11 December 2025
EMADOC-1700519818-2671004
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vueway

International non-proprietary name: gadopiclenol

Procedure No. EMA/VR/0000249008

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands

Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ADME: Absorption, Distribution, Metabolism, Excretion

AE: Adverse event

AESI: Adverse event of special interest

AST: Aspartate Amino Transferase

AUC: Area Under the Curve

BBB: Blood-Brain Barrier

BUN: Blood Urea Nitrogen

CNR: Contrast-to-Noise Ratio

CNS: Central Nervous System

ECG: Electrocardiogram

EMA: European Medicines Agency

FAS: Full Analysis Set

GBCA: Gadolinium-Based Contrast Agent

Gd: Gadolinium

GCP: Good Clinical Practice

GLP: Good Laboratory Practices

HED: Human Equivalent Dose

ICH: International Conference on Harmonization

ICP-MS: Inductively-coupled plasma – mass spectrometry

IEC: Independent Ethics Committee

IRB: Institutional Review Board

IV: Intravenous

LBR: Lesion to background ratio

Max: Maximum

Min: Minimum

MRI: Magnetic Resonance Imaging

NSF: Nephrogenic systemic fibrosis

PK: Pharmacokinetics

PD: Pharmacodynamic

PIP: Paediatric Investigation Plan

PopPK: Population Pharmacokinetics

PSP: Pediatric Study Plan

PV: Perivenous

SAE: Serious Adverse Event

SC: subcutaneous

SD: Sprague-Dawley

SD: Standard Deviation

SEM: Standard Error of the Mean

SFN: Small Fiber Neuropathy

TEAE: Treatment Emergent Adverse Event

TSRB: Trial Safety Review Board

T1: Longitudinal relaxation time

T2: Transverse relaxation time

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Guerbet submitted to the European Medicines Agency on 28 March 2025 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of new population (0 to 2 years of age patients) for Elucirem / Vueway, based on final results from study GDX-44-015; this is a phase ii clinical study concerning gadopiclenol pharmacokinetics, safety and efficacy in pediatric patients < 2 years of age undergoing contrast-enhanced MRI; extension of indication is also supported with the non-clinical data. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 0.4 of the RMP has also been submitted. As part of the application, the MAH requested a 1-year extension of the market protection.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/0294/2024 and P/0293/2024 for Elucirem & Vueway on the agreement of paediatric investigation plans (PIPs).

At the time of submission of the application, the PIPs P/0294/2024 for CNS and P/0293/2024 for body, were completed.

The PDCO issued an opinion on compliance for the PIPs P/0294/2024 and P/0293/2024.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the WSA did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

WSA request for additional market protection

The WSA requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Reference is made to the CHMP's separate assessment report on the significant clinical benefit in comparison with existing therapies.

Scientific advice

The WSA did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure:

Rapporteur: Patrick Vrijlandt Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	28 March 2025
Start of procedure:	26 April 2025
CHMP Rapporteur's preliminary assessment report circulated on:	13 June 2025
PRAC Rapporteur's preliminary assessment report circulated on:	24 June 2025
Joint Rapporteur's updated assessment report circulated on:	18 July 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 July 2025
WS responses submitted to the CHMP on:	10 October 2025
CHMP Rapporteur's preliminary assessment report on the WSA's responses circulated on:	7 November 2025
PRAC Rapporteur's preliminary assessment report on the WSA's responses circulated on:	11 November 2025
Joint Rapporteur's updated assessment report circulated on:	4 December 2025
CHMP opinion:	11 December 2025
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Elucirem / Vueway in comparison with existing therapies	11 December 2025

2. Scientific discussion

2.1.1. Problem statement

Disease or condition

Gadolinium-based contrast agents (GBCAs) are complexes of gadolinium (III) with different types of organic chelators. They are used for contrast enhancement in magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). Intra-articular GBCA formulations are also used in arthrography for MR of joints. Within the class, they can be differentiated in linear or macrocyclic compounds and whether they are ionic or non-ionic.

Gadopiclenol is a chemical entity that was developed by Guerbet. It is a non-ionic macrocyclic gadolinium (Gd) complex intended to be used in humans, as a contrast agent for Magnetic Resonance Imaging (MRI). The **current** therapeutic indication for Elucirem/Vueway 0.5 mmol/ml solution for injection is as follows:

This medicinal product is for diagnostic use only.

Elucirem/Vueway is indicated in adults and children aged 2 years and older for contrast-enhanced magnetic resonance imaging (MRI) to improve detection and visualization of pathologies with disruption of the blood-brain-barrier (BBB) and/or abnormal vascularity of:

- the brain, spine, and associated tissues of the central nervous system (CNS);
- the liver, kidney, pancreas, breast, lung, prostate, and musculoskeletal system.

It should be used only when diagnostic information is essential and not available with unenhanced MRI.

Claimed therapeutic indication

The **proposed** therapeutic indication for Elucirem/Vueway 0.5 mmol/ml solution for injection is:

This medicinal product is for diagnostic use only.

Elucirem/Vueway is indicated in adults and children from birth for contrast-enhanced magnetic resonance imaging (MRI) to improve detection and visualization of pathologies with disruption of the blood-brain-barrier (BBB) and/or abnormal vascularity of:

- the brain, spine, and associated tissues of the central nervous system (CNS);
- the liver, kidney, pancreas, breast, lung, prostate, and musculoskeletal system.

It should be used only when diagnostic information is essential and not available with unenhanced MRI.

Management

Gadolinium-based Contrast Agents (GBCAs) are widely recognised as critical for optimal MRI visualisation of lesions and are regarded as particularly valuable for tumour detection/anatomical characterisation (EPAR, EMEA/H/A-31/1437).

GBCAs are classified as linear or macrocyclic agents based on the chemical structure of their ligand. Macrocyclic agents have shown a better safety profile due to higher stability, less risk of dissociation, and less release of free gadolinium (Gd). Associations between GBCAs and nephrogenic systemic

fibrosis (NSF) and gadolinium deposition in the brain and other organs have been reported. In this context, it is recommended to use the minimum GBCA dose that provides sufficient contrast enhancement for diagnosis in routine practice. (EPAR, EMEA/H/A-31/1437) Thus, the development of high-relaxivity GBCAs meets a true medical need. Such agents would allow the reduction of the injected dose with the same efficacy as the other available GBCAs.

Gadopiclenol is a macrocyclic GBCA characterised by a very high r1 relaxivity, at least two-fold higher compared to other available GBCAs, whatever the magnetic field strength.

2.1.2. About the product

Mode of action

Gadopiclenol is a non-ionic macrocyclic gadolinium Gd complex intended to be used in humans, by intravenous (IV) administration, as a contrast agent for MRI.

In MRI, visualization of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occurs with:

- differences in proton density
- differences of the spin-lattice or longitudinal relaxation times (T_1)
- differences in the spin-spin or transverse relaxation time (T_2).

Contrast-enhanced MRI utilises extracellular GBCAs as the clinical standard for detecting and delineating lesions and associated tissues. Following administration of a GBCA, lesions are further characterised by their temporal and spatial patterns of signal enhancement produced by the contrast agent. The paramagnetic metal gadolinium (Gd3+) is the rare earth element responsible for the enhancement effect of GBCA in MRI. The Gd ion has paramagnetic properties due to its 7 unpaired electrons leading to a high magnetic moment and very labile water coordination properties.

Complexed Gd enhances MR signal by shortening the T1 and T2 relaxation times in targeted tissues, which results in increased signal intensity in T1-weighted sequences and reduced signal intensity in T2-weighted sequences. The extent to which a contrast agent can affect the relaxation rate of tissue water (1/T1 or 1/T2) is termed relaxivity (r1 or r2). At the main magnetic field used in routine radiological practice (1.5 T), gadopiclenol has at least a two-fold higher r1 relaxivity compared to other available GBCAs. Both relaxivities r1 and r2 display only a slight dependence on the strength of the magnetic field. The T1 shortening effect, which depends on relaxivity, is associated with improved tissue/lesion detection and visualization and assistance in lesion characterisation.

Due to its high relaxivity, it is anticipated that gadopiclenol can be given at a half dose of gadolinium compared to other non-specific gadolinium-containing contrast agents while providing the same contrast enhancement.

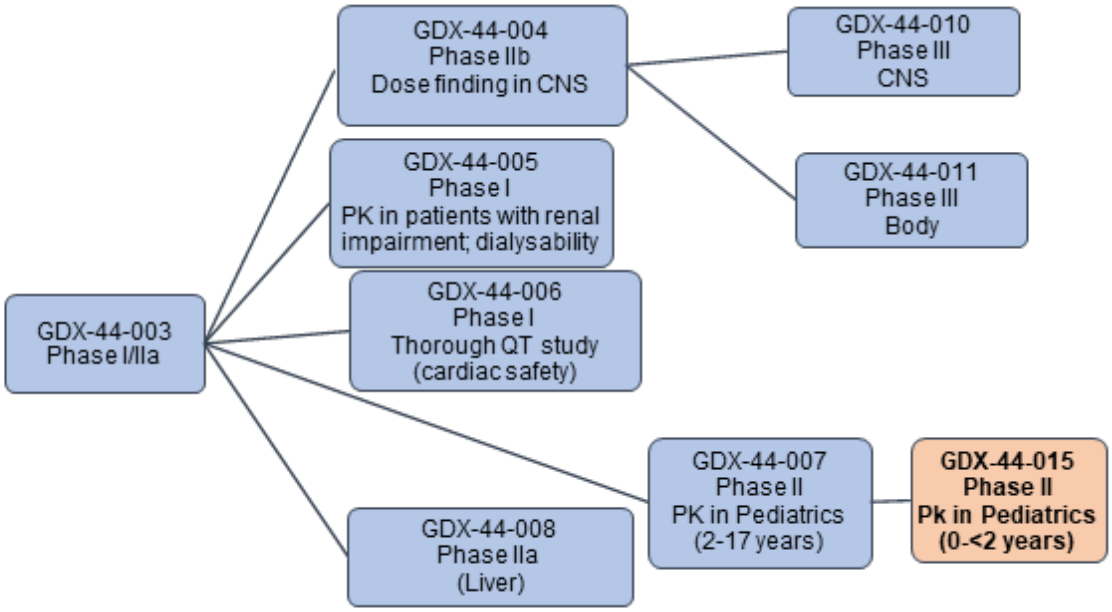
Pharmacological classification

paramagnetic contrast media, ATC code: V08CA12.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

An overview of the clinical development program of gadopiclenol is presented below.

Figure 1: Clinical Development Program for gadopiclenol - completed Studies



The development is considered compliant in general with CHMP guidance

- EMA guideline on clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev1) 2009.
- EMA Appendix 1 to the guideline on clinical evaluation of diagnostic agents (CPMP/EWP/1119/98 Rev.1) on imaging agents

Paediatric investigation plan (PIP)

This application is in accordance with the currently agreed PIPs (EMEA-001949-PIP01-16-M07 for CNS and EMEA-001949-PIP02-18-M05 for body).

In accordance with Article 23(2)(a)(b)(c) of Regulation (EC) No 1901/2006, as amended, Guerbet requested (EMA/PE/0000235656 & EMA/PE/0000235681) EMA to check whether all studies conducted are in compliance with the agreed paediatric investigation plan as set out in the EMA's decisions P/0294/2024 (regarding EMEA-001949-PIP01-16-M07 for CNS) and P/0293/2024 (regarding EMEA-001949-PIP02-18-M05 for body) of 16 August 2024. In March 2025, the PDCO adopted an opinion confirming the compliance of all studies in the agreed paediatric investigation plans as set out in the latest Agency's decisions P/0294/2024 (regarding EMEA-001949-PIP01-16-M07 for CNS) and P/0293/2024 (regarding EMEA-001949-PIP02-18-M05 for body) of 16 August 2024.

The studies included in the agreed PIPs are presented below:

Table 1: Overview of measures included in EU Paediatric Investigation Plan EMEA-001949-PIP01-16-M07 for CNS

Area	Description
Quality-related studies	**Study 1** Development of an additional volume for the solution for injection to avoid risk of overdose *(This study is the same as Study 1 in EMEA-001949-PIP02-18 and subsequent modifications thereof.)*
Non-clinical studies	**Study 2** Dose-range finding toxicity study in rats to determine the toxicity of gadopiclenol in the neonatal and juvenile (pre-post weaning) rats in order to determine appropriate dose levels for the definitive juvenile rat study. *(This study is the same as Study 2 in EMEA-001949-PIP02-18 and subsequent modifications thereof.)*
	Study 3 Definitive juvenile toxicity to determine the toxicity of gadopiclenol in the neonatal and juvenile (pre-post weaning) rats *(This study is the same as Study 3 in EMEA-001949-PIP02-18 and subsequent modifications thereof.)*
Clinical studies	**Study 4 (GDX-44-007)** Non-comparative pharmacokinetics, efficacy and safety in children from 2 to less than 18 years of age presenting central nervous system (CNS) lesions (intracranial, spine and associated tissues), who are scheduled to undergo routine contrast-enhanced MRI of CNS or body. *(This study is the same as Study 4 in EMEA-001949-PIP02-18 and subsequent modifications thereof.)*
	Study 5 Non-comparative pharmacokinetic, efficacy and safety study in children from birth to less than 2 years of age scheduled to undergo routine contrast-enhanced MRI of CNS or body *(This study is the same as Study 5 in EMEA-001949-PIP02-18 and subsequent modifications thereof.)*
Extrapolation, modelling and simulation studies	Not applicable
Other studies	Not applicable
Other measures	Not applicable

Table 2: Overview of measures included in EU Paediatric Investigation Plan EMEA-001949-PIP02-18-M05 for body

Area	Description
Quality-related studies	**Study 1** Development of an additional volume for the solution for injection to avoid risk of overdose *(this study is the same as Study 1 in EMEA-001949-PIP01-16 and subsequent modifications thereof.)*
Non-clinical studies	**Study 2** Dose-range finding toxicity study in rats to determine the toxicity of gadopiclenol in the neonatal and juvenile (pre-post weaning) rats in order to determine appropriate dose levels for the definitive juvenile rat study. *(This study is the same as Study 2 in EMEA-001949-PIP01-16 and subsequent modifications thereof.)*
	Study 3 Definitive juvenile toxicity to determine the toxicity of gadopiclenol in the neonatal and juvenile (pre-post weaning) rats *(This study is the same as Study 3 in EMEA-001949-PIP01-16 and subsequent modifications thereof.)*
Clinical studies	**Study 4 (GDX-44-007)** Non-comparative pharmacokinetics, efficacy and safety in children from 2 to less than 18 years of age presenting central nervous system (CNS) lesions (intracranial, spine and associated tissues), who are scheduled to undergo routine contrast-enhanced MRI of CNS or body. *(This study is the same as Study 4 in EMEA-001949-PIP01-16 and subsequent modifications thereof.)*
	Study 5 Non-comparative pharmacokinetic, efficacy and safety study in children from birth to less than 2 years of age scheduled to undergo routine contrast-enhanced MRI of CNS or body *(This study is the same as Study 5 in EMEA-001949-PIP01-16 and subsequent modifications thereof.)*
Extrapolation, modelling and simulation studies	Not applicable
Other studies	Not applicable
Other measures	Not applicable

2.1.4. General comments on compliance with GLP and GCP

- GLP

One non-GLP study was presented in support of the current application.

- GCP

The WSA claimed the paediatric clinical trials were performed in accordance with GCP.

2.2. Non-clinical aspects

2.2.1. Introduction

In the initial marketing authorisation application, the following studies were included and assessed:

- efficacy studies with *in vitro* relaxometry and with experimental imaging in mice and rats,
- *in vitro* and *in vivo* safety pharmacology studies on main body systems,
- Absorption Distribution Metabolism Excretion (ADME) studies in rodents (rats) and non-rodents (dog),
- single and repeated dose (up to 28 days) toxicity studies in rodents (rats) and non-rodents (dog),
- *in vitro* and *in vivo* genotoxicity testing,
- reproduction toxicity studies in rats and rabbits, including juvenile studies in rats,
- local tolerance,
- immediate hypersensitivity in guinea pigs,
- impurity toxicity testing.

In addition to the "classical regulatory non-clinical studies", supportive (non-GLP) studies were conducted with the aim to assess the tolerance of gadopiclenol and the potential risk of NSF disease after repeated administrations in renally-impaired rats. The long-term tissue Gd retention and speciation analysis of Gd was also investigated in healthy rats. Gadopiclenol was compared to several marketed GBCAs (linear and macrocyclic) in these studies at the same dose level as other GBCAs.

In the current variation procedure, a new non-clinical study was submitted. This concerns a supportive study performed in rats, assessing the global Gd exposure after a single administration of gadopiclenol at Human Equivalent Dose (HED), i.e., a half gadolinium-dose of gadopiclenol compared to the other non-specific marketed GBCAs.

No new non-clinical pharmacology or pharmacokinetic studies have been performed.

2.2.2. Toxicology

Other toxicity studies

In the preclinical research program of gadopiclenol, three exploratory (non-GLP) studies were conducted to assess Gd retention in brain and other tissues. All these studies were performed at the similar dose levels than other non-specific marketed GBCAs:

- 1-month brain gadolinium retention and MRI hyperintensities in healthy rats after repeated injections
- 24-min MRI enhancement follow-up of the 4th ventricle after single injection

- 1-year brain and all body Gd retention, speciation and safety in healthy rats after repeated injections.

ER-21-00015 study

A new supportive study (ER-21-00015) was designed to provide information about time-dependent Gd presence and wash-out in various organs after single gadopiclenol administration of a half gadolinium-dose of gadopiclenol compared to the other non-specific marketed macrocyclic GBCAs in healthy rats, to better apprehend the behavior of this GBCA in conditions close to the routine clinical use. To illustrate the lower exposure to Gd that the concept of gadopiclenol injected at half-Gd dose offers, the study was conceived with repeated timepoints of sampling to determine the Gd concentration found in the different organs, from 3.5 hours (plasma), 1 day or 1 week, to five months post-injection of the marketed GBCAs.

