocol Set, due to a major deviation.

Statistical analyses

No statistical analyses for this end point

Primary: Gadopiclenol concentration 20 min post-injection (C20 min)

End point title	Gadopiclenol concentration 20 min post-injection (C20 min)[9]

End point description:

Exposure parameter by age group predicted from the final model in participants with normal renal function receiving gadopiclenol 0.05 mmol/kg

End point type	Primary

End point timeframe:

Three blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (10-60 min, 2-4 hours, 6-8 h). Each time window contained 4 time points for blood collection.

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: The primary criteria was pharmacokinetics in plasma for pediatric patients aged up to 23 months
(inclusive) assessed based on the following pharmacokinetic parameters determined from the population PK (popPK) model: simulated concentrations at 10, 20, and 30 minutes post injection (C10 min, C20 min, C30 min); Area Under the Curve (AUC); Elimination half-life; Total clearance (CL); Volume of distribution. Descriptive statistical analysis was performed for pharmacokinetic profile in plasma.

End point values	Group1: 3-23 months	Group 2: 28-89 days	Group 3: 0-27 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	2	0[10]	
Units: mg/L				
geometric mean (geometric coefficient of variation)	161.5 (± 17.2)	149.8 (± 13.4)	()	

Notes:

[10] - The patient aged 0-27 days was excluded from the Per Protocol Set, due to a major deviation.

Statistical analyses

No statistical analyses for this end point

Primary: Gadopiclenol concentrations 30 min post-injection (C30 min)

End point title	Gadopiclenol concentrations 30 min post-injection (C30 min)[11]

End point description:

Exposure parameter by age group predicted from the final model in participants with normal renal function receiving gadopiclenol 0.05 mmol/kg

End point type	Primary

End point timeframe:

Three blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (10-60 min, 2-4 hours, 6-8 h). Each time window contained 4 time points for blood collection.

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: The primary criteria was pharmacokinetics in plasma for pediatric patients aged up to 23 months
(inclusive) assessed based on the following pharmacokinetic parameters determined from the population PK (popPK) model: simulated concentrations at 10, 20, and 30 minutes post injection (C10 min, C20 min, C30 min); Area Under the Curve (AUC); Elimination half-life; Total clearance (CL); Volume of distribution. Descriptive statistical analysis was performed for pharmacokinetic profile in plasma.

End point values	Group1: 3-23 months	Group 2: 28-89 days	Group 3: 0-27 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	2	0[12]	
Units: mg/L				
geometric mean (geometric coefficient of variation)	109.4 (± 22.4)	116.2 (± 13.3)	()	

Notes:

[12] - The patient aged 0-27 days was excluded from the Per Protocol Set, due to a major deviation.

Statistical analyses

No statistical analyses for this end point

Primary: Clearance

End point title	Clearance[13]

End point description:

Individual predicted final model parameters scaled by body weight

End point type	Primary

End point timeframe:

Three blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (10-60 min, 2-4 hours, 6-8 h). Each time window contained 4 time points for blood collection.

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: The primary criteria was pharmacokinetics in plasma for pediatric patients aged up to 23 months
(inclusive) assessed based on the following pharmacokinetic parameters determined from the population PK (popPK) model: simulated concentrations at 10, 20, and 30 minutes post injection (C10 min, C20 min, C30 min); Area Under the Curve (AUC); Elimination half-life; Total clearance (CL); Volume of distribution. Descriptive statistical analysis was performed for pharmacokinetic profile in plasma.

End point values	Group1: 3-23 months	Group 2: 28-89 days	Group 3: 0-27 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	2	0[14]	
Units: L/h/kg				
arithmetic mean (standard deviation)	0.128 (± 0.035)	0.097 (± 0.004)	()	

Notes:

[14] - The patient aged 0-27 days was excluded from the Per Protocol Set, due to a major deviation.

Statistical analyses

No statistical analyses for this end point

Primary: Central volume of distribution (V1)

End point title	Central volume of distribution (V1)[15]

End point description:

Individual predicted final model parameters scaled by body weight

End point type	Primary

End point timeframe:

Three blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (10-60 min, 2-4 hours, 6-8 h). Each time window contained 4 time points for blood collection.