After gadopiclenol administration in rats at the HED, the global Gd exposure over Day 1 to Month 5 or Week 1 to Month 5 (depending on the structure) was found to be inferior compared to the other macrocyclic GBCAs in the plasma (Hour 3.5 to Month 2), in the CNS (cerebellum, cortical brain, subcortical brain and brain stem), in the PNS (spinal cord, spinal nodes, footpads, except the sciatic nerve), in bone marrow and in spleen. In skin, sciatic nerve, liver and kidney, the Gd exposure after gadopiclenol injection was lower compared to gadoterate and gadobutrol, but not compared to gadoteridol, showing a reduced Gd exposure over the studied period. In the mineral femur, the Gd exposure after gadopiclenol administration was higher compared to all macrocyclic GBCAs (or equivalent to the one in gadobutrol in the epiphysis).

In conclusion, after a single half-gadolinium-dose of gadopiclenol or a full-gadolinium-dose of other macrocyclic GBCAs, the measured exposure to Gd (up to 5 months) after gadopiclenol injection was globally reduced compared to the other macrocyclic GBCAs, except in the mineral bone.

2.2.3. Ecotoxicity/environmental risk assessment

Table 3. Summary of main study results

Substance (INN/Invented Name): Gadopiclenol			
CAS-number (if available): 933983-75-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-4.2	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-4.2	not B
	BCF	Not investigated	
Persistence	ready biodegradability	not readily biodegradable	
Toxicity	NOEC algae	>100 mg/L	not T

	NOEC crustacea NOEC fish	>11 mg/L >11 mg/L	
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined (treatment regime)	0.14	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\ soil}$= 126, 96, 444, 1094 and 4732 L/kg	considering the wide range of K_{oc} values, the worst case is used in the risk assessment. No adsorption in sludge observed
Ready Biodegradability Test	OECD 301B	not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 8/23 d (l/l) $DT_{50,\ sediment}$ = 19/18 d (l/l) $DT_{50,\ system}$ = 26/29 d (l/l) % shifting to sediment = 15-41%	l=lake; DT_{50} values at 20°C; Significant shifting to sediment observed.

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	EC10	>100	mg/L	growth rate and yield (no effects observed)
Daphnia sp. Reproduction Test	OECD 211	EC10	>11	mg/L	mortality, reproduction and growth (no effects observed)
Fish, Early Life Stage Toxicity	OECD 210	EC10	>11	mg/L	survival,

Test/*Pimephales promelas*					reproduction and growth (no effects observed)
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	µg/L	Respiration (no effects observed)
Phase IIb Studies					
Sediment dwelling organism	OECD 218	EC10	≥3138	mg/kg	normalised to 10% o.c.

2.2.4. Discussion on non-clinical aspects

Gadolinium Deposition, Speciation and Safety in Brain and Other Organs

Long-term gadolinium deposition after injection of GBCAs has been highlighted following the publication of several studies, initially showing T1 hypersignals in specific regions of the brain (*globus pallidus* and *dentate nucleus*) of patients with normal renal function, receiving multiple administrations of linear GBCAs ((Kanal., 2015); (Malayeri., 2016); (Semelka., 2016)). Postmortem studies have provided pathologic confirmatory evidence that T1 hypersignal seen on MRI is the result of gadolinium gradual deposition ((Kanda., 2015); (McDonald., 2015)). Several studies showed that brain and tissue Gd deposition is more likely to occur with linear GBCAs, which are more prone to dissociation into free gadolinium, compared with more stable macrocyclic GBCAs ((Radbruch., 2015); (Robert., 2016)). Gadolinium deposition in the brain and in other tissues needs to be specified as either deposition of the intact chelate that is cleared over time (for both linear and macrocyclic GBCAs) or as potentially permanent dechelated Gd deposition (caused exclusively by linear GBCAs) ((Frenzel., 2017); (Gianolio., 2017); (Robert., 2015); (Robert., 2018)). To date, there is no demonstration that any signs or symptoms of adverse health effects nor any pathological changes are associated with this Gd presence in the brain, presence which is prolonged in the case of linear agents.

At the end of 2017, after an extensive review of efficacy and safety data available on all GBCAs (EMEA/H/A-31/1437), in the context of reports of Gd deposition in the brain, the EMA in order to prevent any risks that could potentially be associated with gadolinium brain deposition recommended to restrict the use of some linear agents (gadoxetic acid and gadobenic acid) used in MRI body scan and suspended the marketing authorisations of others (Magnevist (gadopentic acid), Omniscan (gadodiamide) and Optimark (gadoversetamide)). The indications of MultiHance (gadobenic acid) were restricted, at this occasion, to liver imaging. At the same time, the recommendation for macrocyclic agents (gadobutrol, gadoteric acid and gadoteridol) which are more stable and have a lower propensity to release gadolinium than linear agents was that these products could continue to be used in their current indications but in the lowest doses that enhance images sufficiently and only when unenhanced body scans are not suitable. See EPAR Article 31 referral, EMEA/H/A-31/1437.

Assessment of paediatric data on non-clinical aspects

A single supportive new non-clinical study was submitted within the current variation procedure (ER-21-00015). In this study in rats, distribution of gadolinium to several organs was evaluated, after a single dose with a maximum observation time of 5 months. The concentration of Gd was lower as compared to other marketed macrocyclic GBCAs in every organ tested except for the femur diaphysis and epiphysis. The difference in concentration in these bone structures were highest at Day 1 and

remained increased at month 5 compared to gadoterate and gadoteridol, but equivalent to gadobutrol. The clinical relevance of this finding is unknown, although no bone toxicity has been reported for gadopiclenol products so far. In previous animal studies no effects on bone were reported either. However, the method is an estimation over a determined period. Consequently, the first timepoint studied was 24h after injection, and the evaluation does not represent the total exposure. Moreover, the method includes the phases of Gd distribution, Gd elimination and Gd retention, but it was not designed to evaluate the potential safety impacts of this long-term Gd accumulation. In can be concluded that gadopiclenol is unlikely to have a less favourable safety profile to other marketed GBCAs, or for children aged below 2 years as compared to above 2 years of age.

Environmental risk assessment

There are no new data regarding the environmental risk assessment. Since the assessment in the original marketing authorization application did not make a distinction for age groups, the conclusions remain applicable to the current procedure in which children aged 0 to 2 years of age are added to the indication.

2.2.5. Conclusion on the non-clinical aspects

Considering the above data, gadopiclenol is not expected to pose a risk to the environment.

There are no objections to the extension of indication from a non-clinical point of view.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the WSA.

The WSA has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 4: Tabular overview of clinical studies

Study ID **Year**	**Number of Center(s)** **Location(s)**	**Design** **Phase** **Control Type**	**Study and Control Drugs** **Dose, Route and Regimen**	**Study Objectives**	**Considering Patients Aged <2 Years**				**Primary endpoint**
					Number of Patients Included	**Duration of Treatment**	**Gender Male/Female** **Mean Age (SD); range**	**Inclusion Criteria** **Diagnosis**	
GDX-44-015 2022-2024	11 centers in Europe and the USA	Phase II open-label, uncontrolled,	Gadopiclenol IV injection 0.05 mmol/kg	PK, safety and efficacy of gadopiclenol in pediatric patients aged <2 years	36	Single dose	18 (50.0%) M/ 18 (50.0%) F Mean (SD) age: 12.15 (6.77) months Range: 0.8-23.6 months	Female or male pediatric patient aged from birth to 23 months of age inclusive, with known or highly suspected abnormalities/ lesion(s), scheduled to undergo contrast-enhanced MRI of any body region including CNS	Primary endpoint is PK profile

2.3.2. Pharmacokinetics

Special populations

A study was performed to evaluate the pharmacokinetic profile of gadopiclenol in plasma following a single intravenous injection of 0.05 mmol/kg body weight (BW) in a pediatric population aged up to 23 months (inclusive) scheduled for a contrast-enhanced MRI examination of any body region, including central nervous system (study GDX-44-015). Sparse blood sampling was performed, in combination with a population PK (pop PK) approach. A total of 3 blood samples per patient were taken post-injection for PK analysis, one within each window (10-60 minutes, 2-4 hours, 6-8 hours). Each time window contained 4 time points for blood collection. One of the time points within each time window was randomly allocated to the patients by Interactive Web Response System (IWRS). Patients were recruited into 3 predefined age groups: 3 to 23 months (n=33, 16 male, 17 female, 4.2 – 13.7 kg), 28 days to less than 3 months (n=2, 1 male, 1 female, 4.9 – 5.3 kg) and from birth to 27 days (term newborns, n=1, male, 4.5 kg). The subject in the newborn group was however excluded from the PK dataset due to a major protocol deviation (the PK samples were defrosted by mistake during the storage period) and therefore there were no PK data from birth to 27 days and the total PK dataset contained 35 patients.

For gadopiclenol analysis, blood was collected into lithium heparin tubes. Plasma was obtained within 30 minutes after blood collection by centrifugation at approximately 3000 rpm for 10 minutes and aliquots were stored into polypropylene tubes at maximum temperature -15ºC or below for analysis (maximal time between end of centrifugation and freezing: < 2 hours).

Gadopiclenol concentrations in plasma were determined using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method. This method was already validated in the original procedure (5 – 2500 µg/mL). An amendment to this validation was provided in the current submission (Amendment 4 to validation report). Specificity was shown in hyperlipemic and 5% haemolysed human plasma. Further, additional stability testing was performed in sodium heparinized human plasma (see Table 5) and in human urine (data not presented).

Table 5: Summary of gadopiclenol stability results (GDX-44-002 + amendment)

	in sodium heparinized human plasma
Stability period at automatic sampler temperature	Stable 63 hours 59 minutes at the target temperature of +4°C.
Bench top stability period	Stable 4 hours 20 minutes at room temperature in plasma. Stable 4 hours at room temperature in blood.
3 freeze and thaw cycles stability	Stable after 3 freeze/thaw cycles at the target temperatures of -20°C and -80°C, and thaw at room temperature.
Short term stability period	Stable 4 hours and 12 minutes at room temperature (after a freezing period at the target temperature of -20°C). Stable 4 hours and 5 minutes at room temperature (after a freezing period at the target temperature of -80°C).
Long term stability period	Stable for 42, 559 and 1111 days at the target temperature of -20°C and stable for 40 days at the target temperature of -80°C.

	in sodium heparinized human plasma
	(stability at -20°C can be extrapolated to -80°C according to ICH M10 Guideline -May 2022)

In study GDX-44-015, 107 plasma samples were analysed. Chromatograms were provided for 20% of the subjects. Samples were stored at -20 °C for a maximum of 518 days. QC samples were analysed at 15, 150, 1250 and 2000 µg/mL. Accuracy was 98.25 – 103.91% and precision was 0.03 – 7.14%. One sample was reassayed. Incurred sample reanalysis was performed on 28 samples, 75% of which were found to be within 20% of initial concentrations.

Pop PK analysis

Objectives

- To assess whether the PopPK model previously developed for adults and children of 2-17 years of age for gadopiclenol is predictive of exposure for the pediatric population aged up to 23 months (inclusive);
- To update the PopPK model previously developed for adults and children of 2-17 years of age with data obtained in pediatric population <2 years from the GDX-44-015 study;
- To search population specific covariates that can explain any difference between pediatric patients < 2 years and older patients;
- To predict PK parameters and exposure in pediatric patients <2 years receiving IV injection of gadopiclenol for contrast-enhanced MRI;
- To simulate PK parameters and exposure in pediatric patients <2 years receiving IV injection of other doses of gadopiclenol (0.025 mmol/kg, 0.1mmol/kg)

Data

The original model included 134 patients from studies GDX-44-003 (adult patients with normal renal function), GDX-44-005 (including adult patients with renal impairment [mild, moderate or severe]) and GDX-44-007 (pediatric patients 2-17 years old).

The GDX-44-015 analysis set included 35 participants with a good balance between male (48.6%) and female (51.4%). Median age was 12 months (range 1 to 23 months), and body weight ranged from 4.2 to 13.7 kg with a median of 9.1 kg.

The whole dataset combining GDX-44-015 with the reference population included 169 participants (134 from the reference dataset + 35 from GDX-44-015) balanced between male (50.3%) and female (49.7%). Seventy-eight (78) participants out of 169 (46%) were adults. The median age was 16 years (range 0 to 71) for the whole population.

The body weight ranged from 4.2 to 100.2 kg with a median of 56.8 kg in the whole population and 73.95 kg for adult participants. The serum creatinine (Screat) level at baseline appeared significantly higher in adults than in children.

Values below LOQ were removed if they represented no more than 15% of the total samples. If BLQ samples represented more than 15% of the total samples, or appeared to be treatment-dependent, an alternative method was to be considered (M3 or M4). Missing PK concentrations for other reasons were not replaced and set to missing. Actual sampling / dosing times were used.

The dataset from study GDX-44-015 comprised 104 concentration records from 35 patients. Eleven values (10.6%) were missing, all of them were BLQ values reported in the late phase of the PK. Moreover, no blood sample was taken during the 6-8h time window for patient 1002. The whole dataset comprised 1358 concentration records from 169 participants, 157 of which were missing, all but 3 were below LOQ (11%).

Model development

Pop PK analysis was performed by non-linear mixed effect modelling using NONMEM version 7.2. The first-order conditional estimation (FOCE) method was used to estimate model parameters. At first, preliminary checks were performed to assess whether the existing model was sufficiently predictive of data collected in paediatric patients < 2 years.

The population PK model selected on previous data was a two-compartment model with elimination from the central compartment (see Figure 2). The model was parameterized in terms of clearance (CL), central volume of distribution (V1), inter-compartment clearance (Q) and peripheral volume of distribution (V2). All parameters were scaled to body weight using fixed allometric rules. Two different equations were used to estimate the influence of eGFR on pharmacokinetic parameters for adults and children separately. Exponential models were used to describe the interindividual variability on CL, V1 and V2 and a proportional model was considered as error. Later, in this model a single formula was implemented in the pop PK model based on serum creatinine (Screat) to describe how CL is affected by renal function for adults and children, instead of describing the effect of eGFR on CL by two different formulas.

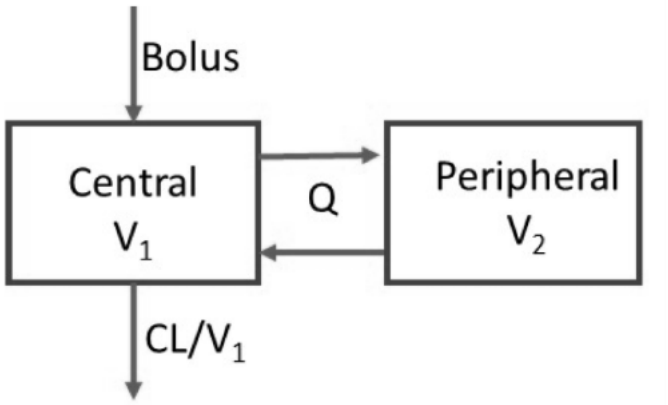


Figure 2: Structure of gadopiclenol pop PK model

Preliminary checks confirmed that the 2-compartmental model with linear elimination from the central compartment used in previous analyses to characterize gadopiclenol PK was suitable for the pediatric patients included in the GDX-44-015 study. Standard allometric scales were applied on all parameters and Screat was used to adjust the clearance (CL) of gadopiclenol to the renal function.

However, the elimination of gadopiclenol in GDX-44-015 patients seemed slower than what the reference model can predict and a slight overprediction of the concentrations collected within the early time window (10-60 minutes) was observed (see Figure 3). According to the applicant, the maturation of renal function was not sufficiently taken into account in the original model.

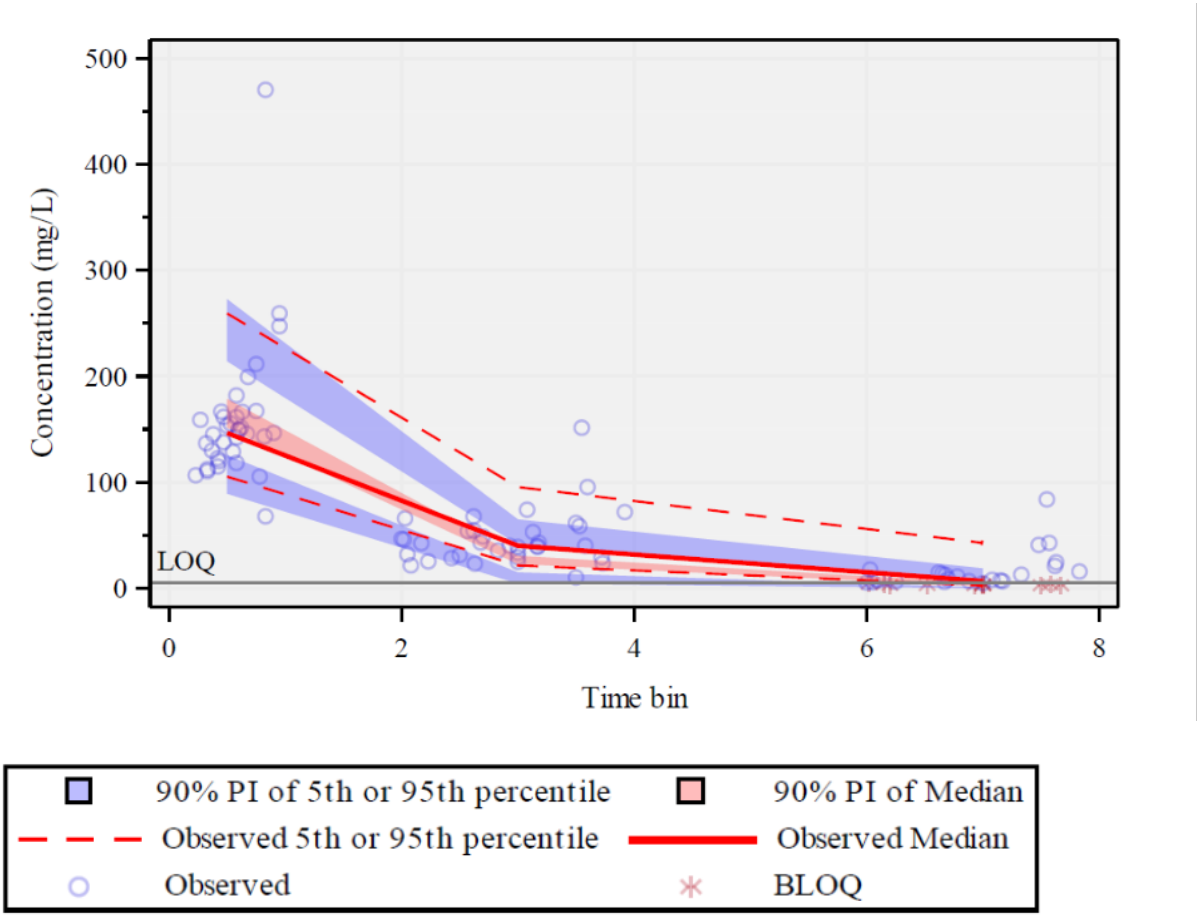


Figure 3: External pcVPC for patients from study GDX-44-015 using the original gadopiclenol model

These limitations required some adjustment in the model for children <2 years:

- The slight lack of fit in the terminal phase of the kinetics, suggesting that the relationship between Screat and CL did not describe adequately the maturation of renal function in children under 2 years old, was solved by including a maturation of the renal function component, based on the post-menstrual age (PMA), to the elimination. The maturation factor (MF) was used to describe the maturation of the renal fraction of elimination. This validated model (Rhodin et al) is widely used to describe renal maturation using the PMA in neonates and young children.
- The overprediction of the concentrations observed within early time windows (10 - 60 min) for GDX-44-015 patients was addressed by challenging the standard allometric scales and resulted in an estimated exponent of 0.763 for weight effect on V1 (instead of the standard value 1). According to the applicant, this slight overprediction of the gadopiclenol concentrations observed within early time windows could be explained by gadopiclenol distribution in extracellular water. It is possible that in neonates and infants who have proportionally higher total body water than adults, the standard allometric scales with exponent fixed to 1, as applied to volumes of distribution (V), do not adequately describe the relationship between V and body weight in children below 2 years old, resulting in an underestimation of the volume and overpredicted concentrations.

A direct body weight effect could not be estimated on CL due to its correlation with Screat, therefore the effects were estimated for inter-compartment clearance (Q), central volume of distribution (V1) and peripheral volume of distribution (V2) and the exponent 0.75 was kept fixed for CL.

Therefore, the final model was obtained by combining the PMA-based maturation of renal function and the estimated weight effect on V1. Apart from the maturation factor and the effect of weight on V1, no additional covariates were added to the model.

Parameters estimates for the final model are presented in Table 6.

Table 6: Final model for gadopiclenol incorporating renal maturation for children below 2 years old

Parameter	**Estimate (%RSE)**	**95% CI**	**Variability (CV%) Correlation (R%)**
$CL(L/h) = q_1(Weight/70)^{0.75} * MF_{renal} * (1-q_5*EXP(- EXP(- q_6*(Screat - q_7))))*EXP(h_1)$ **$MF_{renal}=PMA^{3.4}/(47.7^{3.4}+PMA^{3.4})$**			
q_1: CL typical value	5.95 (2.79)	(5.62;6.28)	
q_5: Asymptotic (maximal) effect of Screat on CL	0.877 (1.29)	(0.855;0.899)	
q_6: growth rate of CL	0.0298 (14.2)	(0.0215;0.0381)	
q_7: inflexion point of adults CL	103 (3.46)	(96;110)	
h_1 (IIV CL)	0.0509 (10.8)	(0.0402;0.0616)	CV=22.6%
$Q (L/h) = q_2(Weight/70)^{0.75}*EXP(h_2)$			
q_2: Q typical value	4.07 (8.48)	(3.39;4.75)	
h_2 (IIV Q)	0.329 (29.9)	(0.136;0.522)	CV=57.4%
$h_{2,1}$ (cov CL, Q)	0.0176 (114)	(-0.0216; 0.0568)	R=13.6%
$V_1 (L)=q_3(Weight/70)^{q8}*EXP(h_3)$			
q_3: V_1 typical value	7.27 (3.05)	(6.83;7.71)	
q_8: Effect of weight	0.763 (3.62)	(0.709; 0.817)	
h_3 (IIV V_1)	0.0769 (15.7)	(0.0532; 0.101)	CV=27.7%
$h_{3,1}$ (cov CL, V_1)	0.0175 (49.0)	(0.000703; 0.0343)	R=28.0%
$h_{3,2}$ (cov Q, V_1)	-0.130 (22.0)	(-0.186; -0.0739)	R=-81.7%
$V_2 (L)=q_4(Weight/70)*EXP(h_4)$			
q_4: V_2 typical value	4.73 (6.74)	(4.10;5.36)	
h_4 (IIV V_2)	0.223 (23.6)	(0.120;0.326)	CV=47.2%
$h_{4,1}$ (cov CL, V_2)	-0.00961 (127)	(-0.0335; 0.0143)	R=-9.02%

$h_{4,2}$ (cov Q, V_2)	0.0821 (65.7)	(-0.0235; 0.188)	R=30.3%
$h_{4,3}$ (cov V_1, V_2)	-0.0470 (41.3)	(-0.0850; -0.00898)	R=-35.9%
Residual error			
e_1: proportional component	0.0205 (3.37)	(0.0191 ;0.0219)	CV=14.3%

Cov: covariate; RSE: root square error, CI: confidence interval; CV: coefficient of variation; CL: clearance; PMA: post-menstrual age;

The pcVPC for patients from study GDX-44-015 using the final model shows clear improvement, compared to the fit when the original model was used (see Figure 4).

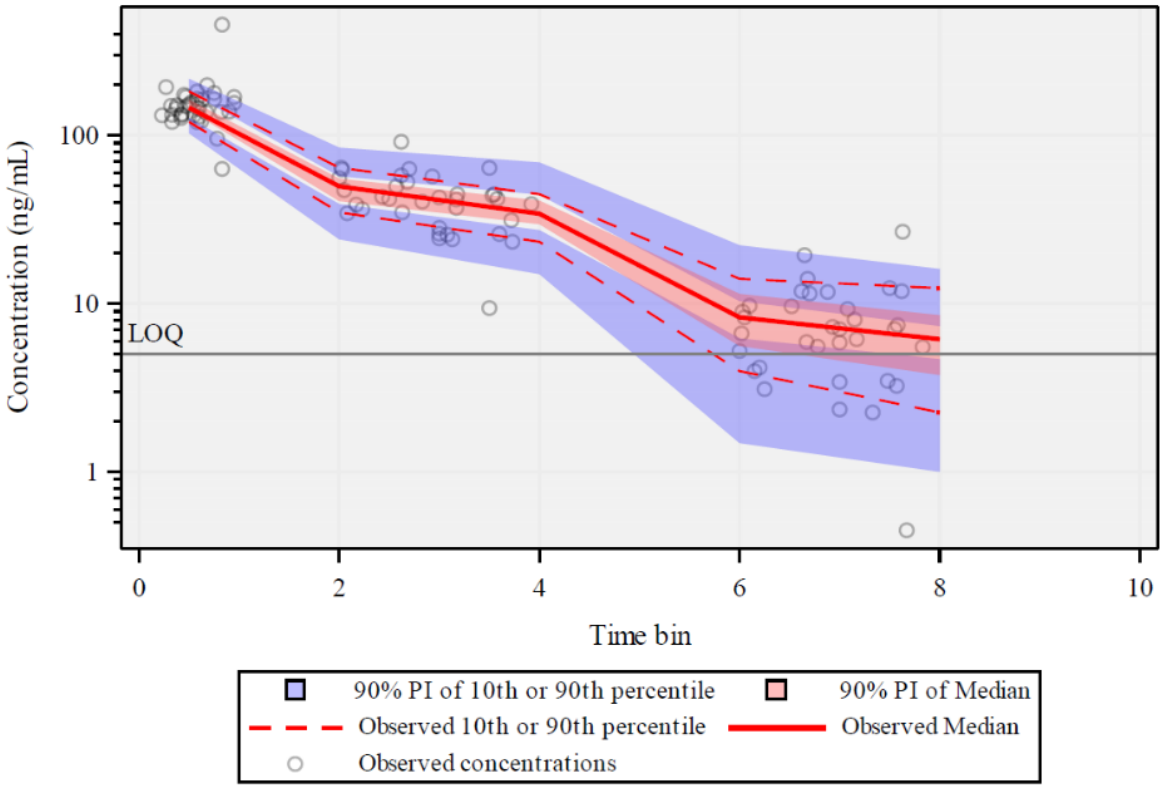


Figure 4: pcVPC for patients from study GDX-44-015 (log scale)

Goodness of fit plots with concerned concentrations versus individual predicted concentrations are shown in Figure 5.

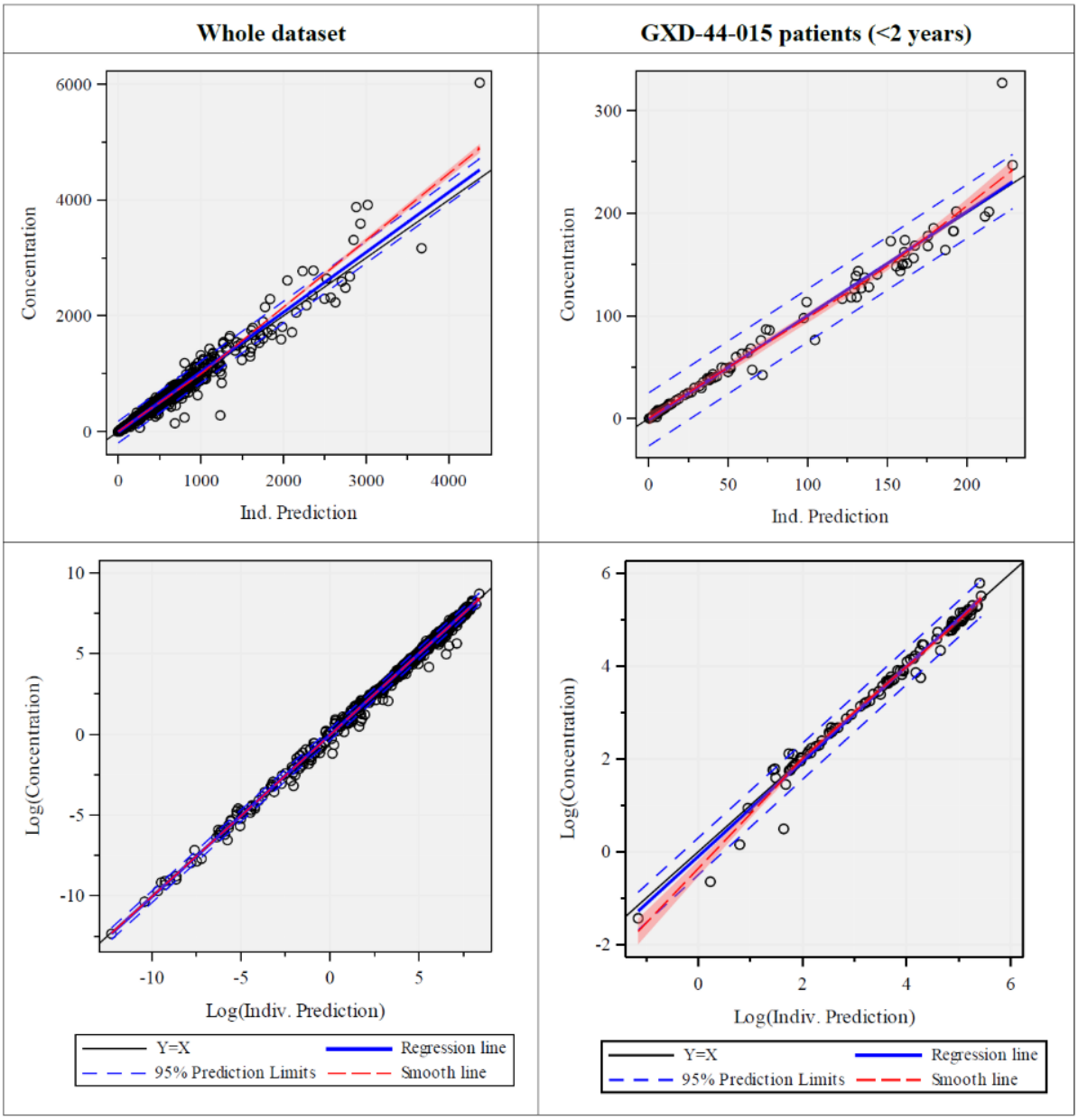


Figure 5: Goodness of fit plots: concentrations vs individual predictions (upper: natural scale; lower: log scale)

The typical CL for a participant of 70 kg with normal renal function was estimated at 5.95 L/h with weight dependence captured by a fixed allometric rule of exponent 0.75. The CL was reduced for renal impaired patients in relation to their Screat level. Similarly, the CL was also reduced for pediatric patients below 2 years in relation to the maturation of their renal function. The central volume of distribution was estimated at 7.27 L for a participant of 70 kg with weight dependence captured by fixed allometric rule of estimated exponent 0.763. Peripheral volume of distribution and inter-compartment clearance were estimated at 4.73 L and 4.07 L/h, respectively, for a participant of 70 kg, with weight dependence captured by fixed allometric rules of exponents 1 and 0.75, respectively.

Parameters derived from final model

Individual predictions (Empirical Bayes Estimates) were used to derive PK exposure parameters (AUC, $t_{1/2}$, concentrations at 10, 20 and 30 min). PK exposure parameters are summarized by age group for

the dose 0.05 mmol/kg and participants with normal renal function in Table 7. These results showed that median $t_{1/2}$ was consistent across all age groups. Regarding other parameters (AUC0-∞, C10, C20 and C30), the exposures were in the same order of magnitude in children from 7 years old and adults. Under 6 years, the concentrations measured at 10 and 20 minutes decreased with age, while for AUC0-∞ and C30, a drop could be observed for patients below 6 years old. This reduction of AUC and C30 was not accentuated in younger patients (3-23 months or <3 months).

Table 7: Summary of exposure parameters by age group predicted from the final model in participants with normal renal function receiving gadopiclenol 0.05 mmol/kg

		GM (CV%)					
Age group	**N**	**$AUC_{0\text{-}inf}$ (h.mg/L)**	**$t_{1/2}\alpha$ (h)**	**$t_{1/2}\beta$ (h)**	**$C_{10\ min}$ (mg/L)**	**$C_{20\ min}$ (mg/L)**	**$C_{30\ min}$ (mg/L)**
Adults	9	571.5 (17.4)	0.4 (64.2)	1.7 (28.6)	350.2 (15.0)	236.2 (14.2)	154.3 (17.3)
12-17 years	18	639.8 (17.6)	0.3 (30.7)	1.8 (28.1)	396.5 (13.1)	254.5 (11.4)	160.4 (16.3)
7-11 years	19	543.4 (19.3)	0.3 (22.8)	1.6 (11.6)	341.6 (15.0)	230.5 (13.4)	148.0 (17.0)
2-6 years	19	446.1 (23.4)	0.3 (29.7)	1.7 (19.8)	285.1 (14.1)	187.1 (14.6)	117.1 (19.7)
3-23 months	33	392.3 (27.6)	0.3 (30.3)	1.5 (21.4)	226.8 (15.8)	161.5 (17.2)	109.4 (22.4)
28 days-<3 months	2	493.3 (9.9)	0.3 (30.3)	2.1 (8.4)	190.4 (16.2)	149.8 (13.4)	116.2 (13.3)

GM: geometric mean; CV: coefficient of variation

The individual PK parameters as estimated by the model were normalized to body weight and are summarized in Table 8.

Table 8: Summary of individual predicted final model parameters scaled by body weight

			CL (L.h-1/kg)	V_1 (L/kg)	Q (L.h-1/kg)	V_2 (L/kg)
Age group	Renal impairment	N	Mean (SD) Min/Median/Max	Mean (SD) Min/Median/Max	Mean (SD) Min/Median/Max	Mean (SD) Min/Median/Max
Adults	Normal	54	0.085 (0.013) 0.057/0.0842/0.128	0.114 (0.033) 0.058/0.1071/0.196	0.064 (0.035) 0.017/0.0594/0.174	0.069 (0.043) 0.034/0.0580/0.348
	Mild	8	0.061 (0.019) 0.031/0.0601/0.091	0.109 (0.016) 0.082/0.1080/0.130	0.047 (0.025) 0.018/0.0450/0.087	0.146 (0.116) 0.058/0.0922/0.378
	Moderate	8	0.039 (0.011) 0.027/0.0373/0.055	0.112 (0.025) 0.082/0.1059/0.148	0.058 (0.023) 0.038/0.0514/0.108	0.069 (0.019) 0.035/0.0721/0.099
	Severe	8	0.011 (0.002) 0.008/0.0107/0.013	0.091 (0.019) 0.068/0.0929/0.115	0.089 (0.037) 0.038/0.0960/0.137	0.081 (0.015) 0.056/0.0828/0.101
12-17 years	Normal	18	0.077 (0.013) 0.047/0.0764/0.105	0.095 (0.020) 0.055/0.0927/0.133	0.075 (0.028) 0.044/0.0708/0.148	0.071 (0.041) 0.045/0.0558/0.223
7-11 years	Normal	19	0.091 (0.017) 0.061/0.0838/0.130	0.114 (0.020) 0.075/0.1140/0.143	0.073 (0.016) 0.045/0.0681/0.113	0.061 (0.014) 0.043/0.0595/0.083
2-6 years	Normal	19	0.111 (0.024) 0.065/0.1044/0.168	0.134 (0.024) 0.068/0.1388/0.174	0.089 (0.032) 0.048/0.0828/0.195	0.086 (0.028) 0.057/0.0801/0.169
3-23 months	Normal	33	0.128 (0.035) 0.060/0.1250/0.253	0.176 (0.033) 0.098/0.1707/0.318	0.099 (0.025) 0.037/0.0949/0.178	0.066 (0.014) 0.039/0.0632/0.121
28 days-<3 months	Normal	2	0.097 (0.004) 0.094/0.0965/0.099	0.214 (0.030) 0.192/0.2136/0.235	0.123 (0.029) 0.103/0.1234/0.144	0.066 (0.003) 0.063/0.0655/0.068

CL: clearance; Q: inter-compartment clearance, V_1: central volume of distribution; V_2: peripheral volume of distribution (V2); SD: standard deviation

The shrinkage for each parameter of the model was 4.26% for clearance (CL), 24.89% for inter-compartment clearance (Q), 18.85% for central volume of distribution (V_1) and 22.52% for peripheral volume of distribution (V_2). The shrinkage for the residual error was 17.94%.