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: The primary criteria was pharmacokinetics in plasma for pediatric patients aged up to 23 months
(inclusive) assessed based on the following pharmacokinetic parameters determined from the population PK (popPK) model: simulated concentrations at 10, 20, and 30 minutes post injection (C10 min, C20 min, C30 min); Area Under the Curve (AUC); Elimination half-life; Total clearance (CL); Volume of distribution. Descriptive statistical analysis was performed for pharmacokinetic profile in plasma.

End point values	Group1: 3-23 months	Group 2: 28-89 days	Group 3: 0-27 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	2	0[16]	
Units: L/kg				
arithmetic mean (standard deviation)	0.176 (± 0.033)	0.214 (± 0.03)	()	

Notes:

[16] - The patient aged 0-27 days was excluded from the Per Protocol Set, due to a major deviation.

Statistical analyses

No statistical analyses for this end point

Primary: Inter-compartment clearance (Q)

End point title	Inter-compartment clearance (Q)[17]

End point description:

Individual predicted final model parameters scaled by body weight

End point type	Primary

End point timeframe:

Three blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (10-60 min, 2-4 hours, 6-8 h). Each time window contained 4 time points for blood collection.

Notes:

[17] - 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: The primary criteria was pharmacokinetics in plasma for pediatric patients aged up to 23 months
(inclusive) assessed based on the following pharmacokinetic parameters determined from the population PK (popPK) model: simulated concentrations at 10, 20, and 30 minutes post injection (C10 min, C20 min, C30 min); Area Under the Curve (AUC); Elimination half-life; Total clearance (CL); Volume of distribution. Descriptive statistical analysis was performed for pharmacokinetic profile in plasma.

End point values	Group1: 3-23 months	Group 2: 28-89 days	Group 3: 0-27 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	2	0[18]	
Units: L/h/kg				
arithmetic mean (standard deviation)	0.099 (± 0.025)	0.123 (± 0.029)	()	

Notes:

[18] - The patient aged 0-27 days was excluded from the Per Protocol Set, due to a major deviation.

Statistical analyses

No statistical analyses for this end point

Primary: Peripheral volume of distribution (V2)

End point title	Peripheral volume of distribution (V2)[19]

End point description:

Individual predicted final model parameters scaled by body weight

End point type	Primary

End point timeframe:

Three blood samples per patient were collected post-injection of gadopiclenol for PK analysis, one within each window (10-60 min, 2-4 hours, 6-8 h). Each time window contained 4 time points for blood collection.

Notes:

[19] - 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: The primary criteria was pharmacokinetics in plasma for pediatric patients aged up to 23 months
(inclusive) assessed based on the following pharmacokinetic parameters determined from the population PK (popPK) model: simulated concentrations at 10, 20, and 30 minutes post injection (C10 min, C20 min, C30 min); Area Under the Curve (AUC); Elimination half-life; Total clearance (CL); Volume of distribution. Descriptive statistical analysis was performed for pharmacokinetic profile in plasma.

End point values	Group1: 3-23 months	Group 2: 28-89 days	Group 3: 0-27 days	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	2	0[20]	
Units: L/kg				
arithmetic mean (standard deviation)	0.066 (± 0.014)	0.066 (± 0.003)	()	

Notes:

[20] - The patient aged 0-27 days was excluded from the Per Protocol Set, due to a major deviation

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) occurring from the beginning of patient's participation in the trial (Informed Consent Form signature) until the end of the participation (up to 3 months following gadopiclenol administration.

Adverse event reporting additional description:

Physical examination at visits; Vital signs at 3 times points; Safety laboratory variables centrally analyzed; Estimated glomerular filtration rate (eGFR) centrally calculated; Tolerance at the injection site at 3 time points; Clinical examination for active detection of Nephrogenic Systemic Fibrosis (NSF) at 3-month follow-up safety visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Safety Set

Reporting group description:

All patients who received at least one administration of IMP. This set was used for evaluation of safety, exposure to IMP, description of demographic data and baseline characteristics.