All these values were below 30% and therefore the final model deemed acceptable. The shrinkage was considered moderate and did not preclude the interpretation of graphical display.

Simulations

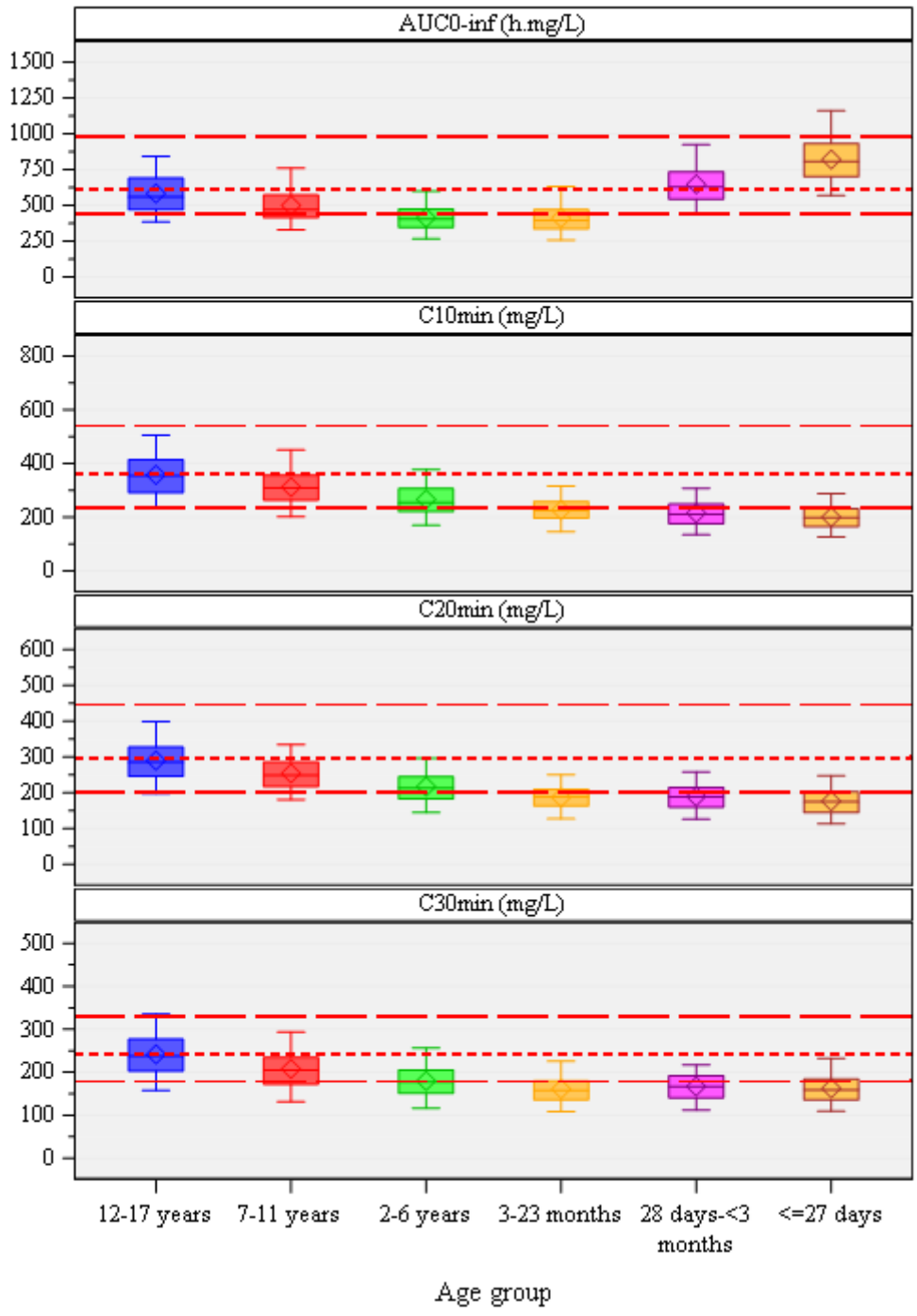
Because the recruitment of study GDX-44-015 could not be completed, with only 2 patients in the group of patients aged from 28 days to <3 months and none in the group of patients <28 days, the exposure in these groups was obtained by simulation. The simulations were performed directly using the PMA-based maturation function considered in the final model. All simulated participants were sampled among participants with normal renal function from the whole dataset. Simulations were performed based on 1000 replicates.

The same pattern was observed for all simulated doses: the early plasma concentrations 10, 20 and 30 minutes following a single administration in children between 12 and 17 years were comparable to those of adults, but below 12 years, they were lower than in adults potentially due to the higher volumes of extracellular fluid and total body water (per body weight). The decrease was progressive for 7-11 and 2-6 years age groups, but below 2 years, they remained in the same range as for the 2-6 years group. For AUC0-∞, an age dependent decrease in exposure was also observed down to the 2-6 years group, but for the 3-23 months group, the AUC was similar to 2-6 years and then, below 3 months, increased to become comparable to adult values as a consequence of lower CL for those children whose renal function is not mature.

Values of AUC0-∞, C10, C20, C30 simulated with the final model for a dose of 0.05 mmol/kg, are summarized as medians in Table 9 and illustrated for pediatric patients in Figure 6.

Table 9: Median simulated values based on the final model

Age group	**Median $AUC_{0-\infty}$ (mg.h/L)**	**Median C_{10} (mg/L)**	**Median C_{20} (mg/L)**	**Median C_{30} (mg/L)**
Adults	612	362	298	243
12-17 years	560	355	286	238
7-11 years	472	308	249	205
2-6 years	406	254	214	178
3 to 23 months	396	224	188	158
28 days to <3 months	628	211	189	167
≤27 days	807	198	175	159



Red short dashed line: Adult reference exposure median - Red long dashed line: Adult reference 5th and 95th percentiles

Figure 6: Simulated exposure parameters from the final model at the dose 0.05 mmol/kg in participants with normal renal function

It was concluded that for the population under 2 years old no adjustment to the dosing regimen based on body weight should be necessary.

Table 10: Final popPK model for gadopiclenol including adults, pediatric patients 2-17 years and <2years old

	CL (L/h/kg)		$t_{1/2}$ (h)	
Age group	**Mean (SD)**	**Median**	**Mean (SD)**	**Median**
Adult	0.085 (0.013)	0.0842	1.8 (0.5)	1.62
12-17 years	0.077 (0.013)	0.0764	1.9 (0.8)	1.78
7-11 years	0.091 (0.017)	0.0838	1.6 (0.2)	1.61
2-6 years	0.111 (0.024)	0.1044	1.8 (0.4)	1.75
3-23 months	0.128 (0.035)	0.1250	1.6 (0.3)	1.45
28 days-<3 months	0.097 (0.004)	0.0965	2.1 (0.2)	2.10

2.3.3. Pharmacodynamics

Mechanism of action

Gadopiclenol is a non-ionic macrocyclic gadolinium (Gd) complex intended to be used in humans, by intravenous (IV) administration, as a contrast agent for magnetic resonance imaging (MRI).

In MRI, visualization of normal and pathological tissue depends in part on variations in the radiofrequency signal intensity that occurs with:

- differences in proton density
- differences of the spin-lattice or longitudinal relaxation times (T_1)
- differences in the spin-spin or transverse relaxation time (T_2).

Contrast-enhanced MRI utilises extracellular Gadolinium-based Contrast Agents (GBCAs) as the clinical standard for detecting and delineating lesions and associated tissues. Following the administration of a GBCA, lesions are further characterised by their temporal and spatial patterns of signal enhancement produced by the contrast agent. The paramagnetic metal gadolinium (Gd3+) is the rare earth element responsible for the enhancement effect of GBCA in MRI. The Gd ion has paramagnetic properties due to its 7 unpaired electrons leading to a high magnetic moment and very labile water coordination properties.

Complexed Gd enhances MR signal by shortening the T1 and T2 relaxation times in targeted tissues, which results in increased signal intensity in T1-weighted sequences and reduced signal intensity in T2-weighed sequences. The extent to which a contrast agent can affect the relaxation rate of tissue water (1/T1 or 1/T2) is termed relaxivity (r1 or r2). At the main magnetic field used in routine radiological practice (1.5 T), gadopiclenol has at least a two-fold higher r1 relaxivity compared to other available GBCAs (Table 11). Both relaxivities r1 and r2 display only a slight dependence on the strength of the magnetic field. The T1 shortening effect, which depends on relaxivity, is associated with improved tissue/lesion detection and visualization and assistance in lesion characterization.

This high relaxivity of gadopiclenol in water is due to its specific structure since the relaxivity is directly proportional to the number of water molecules linked to the gadolinium. For gadopiclenol, two H_2O molecules are linked to gadolinium to complete the nine coordinations of gadolinium (in addition of the 4 nitrogens and the 3 oxygens of the carboxylate functions) whereas only one water molecule is present for the other GBCAs approved by EMA. Due to its high relaxivity, it is anticipated that

gadopiclenol can be given at a half dose of gadolinium compared to other non-specific gadolinium-containing contrast agents while providing the same contrast enhancement.

Table 11: Relaxivity Values of Gadopiclenol and Marketed GBCAs in Water at 1.5 T and 37°C

Relaxitivity at 1.5T	**r_1 ($L.mmol^{-1}.s^{-1}$)**	**r_2 ($L.mmol^{-1}.s^{-1}$)**
Gadopiclenol	**12.2**	**15.0**
Gadopentetic acid (Magnevist)	3.3	3.9
Gadodiamide (Omniscan)	3.3	3.9
Gadobenic acid (MultiHance)	3.8	4.4
Gadoteric acid (Dotarem)	3.0	3.5
Gadoteridol (ProHance)	2.9	3.4
Gadobutrol (Gadovist/Gadavist)	3.3	3.9

2.3.4. Discussion on clinical pharmacology

Pharmacokinetics

A study was performed in children aged < 2 years where sparse blood sampling was performed. The data were used to update a pop PK model that was developed for the original MAA submission, with data in children < 2 years. It is considered that the study was performed adequately. Plasma samples were analysed with a validated LC-MS/MS method and handling of samples was adequate.

The dataset from this study for the pop PK analysis included 33 children aged 3 – 23 months and 2 children aged 28 days to 3 months. Estimations for the age group younger than 3 months relied therefore (largely) on simulation.

Parameters were estimated with acceptable precision, except for the covariance between CL and Q, between Q and V2 and between CL and V2 (RSE is 114%, 65.7% and 127% resp). This suggests that there is no relevant relationship between peripheral volume of distribution and clearance and between clearance and inter-compartment clearance. The only fixed parameters were the allometric scaling exponent 0.75 for the effect of body weight on CL and Q, and 1 for effect of body weight on V2. These are however standard factors. Unexplained interindividual variability for CL and V1 was low (CV 22.6 – 27.7%). For V2 and Q it was moderate to high (CV 47.2 – 57.4%). According to the pop PK report, shrinkage (4.26 – 24.89%) was moderate which is considered acceptable.

Two adjustments were made to the model to achieve a better fit for the paediatric patients from study GDX-44-015: a renal maturation factor was introduced in the formula describing CL and the exponent for weight effect on V1 was estimated instead of using the standard factor 1. After these adjustments, the pcVPC plot and the goodness of fit plots indicate that the final model describes the PK data in paediatric patients under 2 years old sufficiently well. The extrapolation of the data to children < 3 months of age can be considered sufficiently reliable, because the fit of the final model is sufficient and there are sufficient data in children between 3 months and 2 years of age. In children aged 6 years and younger, estimated concentrations at 10 and 20 minutes decreased with age, while estimated AUC decreased with age up to 3 months, but was higher again in the age groups < 3 months. Lower concentrations in children compared to adults are probably caused by their higher total body water.

Increased simulated AUC in children < 3 months compared to older children and adults was observed with the highest in the age group ≤ 27 days. It is plausible that this was caused by the immature renal function in these young children.

Simulated concentrations up to 30 minutes and AUC for children < 2 years have been shown to be sufficiently comparable to those for adults and older children (see Figure 6). Concentrations at 10, 20 and 30 minutes are at the 5th percentile for adults or slightly below, but are comparable to the concentrations for children aged 2 – 6 years, whereas simulated AUC in the ≤ 27 days group is higher than in other age groups, but still within the adult range.

In adults with mild or moderate renal impairment (EPAR Elucirem / Vueway, gadopiclenol, 2023), more than 90 % of the administered dose was recovered in the urine within 48 hours. In patients with severely impaired renal function about 84 % of the administered dose was recovered in the urine within 5 days. PopPK-simulations showed relatively small differences between adults and the paediatric population with mild, moderate and severe renal impairment. (EPAR Elucirem / Vueway, gadopiclenol, 2023). In adult and paediatric patients ≥2 years of age, because of the lack of information on repeated administration, gadopiclenol injections should not be repeated unless the interval between injections is at least 7 days (EPAR Elucirem/Vueway (gadopiclenol), 2023).

Based on these data for children under 2 years old, no adjustment to the dosing regimen is considered necessary. The recommended and maximum dose in paediatric patients (from birth) is 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW). Due to immature renal function in neonates up to 4 weeks of age and infants up to 1 year of age, gadopliclenol should only be used in these patients after careful consideration, at a dose not exceeding 0.05 mmol/kg body weight. Because of the lack of information on repeated administration, gadopliclenol injections should not be repeated unless the interval between injections is at least 7 days.

2.3.5. Conclusions on clinical pharmacology

From a pharmacokinetic point of view, it is agreed that the recommended and maximum dose of 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) can be used for paediatric patients under 2 years of age.

2.4. Clinical efficacy

Clinical efficacy data in support for the use of gadopiclenol in pediatric patients < 2 years of age undergoing contrast-enhanced MRI is based on the results of the study GDX-44-015, a phase 2, open-label, uncontrolled, multicentre, internation study similar to study GDX-44-007 conducted in pediatric patients ages 2 to 17 years (Table 4).

2.4.1. Dose response study(ies)

See section 2.3.2. Pharmacokinetics above for the justification of the proposed posology for the population of 0-2 years of age in the SmPC.

The proposed dose for the additional population targeted by this extension of the indication (paediatric population <2 years) is the same as the current recommended dose for adult and paediatric patients aged 2 years and older, i.e., 0.1 mL/kg body weight (equivalent to 0.05 mmol/kg BW) for all indications.

2.4.2. Main study

Study GDX-44-015- Gadopiclenol pharmacokinetics, safety and efficacy in pediatric patients < 2 years of age undergoing contrast-enhanced MRI

Methods

GDX-44-015 was a phase 2, open-label, uncontrolled, multicentre, international study to investigate the pharmacokinetics, safety, and efficacy in pediatric patients < 2 years undergoing contrast-enhance MRI.

Study participants

The main inclusion criteria were female or male paediatric patient aged from birth to 23 months of age (preterm infants only after neonatal period), with known or highly suspected abnormalities/ lesion(s), scheduled to undergo contrast-enhanced MRI of any body region including CNS.

The neonatal period for preterm newborns is defined as the day of birth through the expected date of delivery plus 27 days. Term is defined as ≥37 completed weeks of amenorrhea.

Following recommendations for use of GBCAs, patients with the following conditions were excluded:

- Acute or chronic renal insufficiency defined as estimated Glomerular Filtration Rate (eGFR) out of age-adjusted normal value calculated based on bedside Schwartz equation
- Known class III/IV congestive heart failure according to the Modified Ross Heart Failure Classification in Children, known cardiac arrhythmia (e.g., heart rhythm anomalies, long QT syndrome),
- History of bleeding disorder, known severe liver disease, electrolyte or fluid imbalance,
- History of hypersensitivity caused by any contrast media / agents (iodinated or gadolinium-based),
- Known contraindication(s) to the use of any GBCA or contra-indication for MRI

Three age groups are defined:

- Group 1: patients aged 3 to 23 months
- Group 2: patients aged 28 days to less than 3 months
- Group 3: patients aged from birth to 27 days (**term newborns**).

Treatments

The study design was identical to study GDX-44-007 conducted in paediatric patients ages 2 to 17 years.

Each patient underwent 5 visits (Figure 7):

- V1 - Screening: up to 7 days before inclusion;

Patient eligibility was appraised.

- V2 - Inclusion: between D1 (gadopiclenol administration) and the end of confinement period;

MRI was performed prior to and after gadopiclenol administration on MR systems (1.5T or 3T). The start of administration was considered as injection time point (T0). The end of confinement period was determined by the last sampling time point randomly allocated within the window 6-8 hours.

- V3 – 1-day safety follow-up;
- V4 – 1-week safety follow-up;
- V5 – 3-month safety follow-up to monitor NSF risk.

Figure 7: ***Schematic of Study Design***

The overall expected trial duration for each patient was about 3 months, the minimum duration being 83 days and the maximum being 104 days.

Three cohorts of patients were included in this study:

- CNS cohort
- Blood vessel cohort
- Body cohort

An age-down staggered approach was used. The inclusions started with the oldest patients in Group 1. The decision to start the inclusions in Group 2 was taken by the Trial Safety Review Board (TSRB) based on safety assessment over one-day period after injection of the first 13 patients in Group 1.

Reading of images

For each investigational site, at least one experienced radiologist was appointed at the start of the trial, it was highly advised to have the same radiologist to read the images of all patients included at the site. Back up radiologist(s) could be involved.

Imaging procedure

Consistent with current clinical practice, MRI units with 1.5T or 3T magnetic field were used, regardless of the manufacturer. The manufacturer and field strength of the MRI device were recorded in the clinical eCRF. MRI scans were acquired before and after gadopiclenol injection. The same parameters settings for the same sequence before and after injection were used for each patient. The imaging sequences/parameters were performed according to site's standard imaging protocol. T1 weighted images before and after injection were obtained.

Treatment

Medicinal Product: gadopiclenol

Pharmaceutical form: 3 mL of sterile, clear, transparent ready-to-use aqueous solution for injection contained in vials of 10 mL.

Concentration: 0.5 M

Patients were dosed according to their body weight (BW) on the day of MRI examination. Gadopiclenol was administered at a dose of 0.05 mmol/kg BW (0.1 mL/kg BW). Gadopiclenol was administered intravenously (IV) manually or by power injector (if the desired volume could be delivered by the injector) as a bolus injection at a recommended rate of 1-2 mL/sec. Contrast-enhanced MRI started shortly after the injection depending on the pulse sequences used and the protocol for the examination. Gadopiclenol was followed by a saline flush to ensure complete administration of the contrast.

A patient IV line had to be established and maintained throughout the examination. General sedation or topical anesthesia was considered to minimize discomfort and distress (and documented in the medical file and in the eCRF as concomitant medication).

Objectives

Primary objective:

- To evaluate the pharmacokinetic profile of gadopiclenol in plasma following single intravenous injection of 0.05 mmol/kg 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).

Secondary objectives:

- To evaluate the safety of gadopiclenol (clinical and biological) up to 3 months following single administration.
- To evaluate the efficacy of gadopiclenol-enhanced MRI by body region (CNS, vessels and pool of others) as assessed by on-site Investigator.

Outcomes/endpoints

The main efficacy endpoints were:

- Qualitative assessments (lesion visualization assessed using 3 co-endpoints: border delineation, internal morphology and degree of contrast enhancement) for up to 3 most representative lesions or vessel abnormalities
- Quantitative parameters (Contrast-to-Noise Ratio [CNR], Lesion-to-Background Ratio [LBR] and percentage of enhancement) for up to 3 most representative lesions or vessel abnormalities.

Additional efficacy endpoints included technical adequacy for diagnosis, overall contrast quality, number and location of lesions detected, change in diagnostic confidence and impact on patient's treatment plan.

Efficacy assessment

Efficacy was assessed by comparing MR images before administration of gadopiclenol (Pre images) to combined MR images before (Pre) and after (Post) gadopiclenol administration (so-called Paired images) within the same patient. Each patient served as his/her own control as it was deemed unnecessary to expose paediatric patient to a comparator product. MR images were assessed by the on-site radiologist.

Table 12 below summarizes the definitions of the efficacy endpoints in study GDX-44-015.

Table 12: Definitions of Efficacy Endpoints in GDX-44-015

GDX-44-015	
Efficacy endpoints	
Lesion visualization (lesion border delineation, internal morphology and degree of contrast enhancement)	The investigator recorded each of lesion/ vessel visualization parameters for up to 3 most representative lesions or vessels **Border delineation**: defined as the distinction of lesion or vessel from surrounding tissues, and assessed through the following scale: 1 = none: no or unclear delineation 2 = moderate: some areas of clear delineation but also with some significant areas of non-distinct delineation 3 = good: almost clear but not complete delineation 4 = excellent: border outline is sharp with clear and complete delineation **Internal morphology:** identification of lesion architecture and the internal features and homogeneity of vessel enhancement and assess through the following scale: 1 = poor: poorly seen 2 = moderate: majority of lesion or vessel is poorly seen 3 = good: majority of lesion or vessel is clearly seen but with minor parts of lesion invisible 4 = excellent: lesion or vessel is well seen **Degree of contrast enhancement:** a qualitative assessment according to the following scale: 1 = no: no enhancement 2 = moderate: weakly enhanced 3 = good: clearly enhanced 4 = excellent: clearly and brightly enhanced
Quantitative parameters	The following parameters were assessed for up to 3 most representative lesions (largest enhancing lesions).
Contrast to Noise Ratio (CNR) on post-injection images	CNRpost= SIlpost− SIhtSDnoise $$CNRpost = \frac{SI_{lpost} - SI_{ht}}{SD_{noise}}$$ SIpost = Signal intensity of lesion on post injection T1 weighted images. SI_{ht} = Signal intensity of healthy tissue. SD_{noise} = Standard Deviation of background noise on post injection T1 weighted images.
Percentage enhancement (E%) of lesion(s)	E%= SIpost− SIpreSIprex100 $$E\% = \frac{SI_{post} - SI_{pre}}{SI_{pre}} \text{x} 100$$ SI_{post} = Signal intensity of lesion on post injection T1 weighted images. SI_{pre} = Signal intensity of lesion on pre injection T1 weighted images.

GDX-44-015	
Efficacy endpoints	
Lesion to Background Ratio (LBR) on post-injection images	LBR post =SI postSb $\text{LBR post} = \frac{SI\ post}{Sb}$ SIpost = Signal intensity of lesion on post injection T1 weighted images SI_b= Signal intensity of background (surrounding healthy tissue of the lesion) on post injection T1 weighted images
Technical adequacy of images	Images were evaluated as technically adequate for diagnosis using a 4point scale and as assessable or not. The technical adequacy of images was rated on a 4-point scale: 1 = non diagnostic 2 = poor 3 = fair 4 = good Images were evaluated as assessable or not and if not, the reason had to be recorded: 1 = Artifacts due to patient 2 = Artifacts due to machine 3 = Injection technical failure 4 = Inadequate anatomic coverage 5= Other, specify
Overall contrast quality	Overall contrast quality was assess on a 5-point scale: 1 = none 2 = poor 3 = moderate 4 = good 5= excellent
Number, and location of lesions/abnormal vessels and largest diameter (lesions only)	• Number of lesions on Pre and Paired images • For each of the 3 most representative lesions: • The largest diameter of the lesion • The location of the lesion
Change in diagnosis from Pre to Paired MRI	Yes/no/not assessable
Diagnostic confidence	defined as the degree of confidence that the information on the images represents the true and complete clinical picture of a subject. The degree of confidence was rated on a 5 point scale: 1 = nil: Very uncertain 2 = poor: Uncertain 3 = moderate: Moderately certain 4 = high: Good certainty 5 = excellent: Very certain When the investigator/independent blinded reader chose 'not assessable' for diagnosis, by definition the confidence level was 1 (= very uncertain).

GDX-44-015	
Efficacy endpoints	
Change in diagnostic confidence from Pre to Paired MRI	the degree of confidence that the information on the images represented the true and complete clinical picture of a patient: yes/no/not assessable
Change in treatment plan from Pre to Paired MRI	yes/no/not assessable

Sample size

The sampling design was evaluated through simulations for 45 and 40 infants, using a gadopiclenol popPK model that had been validated in paediatric patients from 2 to 17 years of age and refined to account for renal maturation in infants. With 45 infants, the sampling design was considered appropriate to collect informative samples for the determination of PK in the infant population. An important between-subject variability on volumes of distribution was anticipated, which did not invalidate the sampling design being of limited interest as far as the inter-individual variability (IIV) for clearance (CL) is correctly estimated.

Assuming that about 10% of patients included in the trial would not be evaluable for the primary criteria, a sample size of 50 patients, in agreement with the pediatric plans (PIP), should allow to achieve the study objectives.

The expected sample size of 50 patients was to be distributed between 3 age groups, as follows:

- Group 1: at least 20 patients aged 3 to 23 months (inclusive)
- Group 2: at least 12 patients aged 28 days to less than 3 months
- Group 3: at least 5 patients aged from birth to 27 days (term newborns)

At least 25 patients (50%) were scheduled to undergo a contrast-enhanced MRI of CNS (CNS cohort).

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 (see below "conduct of study").

Randomisation

Not applicable

Blinding (masking)

Not applicable

Statistical methods

All efficacy analyses were descriptive and were done using the Full Analysis Set (FAS) and presented per cohort and overall.

Results

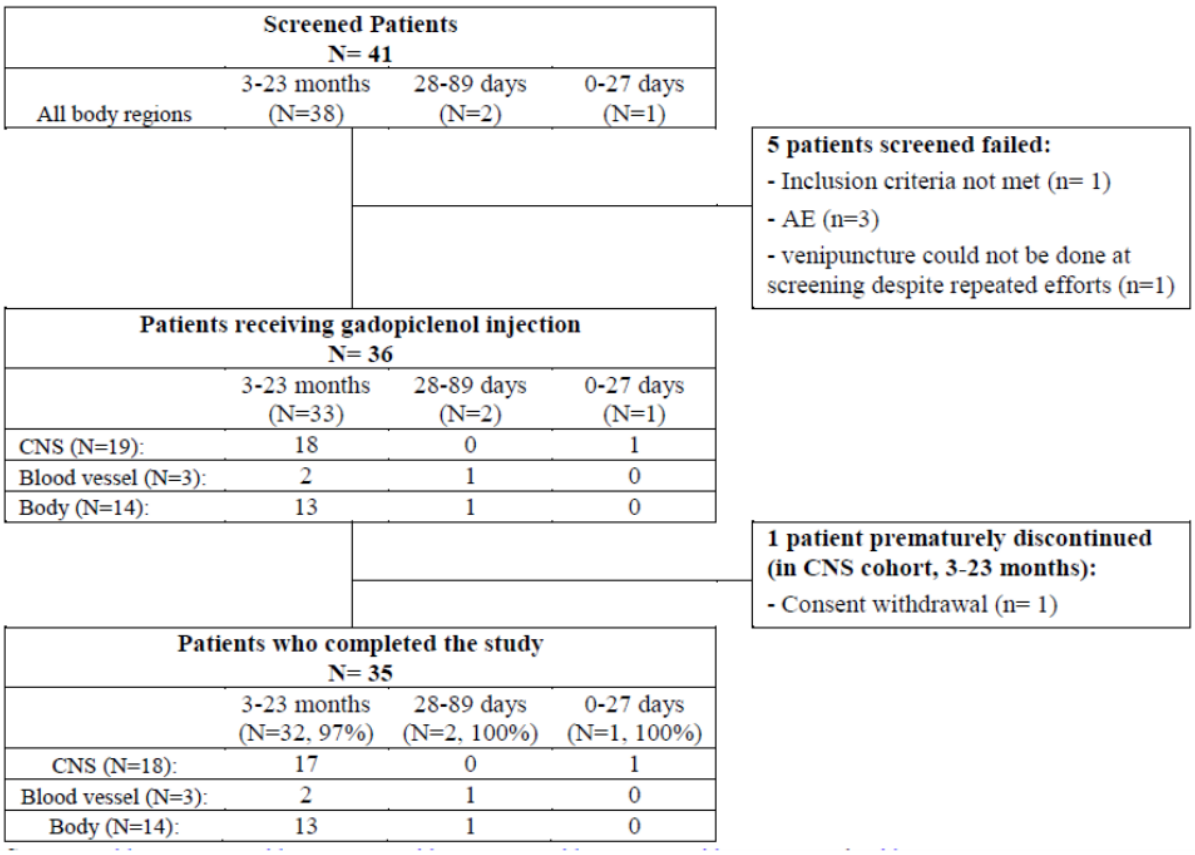
Participant flow

A total of 41 patients were enrolled in 11 centers from three countries: 23 (56.1%) from six centers in Poland, 13 (31.7%) from three centers in Hungary, 5 (12.2%) from two centers in the USA (Figure 8). Overall, 38 were in the 3-23 months age group, 2 in the 28-89 days age group and 1 in the 0-27 days age group.

Among them, five patients were screen failed, all in the 3-23 months age group, due to inclusion criteria not met (one patient not fulfilling the age criterion), adverse event (3 patients, due to respiratory tract infection) or impossibility to perform the venipuncture at screening despite repeated efforts (one patient).

Therefore, 36 patients received an injection of gadopiclenol: 19 in the CNS cohort (18 aged 3-23 months, 1 aged 0-27 days), 3 in the blood vessel cohort (2 aged 3-23 months and 1 aged 28-89 days) and 14 in the body cohort (13 aged 3-23 months and 1 aged 28-89 days). One patient prematurely discontinued the study before the 1-day safety follow-up due to withdrawal of consent. All other treated patients underwent all safety follow-up visits (at 1 day, 1 week and 3 months post administration).

Figure 8: Patients Overall Disposition - All Enrolled Patients Set



Protocol deviations

A single major protocol deviation (impacting the popPK model) was reported. A blood/plasma PK sample storage temperature excursion was reported for the samples from the patient in the 0-27 days

age group. The PK primary and backup samples were defrosted by mistake during the storage period at Eurofins Central Laboratory.

A total of 69 non-major protocol deviations were reported for 34 patients (82.9%): 32 patients out of the 38 enrolled in the 3-23 months age group, 1 out of the 2 enrolled in the 28-89 days age group and the patient enrolled in the 0-27 days age group (Table 11).

The most frequently reported non-major deviations were "biochemistry sample not performed, or missing results" (12 patients), "deviations related to ICF management process" (8 patients), "blood/plasma PK sample management not respected" (7 patients).

Table 13: Non-Major Protocol Deviations – All Enrolled Patients Set

	Total (N=41)*	
	n (%) patients	n deviations
At least one non major protocol deviation	**34 (82.9%)**	**69**
Gadopiclenol administration	**7 (17.1%)**	**7**
- Gadopiclenol management not respected	4 (9.8%)	4
- Gadopiclenol temperature excursion	3 (7.3%)	3
Good clinical practice (GCP) deviation	**16 (39.0%)**	**25**
- Deviations related to ICF management process	8 (19.5%)	11
- Source document management not appropriate	6 (14.6%)	8
- AE/SAE management not appropriate	5 (12.2%)	6
Missing data	**15 (36.6%)**	**18**
- Some but not all plasma PK samples not obtained	1 (2.4%)	1
- Vital signs not measured or results missing	1 (2.4%)	1
- Biochemistry sample not performed, or results are missing	12 (29.3%)	12
- Hematology sample not performed, or results are missing	2 (4.9%)	2
- Physical examination not performed	1 (2.4%)	1
- Adequate MRI sequence not performed	1 (2.4%)	1
Non respect of trial schedule and procedures	**15 (36.6%)**	**19**
- Blood/plasma PK sample management not respected	7 (17.1%)	7
- Blood/plasma PK sample storage temperature excursion	1 (2.4%)	1
- Injection and plasma PK sampling performed through the same IV line	1 (2.4%)	1
- Plasma PK samples collected out of the scheduled time windows	2 (4.9%)	2
- Vital signs performed out of the scheduled time windows	2 (4.9%)	2
- One week safety follow-up performed out of the scheduled time windows	2 (4.9%)	2
- 3-month safety follow-up performed out of the scheduled time windows	3 (7.3%)	3
- Total blood volume collected exceed authorized volume	1 (2.4%)	1

n deviations = number of deviations as one patient may have more than one deviation by category and overall.
* Total number of patients includes screen failure patients.

Recruitment

Conduct of the study

Protocol amendments

The initial protocol v1.0, dated 03-Sep-2021, was amended 3 times:

Protocol V2.0 Amendment 1, dated 21-Jul-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 may 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.

Protocol V3.0 Amendment 2, dated 24-Jun-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 had not been applicable and was not distributed to sites. The changes were implemented in the following version v4.0.

Protocol V4.0 Amendment 3, dated 09-Oct-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.

Early termination

Following consultation with FDA and EMA and their favourable opinion for reducing the sample size initially considered, an early termination of the study was decided on 17 July 2024. The enrolment target 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 related to any safety or tolerability concern or event with the use of gadopiclenol.

Pharmacokinetic samples collected from the first 33 patients included in the study in the 3-23 months age group (Group 1) 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 meet 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 were predicted by simulation, since the preliminary evaluation performed on the data collected from the first 33 patients demonstrated that the following conditions were met:

1. There was 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 was appropriately incorporated in the model,
3. Reducing the sample size did not compromise the achievement of the primary objective.

From 17 July 2024, no further patients were screened or received an injection of gadopiclenol, while all ongoing patients were followed for 3 months post gadopiclenol administration as per protocol.

Baseline data

Demographics

Study GDX-44-015 included 36 patients who received one dose of gadopiclenol: 33 in the 3-23 months age group, 2 in the 28-89 days age group and 1 in the 0-27 days age group.

The mean age in the 3-23 months age group was 13.11 months (±6.22). The weight of patients ranged from 4.2 to 13.7 kg, with a mean (SD) of 9.03 (2.44) kg. No preterm neonates were included. The demographics and baseline characteristics for the Safety set are summarised in the Table 14 below. Similar results were obtained for the Full Analysis Set (one patient less, see paragraph 'Number analysed' below).

Table 14: GDX-44-015 - Demographic Data - Safety Set

	By age group			By region imaging cohort			
	3-23 months (N=33)	28-89 days (N=2)	0-27 days (N=1)	CNS (N=19)	Blood Vessel (N=3)	Body (N=14)	Total (N=36)
Age (months)							
n	33	2	1	19	3	14	36
Mean (SD)	13.11 (6.22)	1.94 (0.14)	0.8 (NE)	13.98 (6.61)	13.20 (9.74)	9.45 (5.96)	12.15 (6.77)
Median	12.25	1.94	0.8	13.21	17.58	9.64	11.56
Sex							
n	33	2	1	19	3	14	36
Male	16 (48.5%)	1 (50.0%)	1 (100%)	10 (52.6%)	2 (66.7%)	6 (42.9%)	18 (50.0%)
Female	17 (51.5%)	1 (50.0%)	0	9 (47.4%)	1 (33.3%)	8 (57.1%)	18 (50.0%)
Height (cm)							
n	33	2	1	19	3	14	36
Mean (SD)	75.8 (7.8)	57.0 (1.4)	55.0 (NE)	77.1 (7.9)	74.7 (16.2)	70.2 (8.5)	74.2 (9.2)
Median	75.0	57.0	55.0	77.0	83.0	70.5	73.5
Min. ; Max.	54 ; 87	56 ; 58	55 ; 55	55 ; 87	56 ; 85	54 ; 83	54 ; 87
Weight (kg)							
n	33	2	1	19	3	14	36
Mean (SD)	9.40 (2.18)	5.10 (0.28)	4.50 (NE)	9.65 (2.15)	9.13 (3.67)	8.16 (2.49)	9.03 (2.44)
Median	9.20	5.10	4.50	9.30	11.00	8.15	9.05
Min. ; Max.	4.2 ; 13.7	4.9 ; 5.3	4.5 ; 4.5	4.5 ; 13.7	4.9 ; 11.5	4.2 ; 13.0	4.2 ; 13.7

Previous imaging experience

Among the 36 patients of the safety set, 19 (52.8%) had already undergone an imaging procedure with administration of contrast agent: 18 in the 3-23 months age group and the patient in the 0-27 days age group. This latter had an examination with a contrast agent other than a gadolinium complex, iodinated contrast agent, barium or diagnostic radiopharmaceutical, but not otherwise specified. Among the other 18 patients who had experienced a previous administration of a contrast agent, 17 had received a gadolinium complex (for 1 to 8 examinations).

Disease Diagnosis

The diagnosis at study entry for the patient in the 0-27 days age group was cerebral haematoma. The two patients in the 28-89 days age group presented with hereditary haemorrhagic telangiectasia and benign hepatic neoplasm. For the patients in the 3-23 months age groups, the diagnoses are presented in the Table 15 below.

The imaging procedure documenting the trial disease was an ultrasound for 19 patients, an MRI for 13 patients, another imaging procedure for one patient and the data was missing for the 3 patients in the 28-89 days and 0-27 days age groups. The time interval from the most recent imaging procedure and the study procedure with gadopiclenol ranged from 4 to 506 days, with an overall median of 56 days (median of 94.5 days in the CNS cohort, 115.5 days in the Blood vessel).

Table 15: Trial Disease diagnosis of patients aged 3-23 months

	3-23 months (N=33)		3-23 months (N=33)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (39.4%)	**Nervous system disorders**	6 (18.2%)
Brain neoplasm	2 (6.1%)	Hydrocephalus	2 (6.1%)
Haemangioma	2 (6.1%)	Cerebral atrophy	1 (3.0%)
Astrocytoma, low grade	1 (3.0%)	Haemorrhage intracranial	1 (3.0%)
Chest wall tumour	1 (3.0%)	Pineal gland cyst	1 (3.0%)
Ewing's sarcoma	1 (3.0%)	White matter lesion	1 (3.0%)
Ganglioglioma	1 (3.0%)	**Endocrine disorders**	1 (3.0%)
Juvenile xanthogranuloma	1 (3.0%)	Pituitary cyst	1 (3.0%)
Lymphangioma	1 (3.0%)	**Eye disorders**	1 (3.0%)
Muscle neoplasm	1 (3.0%)	Optic atrophy	1 (3.0%)
Neuroblastoma	1 (3.0%)	**Hepatobiliary disorders**	1 (3.0%)
Optic glioma	1 (3.0%)	Liver disorder	1 (3.0%)
Congenital, familial and genetic disorders	9 (27.3%)	**Musculoskeletal and connective tissue disorders**	1 (3.0%)
Lymphatic malformation	2 (6.1%)	Soft tissue mass	1 (3.0%)
Cerebral cavernous malformation	1 (3.0%)	**Renal and urinary disorders**	1 (3.0%)
Congenital hydrocephalus	1 (3.0%)	Ureterocele	1 (3.0%)
Congenital spinal cord anomaly	1 (3.0%)		
Cryptorchism	1 (3.0%)		
Hypothalamic hamartoma	1 (3.0%)		
Urinary tract malformation	1 (3.0%)		
Vascular malformation	1 (3.0%)		

Numbers analysed

Among the 36 subjects who received one injection of gadopiclenol (Safety Set), one patient aged 3-23 months was excluded from the Full Analysis Set (FAS), as the post-contrast images were not available (the patient experienced an adverse event [choking] at the injection time). Therefore, the FAS included 35 patients analysed for efficacy (Table 16). The patient aged 0-27 days was excluded from the Per Protocol Set, due to a major deviation impacting the popPK model, therefore 35 patients were included in the PK analysis.

Table 16: Overview of data sets analysed

	By age group			By region imaging cohort			
	3-23 months (N=38)	28-89 days (N=2)	0-27 days (N=1)	CNS (N=19)	Blood Vessel (N=3)	Body (N=14)	Total (N=41)
Full Analysis Set	32 (84.2%)	2 (100%)	1 (100%)	18 (94.7%)	3 (100%)	14 (100%)	35 (85.4%)
Safety Set	33 (86.8%)	2 (100%)	1 (100%)	19 (100%)	3 (100%)	14 (100%)	36 (87.8%)
Per Protocol Set	33 (100%)	2 (100%)	0	18 (94.7%)	3 (100%)	14 (100%)	35 (97.2%)

Percentages for the Full Analysis Set and the Safety Set are based upon number of patients in the All Enrolled Set
Percentages for the Per Protocol Set are based upon number of patients in the Safety Set.
CNS: Central Nervous System

Outcomes and estimation

Image adequacy

Table 17: Images Adequacy – Pre and Paired Images – Full Analysis Set

	CNS Cohort (N=18)		Blood Vessel Cohort (N=3)		Body Cohort (N=14)		Total (N=35)	
	Pre images	Paired images	Pre images	Paired images	Pre images	Paired images	Pre images	Paired images
Technical adequacy for diagnosis								
n	18	18	3	3	14	14	35	35
Non diagnostic	0	0	0	0	0	0	0	0
Poor	0	0	0	0	0	0	0	0
Fair	1 (5.6%)	1 (5.6%)	0	1 (33.3%)	1 (7.1%)	1 (7.1%)	2 (5.7%)	3 (8.6%)
Good	17 (94.4%)	17 (94.4%)	3 (100%)	2 (66.7%)	13 (92.9%)	13 (92.9%)	33 (94.3%)	32 (91.4%)
If diagnostic: Assessment of overall contrast quality								
None	2 (11.1%)	1 (5.6%)	0	0	0	0	2 (5.7%)	1 (2.9%)
Poor	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0
Good	8 (44.4%)	8 (44.4%)	2 (66.7%)	2 (66.7%)	8 (57.1%)	8 (57.1%)	18 (51.4%)	18 (51.4%)
Excellent	8 (44.4%)	9 (50.0%)	1 (33.3%)	1 (33.3%)	6 (42.9%)	6 (42.9%)	15 (42.9%)	16 (45.7%)

%: (n row / N column) * 100
CNS: Central Nervous System

Lesion detection

Table 18: Number of Detected Lesions and Abnormal Blood Vessels – Pre and Paired Images – Full Analysis Set

	CNS Cohort (N=18)		Blood Vessel Cohort (N=3)		Body Cohort (N=14)		Total (N=35)	
	Pre images	Paired images	Pre images	Paired images	Pre images	Paired images	Pre images	Paired images
Total number of detected lesions / abnormal vessels per subject								
n	18	18	3	3	14	14	35	35
Mean (SD)	1.1 (0.8)	1.2 (0.9)	0.7 (0.6)	0.7 (0.6)	1.1 (0.4)	1.1 (0.4)	1.1 (0.7)	1.1 (0.7)
Median	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Min. ; Max.	0 ; 3	0 ; 3	0 ; 1	0 ; 1	1 ; 2	1 ; 2	0 ; 3	0 ; 3
No lesion	3 (16.7%)	3 (16.7%)	1 (33.3%)	1 (33.3%)	0	0	4 (11.4%)	4 (11.4%)
1 lesion	12 (66.7%)	11 (61.1%)	2 (66.7%)	2 (66.7%)	12 (85.7%)	12 (85.7%)	26 (74.3%)	25 (71.4%)
2 lesions	1 (5.6%)	2 (11.1%)	0	0	2 (14.3%)	2 (14.3%)	3 (8.6%)	4 (11.4%)
3 lesions	2 (11.1%)	2 (11.1%)	0	0	0	0	2 (5.7%)	2 (5.7%)
More than 3 lesions	0	0	0	0	0	0	0	0

Table 19: Location of Lesions or Abnormal Blood Vessel – Pre and Paired Images – Full Analysis

	Pre images	Paired images
CNS Cohort (N=18)		
Total number of lesions	**20**	**21**
Lobar	*7 (35.0%)*	*7 (33.3%)*
Left parietal lobe	1 (5.0%)	1 (4.8%)
Right parietal lobe	1 (5.0%)	1 (4.8%)
Left temporal lobe	2 (10.0%)	2 (9.5%)
Right temporal lobe	1 (5.0%)	1 (4.8%)
Left occipital lobe	1 (5.0%)	1 (4.8%)
Right occipital lobe	1 (5.0%)	1 (4.8%)
Other brain locations	*7 (35.0%)*	*8 (38.1%)*
Cranial nerves	3 (15.0%)	3 (14.3%)
Pineal region	1 (5.0%)	1 (4.8%)
Pituitary area	2 (10.0%)	2 (9.5%)
Brainstem	-	1 (4.8%)
Corpus callosum	1 (5.0%)	1 (4.8%)
Cervical	*1 (5.0%)*	*1 (4.8%)*
Intramedullary cervical spine	1 (5.0%)	1 (4.8%)
Lumbosacral	*1 (5.0%)*	*1 (4.8%)*
Extradural lumbosacral spine	1 (5.0%)	1 (4.8%)
Other	*4 (20.0%)*	*4 (19.0%)*
Body cohort (N=14)		
Total number of lesions	**16**	**16**
Head & Neck	*4 (25.0%)*	*4 (25.0%)*
Head	3 (18.8%)	3 (18.8%)
Left neck	1 (6.3%)	1 (6.3%)
Thorax	*1 (6.3%)*	*1 (6.3%)*
Lung	1 (6.3%)	1 (6.3%)
Abdomen & Pelvis	*5 (31.3%)*	*5 (31.3%)*
Liver Left lobe	2 (12.5%)	2 (12.5%)
Liver Quadrate lobe	2 (12.5%)	2 (12.5%)
Left urinary tract	1 (6.3%)	1 (6.3%)
Other	*6 (37.5%)*	*6 (37.5%)*
Blood Vessel Cohort (N=3)		
Total number of lesions	2	2
Other	*2 (100%)*	*2 (100%)*

%: (n row / N Total number of lesions / abnormal blood vessel) * 100
CNS: Central Nervous System. SD: Standard Deviation

The largest diameter of the lesion ranged from 3 to 80 mm, with an overall median of 18 mm, similar for Pre and Paired images in the Body cohort, but lower with Paired images in the CNS cohort (median of 15 mm compared to 17.5 mm with pre-contrast images), probably due to the additional lesion, with a 4 mm diameter.

Lesion Visualization

The assessment of the 3 parameters of lesion visualization showed a general improvement with paired images.

Visualization of the lesion border delineation improved with Paired images from good to excellent for 9 lesions (4 in patients from the CNS cohort, 4 in patients from the Body cohort and 1 in a patient from the Blood vessel cohort). Border delineation was seen only with Paired images for 2 lesions in patients of the Body cohort.

Visualization of internal morphology was generally good to excellent with both Pre and Paired images. A "poor" visualization was reported for 4 lesions in the Body cohort with Pre images, improving to good (2 lesions) or excellent (2 lesions) with Paired images.

No contrast enhancement was reported with Pre images as expected. With Paired images, no enhancement was reported for 7 lesions in 5 patients in the CNS cohort (3 lesions in the patient aged 0-27 days, and one lesion for 4 patients aged 3-23 months located in the pituitary area, right temporal lobe, pineal region and optic nerve) due to the nature of the lesion (such as congenital malformation, cyst, hematoma). Otherwise, the degree of contrast enhancement was generally graded as good (12/39, 31%) to excellent (17/39, 44%). The level of "excellent" was more often reported in the Body cohort (10/16, 62.5%). (Table 20)

Table 20: Lesion and Abnormal Blood Vessel Visualization by Cohort – Pre and Paired Images – Full Analysis Set

	CNS Cohort (N=18)		**Blood Vessel Cohort (N=3)**		**Body Cohort (N=14)**	
	Pre Images	Paired Images	Pre Images	Paired Images	Pre Images	Paired Images
Border delineation						
N lesions / Abnormal Blood Vessel	20	21	2	2	16	16
None	3 (15.0%)	3 (14.3%)	0	0	2 (12.5%)	0
Moderate	3 (15.0%)	4 (19.0%)	0	0	3 (18.8%)	2 (12.5%)
Good	7 (35.0%)	3 (14.3%)	2 (100%)	1 (50.0%)	8 (50.0%)	5 (31.3%)
Excellent	7 (35.0%)	11 (52.4%)	0	1 (50.0%)	3 (18.8%)	9 (56.3%)
Internal morphology						
N lesions / Abnormal Blood Vessel	20	21	2	2	16	16
Poor	0	0	0	0	4 (25.0%)	0
Moderate	2 (10.0%)	1 (4.8%)	0	0	3 (18.8%)	3 (18.8%)
Good	8 (40.0%)	9 (42.9%)	2 (100%)	2 (100%)	7 (43.8%)	6 (37.5%)
Excellent	10 (50.0%)	11 (52.4%)	0	0	2 (12.5%)	7 (43.8%)
Degree of contrast enhancement						
N lesions / Abnormal Blood Vessel	20	21	2	2	16	16
No enhancement	20 (100%)	7 (33.3%)	2 (100%)	0	16 (100%)	0
Moderate	0	2 (9.5%)	0	0	0	1 (6.3%)
Good	0	5 (23.8%)	0	2 (100%)	0	5 (31.3%)
Excellent	0	7 (33.3%)	0	0	0	10 (62.5%)

Quantitative assessments (lesions)

The median %Enhancement was 35.3% for the CNS cohort and 112.6% for the Body cohort. The LBR was similar in CNS and Body cohort, with a median value of 1.34. A large variability in CNR was observed in the CNS cohort, with a mean (SD) of 125.0 (533.4) (Table 21).

Table 21: Signal Intensity Assessment of Lesions – CNS and Other Body Region Cohorts – Full Analysis Set

	CNS Cohort (N=18)	**Body Cohort (N=14)**	**Total (N=32)**
Signal Intensity on pre images			
Total number of lesions	20	16	36
Mean (SD)	414.44 (497.23)	405.10 (212.00)	410.29 (391.79)
Median	241.70	323.45	295.00
Min. ; Max.	21.0 ; 2251.0	150.0 ; 826.0	21.0 ; 2251.0
Signal Intensity on post images			
Total number of lesions	21	16	37
Mean (SD)	638.61 (707.81)	962.46 (503.20)	778.66 (640.54)
Median	364.10	929.00	590.00
Min. ; Max.	29.0 ; 2815.0	298.0 ; 1709.0	29.0 ; 2815.0

	CNS Cohort (N=18)	Body Cohort (N=14)	Total (N=32)
Percentage of enhancement (%)			
Total number of lesions	20	16	36
Mean (SD)	58.4 (66.0)	150.1 (108.5)	99.2 (97.7)
Median	35.3	112.6	76.5
Min. ; Max.	-10 ; 222	6 ; 404	-10 ; 404
Not seen on pre images	1	0	1
Lesion to background ratio (LBR)			
Total number of lesions	21	16	37
Mean (SD)	1.53 (0.92)	1.97 (2.31)	1.72 (1.66)
Median	1.34	1.34	1.34
Min. ; Max.	0.2 ; 3.4	0.6 ; 10.5	0.2 ; 10.5
Contrast to Noise Ratio (CNR)*			
Total number of lesions	21		
Mean (SD)	125.0 (533.4)		
Median	5.9		
Min. ; Max.	-161 ; 2443		
Missing data	0		

Diagnosis and diagnostic confidence

At least one lesion was detected with Paired images for 31 out of 35 patients (88.6%). For these patients, the diagnosis was a primary tumour in half of the cases in both CNS and Body cohorts. The diagnosis changed between Pre and Paired images for 2 patients in the CNS cohort and 4 patients in the Body cohort (Table 22). These patients had a diagnosis based on Paired images of primary tumour (5 patients) and infectious disease (one patient in the Body cohort).

Table 22: Diagnosis and Change in Diagnosis – Full Analysis Set

	CNS Cohort (N=18)	Blood Vessel Cohort (N=3)	Body Cohort (N=14)	Total (N=35)
Patients with detected lesion on paired image				
n	18	3	14	35
Yes	15 (83.3%)	2 (66.7%)	14 (100%)	31 (88.6%)
No	3 (16.7%)	1 (33.3%)	0	4 (11.4%)
If yes,				
Diagnosis according to paired images				
n	15	2	14	31
Primary tumour	7 (46.7%)	0	7 (50.0%)	14 (45.2%)
Secondary tumour	0	0	0	0
Inflammatory disease	0	0	0	0
Infectious disease	0	0	1 (7.1%)	1 (3.2%)
Vascular disease	2 (13.3%)	1 (50.0%)	0	3 (9.7%)
Congenital malformation	3 (20.0%)	1 (50.0%)	3 (21.4%)	7 (22.6%)
Neurodegenerative disease	0	0	0	0
Other	3 (20.0%)	0	1 (7.1%)	4 (12.9%)
Not assessable	0	0	2 (14.3%)	2 (6.5%)
Diagnosis based on paired images changed compared to pre images				
n	15	2	14	31
Yes	2 (13.3%)	0	4 (28.6%)	6 (19.4%)
No	12 (80.0%)	2 (100%)	5 (35.7%)	19 (61.3%)
Not assessable	1 (6.7%)	0	5 (35.7%)	6 (19.4%)

Among the 31 patients with at least one detected lesion, the diagnostic confidence based on Pre images was nil or poor for 7 patients (6 in the Body cohort, 1 in the CNS cohort), moderate for 8 patients and high to excellent for 16 patients. With Paired images, the diagnostic confidence improved

for 13 patients (41.9%), remained unchanged for 17 patients (54.8%) and was worse for one patient (3.2%) (Table 23). For this patient included in the Body cohort, the diagnostic confidence worsened from poor to nil (diagnosis was "not assessable").

Table 23: Diagnostic Confidence and Change in Diagnostic Confidence – Full Analysis Set

	CNS Cohort (N=18)	Blood Vessel Cohort (N=3)	Body Cohort (N=14)	Total (N=35)
Diagnostic confidence according to pre images				
n patients with detected lesions	15	2	14	31
nil: very uncertain	0	0	1 (7.1%)	1 (3.2%)
Poor: uncertain	1 (6.7%)	0	5 (35.7%)	6 (19.4%)
Moderate: moderately certain	2 (13.3%)	0	6 (42.9%)	8 (25.8%)
High: good certainty	8 (53.3%)	2 (100%)	2 (14.3%)	12 (38.7%)
Excellent: very certain	4 (26.7%)	0	0	4 (12.9%)
Change in diagnostic confidence from pre to paired images				
n	15	2	14	31
Improved	4 (26.7%)	0	9 (64.3%)	13 (41.9%)
Remains unchanged	11 (73.3%)	2 (100%)	4 (28.6%)	17 (54.8%)
Getting worse	0	0	1 (7.1%)	1 (3.2%)
Diagnostic confidence according to paired images				
n	15	2	14	31
nil: very uncertain	0	0	1 (7.1%)	1 (3.2%)
Poor: uncertain	1 (6.7%)	0	0	1 (3.2%)
Moderate: moderately certain	1 (6.7%)	0	6 (42.9%)	7 (22.6%)
High: good certainty	6 (40.0%)	2 (100%)	6 (42.9%)	14 (45.2%)
Excellent: very certain	7 (46.7%)	0	1 (7.1%)	8 (25.8%)

Therapeutic Management

Regarding the impact of gadopiclenol-enhanced images on the therapeutic management, a possible change in treatment plan was reported for half of the patients in the Blood vessel cohort (1 out of 2) and in the Body cohort (7 out of 14) and none of the 15 patients in the CNS cohort (Table 24). For the patient in the Blood vessel cohort, the change was from surgery to "other treatment (patient transferred to another clinic for further examination)" and for the 7 patients in the Body cohort, the change was from biopsy to other treatment (watch and wait, follow-up or conservative treatment) for 4 patients, from surgery to other treatment (propranolol or watchful waiting) for 2 patients and from "biopsy, surgery" to surgery for one patient. For 4 out of these 7 patients, further information on the actual treatment plan was not available. For three cases additional information was provided which confirmed the change in proposed treatment plan (date not presented).

Table 24: Therapeutic Management and Change in Treatment Plan – Full Analysis Set

	CNS Cohort (N=18)	Blood Vessel Cohort (N=3)	Body Cohort (N=14)	Total (N=35)
Therapeutic management proposed based on pre images*				
n patients with detected lesion	15	2	14	31
Surgery	2 (13.3%)	2 (100%)	6 (42.9%)	10 (32.3%)
Biopsy	0	0	5 (35.7%)	5 (16.1%)
Chemotherapy	0	0	2 (14.3%)	2 (6.5%)
Radiotherapy	0	0	0	0
Other treatment	13 (86.7%)	0	2 (14.3%)	15 (48.4%)
Could the treatment plan be changed?				
Yes	0	1 (50.0%)	7 (50.0%)	8 (25.8%)
No	15 (100%)	1 (50.0%)	7 (50.0%)	23 (74.2%)

Not assessable	0	0	0	0
Therapeutic management proposed based on paired images*				
n (patients with a change)		1	7	8
Surgery		0	1 (14.3%)	1 (12.5%)
Other treatment		1 (100%)	6 (85.7%)	7 (87.5%)

CNS: Central Nervous System; %: (n row / N patients) * 100 for detected lesions, %: (n row / N patients with detected lesions) * 100 otherwise; *Only detected lesion have been considered For the item "Therapeutic management proposed", a patient may have more than one answer

Ancillary analyses

Comparison of results in subpopulations

No analysis was performed for subgroups in this population of patients <2 years old but the WSA was requested to show that the results of the different efficacy parameters observed in the age groups 0-27 days and 28-29 days were consistent with the results observed in the age group of 3-23 months. The sample size of two patients aged 28-89 days and one patient aged 0-27 days (3 patients) is small to make relevant comparisons to the older populations, therefore, the results are descriptive.

One patient aged 28-89 days had an MRI of the abdomen for a benign hepatic neoplasm. The level of diagnostic confidence increased from poor with unenhanced images to high with paired images and a potential change of treatment plan from biopsy to follow-up was reported after reading paired images. For the other patient in this age group, undergoing MRI for hereditary haemorrhagic telangiectasia, no lesion was detected. The patient aged 0-27 days had an MRI for temporal intracerebral hematoma left side, but no contrast enhancement was shown.

For the patient who had an enhancing lesion, visualization was improved with paired images and the level of diagnosis confidence changed from "poor" with pre-contrast images to "high" with paired images.

Clinical studies in special populations

All patients had an eGFR in the normal range according to their age.

2.4.3. Discussion on clinical efficacy

Elucirem/Vueway 0.5 mmol/mL solution for injection was approved in the EU in 2023 for contrast-enhanced MRI in adults and children aged 2 years and older to improve detection and visualization of pathologies with disruption of the blood-brain-barrier (BBB) and / or abnormal vascularity of the CNS and other body regions. This application for Elucirem/Vueway is a Type II variation for extending the indication to paediatric patients aged 0 to 2 years.

The application is based on the results of the completed paediatric study GDX-44-015, in line with the approved EU PIPs EMEA-001949-PIP01-16-M07 for CNS and EMEA-001949-PIP02-18-M05 for body, and with the completed full compliance checks (P/0294/2024 and P/0293/2024, respectively).

Dose finding

The proposed dose for the additional population targeted by this extension of the indication (pediatric population <2 years) is the same as the current recommended dose for adult and pediatric patients aged 2 years and older, i.e., 0.1 mL/kg body weight (equivalent to 0.05 mmol/kg BW) for all indications (please see "pharmacology" section in this report for discussion).

Design and conduct of clinical studies

The design of study GDX-44-015 is similar to study GDX-44-007 conducted in paediatric patients aged 2 to 18 years which was part of the initial MAA of Elucirem/Vueway to support the paediatric population of patients aged 2 to 18 years. Although the methods and efficacy endpoints have been discussed and considered acceptable upon submission of study GDX-44-007 in the initial MAA, for clarity these are again discussed shortly below. Only the inclusion criteria differ, which can be expected with a different target population.

Key inclusion criteria were female or male paediatric patient aged from birth to 23 months of age including term neonates for all age groups or preterm infants after the neonatal period, with known or highly suspected abnormalities/ lesion(s), scheduled to undergo contrast-enhanced MRI of any body region including CNS. Three age groups were defined: 1) Group 1 of patients aged 3 to 23 months; Group 2 of patients aged 28 days to less than 3 months; and Group 3 of patients aged from birth to 27 days (term newborns). Term neonates could be enrolled in all age groups, whereas preterm infants could only be enrolled in groups 1 or 2, i.e. after the neonatal period, i.e. the day of birth through the expected date of delivery plus 27 days. This conservative approach is acceptable. Further, it has been reflected in section 4.4 of the SmPC that there is no experience in preterm neonates. The study excluded patients with acute or chronic renal insufficiency, known class III/IV congestive heart failure, known cardiac arrhythmia, history of bleeding disorder, known severe liver disease, electrolyte or fluid balance, and patients with known hypersensitivity to gadolinium, which is considered appropriate.

The design of the study is in line with the approved PIP and appears appropriate. MRI was performed prior to and after gadopiclenol administration on MR systems (1.5T or 3T). The same parameters settings for the same sequence before and after injection were used for each patient. For each investigational site, at least one experienced radiologist was appointed at the start of the trial and it was highly advised to have the same radiologist to read the images of all patients included at the site. The use of local radiologist is not in line with the EMA guideline on clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev. 1). Considering that the primary objective of the paediatric study under review was to evaluate the pharmacokinetic profile of gadopiclenol in the paediatric population aged up to 23 months and clinical efficacy was investigated as secondary endpoint in this study, the image reading procedure can be acceptable in this case.

The study included three cohorts, i.e., a CNS, blood vessel and body cohort. Currently, Elucirem/Vueway 0.5 mmol/mL solution for injection is not indicated for angiography. Consequently, the efficacy results of the blood vessel cohort falls outside the scope of the proposed indication.

The primary objective was to evaluate the PK profile of gadopiclenol in plasma following a single intravenous injection of 0.050 mmol/kg BW (see pharmacology). The secondary objectives were to evaluate the safety up to 3 months following single administration of gadopiclenol and to evaluate efficacy of gadopiclenol-enhanced MRI by body region as assessed by on-site Investigator.

The main efficacy endpoints were qualitative assessments (lesion visualization assessed using 3 co-endpoints: border delineation, internal morphology and degree of contrast enhancement) and quantitative parameters (Contrast-to-Noise Ratio [CNR], Lesion-to-Background Ratio [LBR] and percentage of enhancement) for up to 3 most representative lesions or vessel abnormalities, consistent with standard endpoints for contrast agents, and similar to those assessed in the pivotal studies conducted in adults (GDX-44-010 and GDX-44-011) and those assessed in the study conducted in paediatric patients aged 2 to 18 years (GDX-44-007), and therefore considered acceptable. Additional efficacy endpoints included technical adequacy for diagnosis, overall contrast quality, number and location of lesions detected, change in diagnostic confidence and impact on patient's treatment plan. All efficacy analyses were descriptive and were done using the FAS. Selection of most visible lesions for

analysis is considered methodologically inappropriate, as this leads to positive bias and overestimates efficacy. In the conducted study, however, majority of the subjects (70%) had only 1 lesion and the bias can be considered limited.

The sampling design was considered appropriate to collect informative samples for the determination of PK in the infant population, i.e. the primary objective.

Efficacy data and additional analyses

A total of 41 patients were enrolled in 11 centers from three countries including 23 patients (56.1%) from six centers in Poland, 13 patients (31.7%) from three centers in Hungary, and 5 patients (12.2%) from two centers in the USA. Among them, 5 patients were screen failed due to inclusion criteria not met (n=1), adverse events (n=3) or impossible to perform the venipuncture at screening (n=1). In total, 36 patients received an injection of gadopiclenol including 19 in the CNS cohort (18 aged 3-23 months, 1 aged 0-27 days), 3 in the blood vessel cohort (2 aged 3-23 months and 1 aged 28-89 days) and 14 in the body cohort (13 aged 3-23 months and 1 aged 28-89 days). Three premature infants were included in the study after their neonatal period, all in the 3-23 months age group (n=2 in CNS, n=1 in body cohort). All patients completed the study with the exception of one patient (CNS cohort, aged 3—23 months) who prematurely discontinued the study before the 1-day safety follow-up due to withdrawal of consent. Age group 1 (3-23 months) was well represented with 33 patients. However, the age groups 2 (aged 28-89 days) and 3 (aged 0-27 days) are underrepresented with only 2 and 1 patients, respectively, while the sample size was initially planned to be at least 12 and 5 patients, respectively. Following consultation with FDA and EMA and their favourable opinion for reducing the sample size initially considered, an early termination of the study was decided on 17 July 2024. The enrolment target 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 related to any safety or tolerability concern or event with the use of gadopiclenol. Rather, it was based on the fact that PK data of 33 patients was considered sufficient for the PK model and to meet the study's primary objective. However, due to this decision, the assessment of the efficacy and safety of gadopiclenol in patients 0-2 years of age (secondary objectives) was substantially hampered. Nevertheless, the number of patients was sufficient for the PK model and to achieve the study primary objective. Finally, the results found in the adult CNS and body MRI studies can be extrapolated to the paediatric population since the determinants of contrast enhancements in paediatric and adult diseases are the same and the PK profile of gadopiclenol in paediatric patients aged 0-2 years are comparable to the PK profile in adults and the paediatric population of 2 years and older.

Protocol deviations were comprehensively monitored. Only one major protocol deviation (which impacted the popPK model) was reported. A total of 69 non-major protocol deviations were reported for 34 patients (82.9%), which appear to have had no impact on the evaluation of the efficacy, which is reassuring.

Regarding baseline characteristics, the weight of the paediatric patients ranged from 4.2 to 13.7 kg, with a mean (SD) of 9.03 (2.44) kg. Since the recommended dose of Elucirem/Vueway for the paediatric population is 0.1 ml/kg body weight, the minimum weight of 4.2 kg results in an injection volume of 0.42 ml. However, in the age range of 0-2 years, body weights lower than 4.2 kg can be expected, and consequently smaller volumes may need to be administered. In section 4.2 of the SmPC it is stated that in children, Elucirem/Vueway in vials with a single use syringe of a volume adapted to the amount to be injected should be used in order to have better precision of the injected volume. This information is also considered sufficient for the proposed population of 0—2 years of age. Similar dose recommendations of 0.1 ml/kg have been approved for other GBCAs for the same paediatric population. Further, male and female were well balanced in this study and approximately half (52.8%)

of the study population had already undergone an imaging procedure, of which almost all with a gadolinium complex.

The disease diagnosis at study entry for the patient in the 0-27 days age group was cerebral haematoma and for the two patients in the 28-89 day age group, hereditary haemorrhagic telangiectasia and benign hepatic neoplasm. For the 3-23 months age group, the recruited patients presented a population of which the highest proportion of the disease diagnoses were related to the system organ class (SOC) *"neoplasms benign, malignant and unspecified (incl cysts and polyps)(39.4%)*, followed by *"congenital, familial and genetic disorders" (27.3%)*, *"nervous system disorders" (18.2%)*, and *"endocrine disorders"*, *"Eye disorders"*, *"hepatobiliary disorders"*, *"musculoskeletal and connective tissue disorders"*, and *"renal and urinary disorders"* (3.0% each). None of the lesions based Preferred Term was present in more than 2 patients. It is acknowledged that due to the limited number of patients, several lesion types are under- or not represented. However, as noted above, the results found in the different lesions in the adult CNS and body MRI study can be extrapolated to the paediatric population. This is because the determinants of contrast enhancements in paediatric and adult diseases are the same, and the PK profile of gadopiclenol in paediatric patients aged 0-2 years is comparable to the PK profile in adults (as well as in the paediatric population of 2 years and older).

The technical adequacy for diagnosis was graded as "good" in more than 90% of the cases and "fair" in the remaining cases and consistent across the cohorts. Although no clear differences in technical adequacy could be observed between pre-contrast images and paired images, the technical adequacy was comparable to those found in the adult (level of good: 95% for CNS and 93% for body) and paediatric population aged 2 years and older (level of good: 98% for CNS and 90% for body). Nevertheless, the adult and paediatric population of 2 years and older did show improvements in technical adequacy between pre-contrast and paired images, although relatively small. Differences in improvements in technical adequacy between pre-contrast and paired images can be the result of differences in number of lesions with no contrast enhancement due to the nature of the lesions. It should be noted that, for the younger paediatric population, different types of lesions are normally imaged by MRI compared with the older populations. Furthermore, the spectrum of diseases included lesions for which contrast enhancement is not always expected, such as congenital anomalies. Lesions were observed in 89% of the patients of which the majority of the patients (84% (n=26)) had only one single lesion. The number of lesions identified was similar between pre-contrast and paired images, with the exception of one patient in the CNS cohort for which an additional lesions was detected with paired images. The maximum number of lesions identified in a patient is 3, which were detected in 2 patients (5.7%).

With respect to lesion visualization criteria, improvements in all three parameters (border delineation, internal morphology, degree of contrast enhancement) with paired images compared to pre-contrast images were observed, which was consistent across the different cohorts. Visualization of the lesion border delineation improved with paired images from good to excellent for 9 lesions (4 in patients from the CNS cohort, 4 in patients from the Body cohort and 1 in a patient from the Blood vessel cohort). Visualization of internal morphology was generally good to excellent with both pre-contrast and paired images. However, visualization of internal morphology of 4 lesions in the body cohort with grade "poor" with pre-contrast images improved to good (2 lesions) or excellent (2 lesions) with paired images. As expected, no contrast enhancement was reported with pre-contrast images. With paired images, no enhancement was reported for 7 lesions in 5 patients in the CNS cohort due to the nature of the lesion. Overall, the degree of contrast enhancement was generally graded as good (12/39, 31%) to excellent (17/39, 44%). Similar as found in the paediatric population of 2 years and older, the level of "excellent" was more often reported in the Body cohort (10/16, 62.5%), due to the nature of lesions.

Regarding quantitative assessment, the median percentage of lesion enhancement was 35.3% and 112.6% in the paediatric patients of the CNS and Body cohorts, respectively. As already described above, the low percentage of lesion enhancement in the CNS cohort can be due to the nature of lesions. The mean lesion to background ratio (LBR) were 1.53 and 1.97 in the patients of the CNS and Body cohort, respectively. These findings were much lower than those observed in the adult population (% of enhancement of ~200% for CNS and 145 to 220% for Body; LBR of 2.1 for CNS and 2.8 to 4.4 for Body) and comparable with those observed in the paediatric population of 2 years and older (median % of enhancement of 6.0% for CNS and 88.4% for Body; median LBR of 0.81 for CNS and 0.98 for Body). The observed lower values of % enhancement and LBR observed in the overall paediatric population can be explained by the difference in the type of disease included in the paediatric and adult studies. Congenital anomalies, which represent a frequent indication for paediatric MRI, may not necessarily cause contrast enhancement. Further, the median signal intensity was increased in paired images compared with pre-contrast images (242 vs 364 for CNS and 323 vs. 929 for the Body cohort). Although less pronounced improvements concerning quantitative parameters in the paediatric population compared with the adult population have been observed, the investigator's confidence in diagnosis was still improved for most examinations (26.7% for CNS and 64.3 % for Body MRI). Consequently, the diagnosis changed between pre-contrast and paired images for 2 patients (13.3%) in the CNS cohort and 4 patients (28.6%) in the Body cohort. In this respect, a possible change in treatment plan was reported for 7 out of 14 patients (50%) in the body cohort, but none of the 15 patients in the CNS cohort. For 4 out of these 7 patients, no further information on the actual treatment plan was available. Nevertheless, three cases underscore the relevance of contrast enhance MRI by confirmation of proposed treatment plan, which is reassuring.

Further, the results of the different efficacy parameters have not all been discussed separately for the different age groups. Considering the very limited number of patients included in the age group of 0-27 days and 28-89 days (n=1 and n=2, respectively) compared with the age group of 3-23 months (n=32), standard subgroup analyses are not considered of much value. Nevertheless, the WSA highlighted that, of the 3 patients in the younger age groups, one patient had an enhancing lesion, which visualization was improved with paired images and the level of diagnosis confidence changed from "poor" with pre-contrast images to "high" with paired images consistent with the older age populations, which is reassuring. Moreover, with regards to the three premature infants included in the study after their neonatal period, all in the 3-23 months age group, two of these patients had an MRI for post hemorrhagic hydrocephalus and one patient for suspicion of a tumour or abscess on the chest wall. For one patient (with hydrocephalus) no lesion was identified while one lesion was identified for each of the two other patients. Both lesions were enhancing with an excellent degree of contrast enhancement. For the patient undergoing thorax MRI, diagnostic confidence improved from poor to high. The diagnosis was modified to "infectious disease" and treatment plan was modified from biopsy to conservative treatment. For the other patient, similar results were obtained with pre-contrast and paired images.

2.4.4. Conclusions on the clinical efficacy

Administration of gadopiclenol at 0.05 mmol/kg in paediatric subjects 0-2 years old resulted in enhancement of the CNS and body images, as shown by both qualitative (lesion visualization score) and quantitative parameters (signal intensity, percentage of lesion enhancement and LBR). However, the sample size was very limited, particularly for the youngest age groups of 0-27 days and 28-89 days. Nevertheless, consistent with the conclusions of the initial MAA supporting the paediatric population of 2 years and older, the results from adult CNS and body MRI studies can be extrapolated to the paediatric population. This is because the determinants of contrast enhancements in paediatric

and adult diseases are the same, and the PK profile of gadopiclenol in paediatric patients aged 0-2 years is comparable to the PK profile in adults (and in paediatric population of 2 years and older).

From an efficacy point of view, the extrapolation of the indication for Elucirem/Vueway for patients from birth up to 2 years of age can be considered acceptable.

2.5. Clinical safety

Introduction

The clinical safety data for gadopiclenol had previously been derived from eight phases I to III clinical studies of the initial clinical development program. This evaluation was performed by analysing the adverse events reported in the studies as well as all available data on laboratory measures (biochemistry and haematology), vital signs and electrocardiograms (ECGs). The safety profile of gadopiclenol was assessed in healthy volunteers and patients undergoing MRI of the CNS and other body regions (head & neck, thorax [including breast], abdomen [including liver, pancreas and kidneys], pelvis [including uterus, ovary and prostate] and musculoskeletal [including extremities]).

The eight clinical studies included a total of 1097 subjects, out of which 1047 patients or healthy volunteers received at least one dose of gadopiclenol, including 80 patients aged 2 to 17 years. Gadopiclenol has been tested at doses from 0.025 mmol/kg to 0.3 mmol/kg in adult (from 18 years old) patients and healthy volunteers and was administered at the dose of 0.05 mmol/kg in the Phase III clinical studies in adults as well as in the Phase II study in pediatric patients aged 2 to 17 years old.

With this application, the GDX-44-015 study provides safety data for gadopiclenol in the paediatric population aged less than 2 years.

Safety assessments consisted on:

- Physical examination before gadopiclenol injection and at safety follow-up visits conducted at week 1 and 3 months after gadopiclenol injection,
- Reporting of adverse events (AE) occurring from the beginning of patient's participation in the trial (Informed Consent Form signature) until the end of their participation,
- Vital signs (temperature, blood pressure, pulse rate and peripheral oxygen saturation (SpO2)) measured at 3 time points: prior to gadopiclenol injection, 10-60 min and 1 day after injection,
- Blood samples collected prior to and 1 day after gadopiclenol injection to assess biochemistry and haematology variables (central laboratory),
- Tolerance at the injection site assessed at 3 time points: during injection, 10-60 min and 1 day after gadopiclenol injection,
- Clinical examination for active detection of Nephrogenic Systemic Fibrosis (NSF) at 3-month follow-up safety visit. In case of suspicion of NSF, a deep skin biopsy was to be performed.

Patient exposure

A mean time interval of 7.8 (±6.0) days elapsed between the informed consent form (ICF) signature and gadopiclenol injection (range 1 to 29 days). The duration between gadopiclenol injection and the end of trial ranged from 1 to 183 days, with a mean (SD) of 91.6 (22.1) days.

The calculated volume of gadopiclenol based on the weight of the patient ranged from 0.4 to 1.4 ml, with a mean (SD) value of 0.90 (0.25) ml. The actual volume administered corresponded to the calculated volume for all patients based on their body weight. No overdose occurred.

All 36 patients received a dose of gadopiclenol. The contrast agent was administered manually in 34 patients and with a power injector in 2 patients, both in the CNS cohort and aged 3-23 months. The injection rate was 1 ml/s for 32 patients and 2 ml/s for 4 patients in the 3-23 months age group: 2 in the Body cohort, 1 in the CNS cohort and 1 in the Blood vessel cohort.

The volume of saline flush was 2 ml for the patient in the 0-27 days age group, 5 ml for the 2 patients in the 28-89 days age group and ranged from 1.5 to 18 ml in the 3-23 months age group, with a median of 6 ml.

Adverse events

General frequency of adverse events

Among the 36 patients who received gadopiclenol in the GDX-44-015 study, 19 patients (52.8%) experienced at least one treatment emergent adverse event (TEAE) over the 3-month follow-up period: 17 patients in the 3-23 months age group and the 2 patients included in the 28-89 days age group. No TEAE was reported for the patient in the 0-27 days age group (Table 25).

TEAEs occurred within 7 days following gadopiclenol administration for 10 patients (27.8%) and more than 7 days after gadopiclenol administration for 9 patients (25%).

Only one patient (2.8%) experienced one TEAE considered related to gadopiclenol: erythema. The patient presented with light redness of cheeks and tip of the nose 2h35 after gadopiclenol administration. The event was non-serious, considered of mild intensity and resolved within 1 day without any targeted medication or other action.

Among the 38 reported TEAEs, 26 (68.4%) were of mild intensity, 7 (18.4%) were of moderate intensity and 5 (13.2%) were considered of severe intensity. The severe TEAEs were serious adverse events not related to gadopiclenol.

Most TEAEs (30/38, 78.9%) resolved, 2 serious TEAEs, reported in the same patient, resolved with sequelae (cerebral cyst and intracranial pressure increased). Six TEAEs, reported in 4 patients, were not resolved at the time of last patient's visit (3-month safety follow-up): feeding difficulties, white blood cell increased in one patient and AST and ferritin increased in another patient, and myopia and astigmatism in one patient.

No TEAE was considered related to a study procedure.

Table 25: Treatment Emergent Adverse Events – Overview – Safety Set (GDX-44-015)

	3-23 months (N=33)		28-89 days (N=2)		Total* (N=36)	
	Patients	AE	Patients	AE	Patients	AE
At least one Treatment Emergent Adverse Event (TEAE)	17 (51.5%)	35	2 (100%)	3	19 (52.8%)	38
Distribution of TEAEs per patient						
1	7 (41.2%)		1 (50.0%)		8 (42.1%)	
2	5 (29.4%)		1 (50.0%)		6 (31.6%)	
3 or more	5 (29.4%)		0		5 (26.3%)	
Intensity: at least one TEAE:						
Mild	12 (70.6%)	23	2 (100%)	3	14 (73.7%)	26
Moderate	4 (23.5%)	7	0	0	4 (21.1%)	7
Severe	4 (23.5%)	5	0	0	4 (21.1%)	5

	3-23 months (N=33) Patients	AE	28-89 days (N=2) Patients	AE	Total* (N=36) Patients	AE
At least one TEAE with causal relationship to gadopiclenol	1 (5.9%)	1	0	0	1 (5.3%)	1
At least one TEAE with causal relationship to study procedure	0	0	0	0	0	0
Outcome: at least one TEAE:						
Recovered/resolved	16 (94.1%)	29	1 (50.0%)	1	17 (89.5%)	30
Recovered/resolved with sequelae	1 (5.9%)	2	0	0	1 (5.3%)	2
Not recovered/not resolved	3 (17.6%)	4	1 (50.0%)	2	4 (21.1%)	6
Fatal	0	0	0	0	0	0
Action taken with gadopiclenol Injection: at least one TEAE:						
No action	17 (100%)	35	2 (100%)	3	19 (100%)	38
At least one Treatment Emergent Serious Adverse Event (SAE)	8 (24.2%)	11	0	0	8 (22.2%)	11
Death	0	0	0	0	0	0
Life-threatening	1 (3.0%)	1	0	0	1 (2.8%)	1
Hospitalisation or prolongation of hospitalisation	8 (24.2%)	11	0	0	8 (22.2%)	11
Persistent or significant disability or incapacity	0	0	0	0	0	0
Congenital abnormality or birth defect	0	0	0	0	0	0
Medically important	1 (3.0%)	1	0	0	1 (2.8%)	1
At least one AESI (NSF)	0	0	0	0	0	0
At least one TEAE leading to trial discontinuation	0	0	0	0	0	0

**Total includes the patient in the 0-27 days age group, who did not experience any adverse event*

AESI: Adverse Event of Special Interest (NSF in this study)

A same subject can be counted for several answer categories of a same item (relationship, seriousness, intensity and outcome).

Common adverse events

Among the 38 TEAEs reported in 19 subjects (52.8%), the most frequently reported was vomiting (5 patients, 13.9%). All other TEAEs were reported for one patient each and were mainly reported in the SOC "Infections and infestations" (8 patients, 22.2%) (Table 26).

Table 26: Treatment Emergent Adverse Events by Primary System Organ Class and Preferred Term - Safety Set (GDX-44-015)

SOC	Preferred term	Total (N=36) Patients	AE
Gastrointestinal disorders	**Vomiting**	**5 (13.9%)**	**5**
	Diarrhoea	1 (2.8%)	1
	Nausea	1 (2.8%)	1
Infections and infestations	Bronchitis	1 (2.8%)	1
	Conjunctivitis	1 (2.8%)	1
	Gastroenteritis norovirus	1 (2.8%)	1
	Hand-foot-and-mouth disease	1 (2.8%)	1
	Paronychia	1 (2.8%)	1
	Pneumonia parainfluenzae viral	1 (2.8%)	1
	Respiratory tract infection viral	1 (2.8%)	1
	Upper respiratory tract infection	1 (2.8%)	1
	Viral upper respiratory tract infection	1 (2.8%)	1

Investigations	Aspartate aminotransferase increased	1 (2.8%)	1
	Serum ferritin increased	1 (2.8%)	1
	White blood cell count increased	1 (2.8%)	1
Respiratory, thoracic and mediastinal disorders	Choking	1 (2.8%)	1
	Cough	1 (2.8%)	1
	Nasal congestion	1 (2.8%)	1
	Rhinorrhoea	1 (2.8%)	1
Skin and subcutaneous tissue disorders	Erythema	1 (2.8%)	1
	Rash	1 (2.8%)	1
Eye disorders	Astigmatism	1 (2.8%)	1
	Myopia	1 (2.8%)	1
Nervous system disorders	Cerebral cyst	1 (2.8%)	1
	Intracranial pressure increased	1 (2.8%)	1
General disorders and administration site conditions	Pyrexia	1 (2.8%)	1
Blood and lymphatic system disorders	Microcytic anaemia	1 (2.8%)	1
Immune system disorders	Anaphylactic reaction	1 (2.8%)	1
Metabolism and nutrition disorders	Feeding disorder	1 (2.8%)	1
Product issues	Device malfunction	1 (2.8%)	1
Psychiatric disorders	Anxiety	1 (2.8%)	1
Renal and urinary disorders	Renal failure	1 (2.8%)	1
Surgical and medical procedures	Tumour excision	1 (2.8%)	1
Vascular disorders	Hypertension	1 (2.8%)	1

*%: (n row / N column) *100*

MedDRA dictionary version: MedDRA v27.0 - Mar 2024

Serious adverse event/deaths/other significant events

Serious adverse events

During the 3-month follow-up period, 8 patients experienced at least one SAE (within one week after gadopiclenol administration for 2 patients and from 18 to 74 days post administration for 6 patients) (Table 27). None of these SAEs was considered related to gadopiclenol or to a study procedure. None led to a change in gadopiclenol administration.

The main reason why the AEs were considered serious was due to hospitalization or prolongation of hospitalization. Five of these SAEs were of severe intensity: cerebral cyst and increased intracranial pressure in one patient (resolving with sequelae), pneumonia parainfluenzae viral leading to hospitalization in Intensive Care Unit, bronchitis, disfunction of ventriculoperitoneal shunt system in one patient each, all resolved.

Table 27: Serious Adverse Events (GDX-44-015)

Patient	Cohort Age group	Primary System Organ Class / Preferred Term / Description	Time Between Injection and Event	Seriousness Criteria	Outcome	Intensity	Duration of Event	AE-Targeted Medication / Other AE-Targeted Action
SAEs occurring after gadopiclenol administration (Serious TEAEs)								
1	CNS 3-23 months	Metabolism And Nutrition Disorders / Feeding Disorder / Feeding Difficulties	20 days	Hospitalisation or prolongation of hospitalisation /	Not Recovered/ Not Resolved	Moderate		Yes / Therapeutic Measures Other Than Corrective

Patient	Cohort Age group	Primary System Organ Class / Preferred Term / Description	Time Between Injection and Event	Seriousness Criteria	Outcome Intensity Duration of Event	AE-Targeted Medication / Other AE-Targeted Action
SAEs occurring after gadopiclenol administration (Serious TEAEs)						
						Drug Administration
		Surgical And Medical Procedures / Tumour Excision / Tumour Resection For Suprasellar Optic Glioma	50 days	Hospitalisation or prolongation of hospitalisation	Recovered/Moderate Resolved 6 days	Yes / Procedure
		General Disorders And Administration Site Conditions / Pyrexia / Central Fever	56 days	Hospitalisation or prolongation of hospitalisation	Recovered/Moderate Resolved 24 days	Yes / Procedure
2	CNS 3-23 months	Blood And Lymphatic System Disorders / Microcytic Anaemia / Microcytic Anemia	69 days	Hospitalisation or prolongation of hospitalisation	Recovered/Moderate Resolved 3 days	Yes / No
3	Blood vessels 3-23 months	Infections And Infestations / Gastroenteritis Norovirus / Gastroenteritis - Norovirus	2 days	Hospitalisation or prolongation of hospitalisation	Recovered/Mild Resolved 6 days	Yes / No
4	Body 3-23 months	Infections And Infestations / Pneumonia Parainfluenzae Viral / Hospitalization On Intensive Care Unit - Respiratory Failure, Pneumonia - Hpiv-3 Virus	20 days	Hospitalisation or prolongation of hospitalisation, Life-threatening	Recovered/Severe Resolved 16 days	Yes / Therapeutic Measures Other Than Corrective Drug Administration
5	CNS 3-23 months	Infections And Infestations / Bronchitis / Severe Upper Respiratory Tract Infection With Severe Bronchitis.	5 days	Hospitalisation or prolongation of hospitalisation	Recovered/ Severe Resolved 3 days	Yes / Therapeutic Measures Other Than Corrective Drug Administration
6	CNS 3-23 months	Nervous System Disorders / Cerebral Cyst / Cerebral Sella Turcic Cyst Growth	74 days	Hospitalisation or prolongation of hospitalisation/	Recovered/ Severe Resolved With Sequelae 6 days	Yes / Procedure
		Nervous System Disorders / Intracranial Pressure Increased / Intercranial Hypertension	74 days	Hospitalisation or prolongation of hospitalisation	Recovered/Severe Resolved With Sequelae 6 days	Yes / Procedure
7	CNS 3-23 months	Product Issues / Device Malfunction / Disfunction Of Ventriculoperitoneal Shunt System	18 days	Hospitalisation or prolongation of hospitalisation	Recovered/ Severe Resolved 4 days	Yes / Procedure
8	Body 3-23 months	Renal And Urinary Disorders / Renal Failure / Worsening Of Pre-Existing Renal Failure	43 days	Hospitalisation or prolongation of hospitalisation, Other Medically Important Serious Event	Recovered/ Moderate Resolved 35 days	Yes / Procedure

CNS: Central Nervous System
MedDRA dictionary version: MedDRA v27.0 - Mar 2024

Deaths

No deaths were reported in the patients aged <2 years.

Adverse event of special interest (AESI)

Adverse event of special interest (AESI) was defined in the study as suspected nephrogenic systemic fibrosis (NSF) or symptoms suspected to be related to NSF. No suspected NSF or NSF-related symptoms were reported in the GDX-44-015 study during the follow-up period of 3 months.

Laboratory findings

Clinical laboratory evaluations

Haematology parameters

On average, change from baseline was close to 0 for most parameters. Small mean decreases were observed for haemoglobin small mean increases for lymphocytes and platelets (Table 28).

Table 28: Haematology Parameters - SI Units - Safety Set (GDX-44-015)

	Baseline (N=36)		**Day 2 (N=36)**		**Change from Baseline (N=36)**	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Erythrocytes (10^{12}/L)	36	4.43 (0.72)	34	4.31 (0.52)	34	-0.08 (0.34)
Haemoglobin (g/L)	36	119.2 (16.5)	34	115.2 (12.2)	34	-2.7 (8.6)
Haematocrit (v/v)	36	0.374 (0.052)	34	0.363 (0.037)	34	-0.008 (0.034)
MCV (fL)	36	85.3 (7.1)	34	85.0 (6.6)	34	-0.5 (2.6)
Leukocytes (10^9/L)	36	10.18 (3.59)	34	10.83 (3.29)	34	0.57 (3.03)
Neutrophils (10^9/L)	35	3.169 (1.388)	33	3.401 (1.777)	33	0.170 (1.787)
Lymphocytes (10^9/L)	35	5.730 (2.735)	33	6.285 (2.491)	33	0.520 (1.850)
Monocytes (10^9/L)	35	0.686 (0.263)	33	0.650 (0.226)	33	-0.045 (0.246)
Eosinophils (10^9/L)	35	0.327 (0.242)	33	0.262 (0.198)	33	-0.058 (0.156)
Basophils (10^9/L)	35	0.056 (0.049)	33	0.048 (0.049)	33	-0.006 (0.040)
Neutrophils/Total Cells (%)	35	30.98 (9.87)	33	31.18 (12.24)	33	-0.18 (11.91)
Lymphocytes/Total Cells (%)	35	54.57 (10.83)	33	56.57 (13.67)	33	2.24 (10.51)
Monocytes/Total Cells (%)	35	7.21 (2.97)	33	6.38 (2.55)	33	-0.91 (2.24)
Eosinophils/Total Cells (%)	35	3.40 (2.56)	33	2.53 (1.92)	33	-0