Serious adverse events	Safety Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 36 (22.22%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Tumour excision			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebral cyst			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intracranial pressure increased			
subjects affected / exposed	1 / 36 (2.78%)		
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 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Microcytic anaemia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis norovirus			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia parainfluenzae viral			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device malfunction			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Feeding disorder			

subjects affected / exposed	1 / 36 (2.78%)		
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	15 / 36 (41.67%)		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Serum ferritin increased			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
White blood cell count increased			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Eye disorders			
Astigmatism			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Myopia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Gastrointestinal disorders			

Vomiting subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	5 / 36 (13.89%) 5 1 / 36 (2.78%) 1 1 / 36 (2.78%) 1		
Respiratory, thoracic and mediastinal disorders Choking subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	 1 / 36 (2.78%) 1 1 / 36 (2.78%) 1 1 / 36 (2.78%) 1 1 / 36 (2.78%) 1		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 1 / 36 (2.78%) 1 1 / 36 (2.78%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	 1 / 36 (2.78%) 1		
Infections and infestations Conjunctivitis			

subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Paronychia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Respiratory tract infection viral			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 July 2022	The main changes in this amendment were implemented to allow local testing of creatinine (Cr) and estimated Glomerular Filtration Rate (eGFR) calculation based on bedside Schwartz equation to check the non-inclusion criterion 3. The rational for this change was to shorten turnaround time to obtain eGFR to check patient's eligibility when central laboratory results might not be available at the time of the planned inclusion MRI. Other changes implemented in the amendment were linked to the information regarding completed clinical trials updated in the Investigator's Brochure (IB) version N°11 dated 22 April 2022 and typo corrections.
24 June 2023	The following changes were implemented: • Discontinuation of the aged-down staggered approach to allow the inclusions in Group 3 (patients aged from birth to 27 days), • Inclusion criteria# 2 updated to clarify that it is not mandatory for patients to have previous imaging examinations, • Exceptional circumstances related to COVID-19 restrictions removed, due to the end of COVID-19 pandemic. This version has not been applicable and was not distributed to sites. The changes were implemented in the following version v4.0.
09 October 2023	The protocol V4 includes both amendments 2 described above and Amendment 3. The amendment 3 allows the collection of PK samples from the same line used for the IMP injection, considering that the saline flush after IMP injection will eliminate all remnants of IMP from the line, or alternatively the use of a capillary specimen (for example heel-pricks or finger pricks), in the event of any difficulties to place and/or maintain the peripheral intravenous line into a vein.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

17 July 2024	Following consultation with FDA and EMA and their favorable opinion for reducing the sample size initially considered, an early termination of the study was decided on 17 July 2024. The total number of patients enrollment was reduced to at least 33 patients less than 2 years old and the requirement for a minimum number of enrolled patients less than 28 days old (FDA) or less than 3 months (EMA) was removed. This early termination was not due to any safety or tolerability concern or event with the use of Gadopiclenol. Pharmacokinetic samples collected from the 33 first patients included in the study in the 3-23 months age group were used for a preliminary check of the adequacy of the pre-existing population PK model developed with serum creatinine as covariate, based on PK data obtained in adults, renal impaired subjects and children aged 2 years and older. This preliminary evaluation confirmed that the data for the 33 patients could be included in the existing popPK model and were sufficient to achieve the study objectives. Based on the above rationale and as per the concurrence by the FDA and EMA, the expected exposure parameters for the younger age groups will be predicted by simulation, since the preliminary evaluation performed on the data collected from the first 33 patients demonstrated that the following conditions are met: 1. There is no concern to combine pediatric and pre-existing data in a single population PK model, 2. The maturation of the renal function in children from age groups 2 and 3 is appropriately incorporated in the model, 3. Reducing the sample size will not compromise the achievement of the primary objective. From 17 July 2024, no further patient was screened and received an injection of gadopiclenol while all ongoing patients were followed for 3 months post gadopiclenol administration as per protocol.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to incomplete recruitment in study GDX-44-015, with only 2 patients aged 28-89 days and none aged less than 28 days who could be included in the popPK analysis, exposure in these groups was only obtained by simulation using the final model.

Notes: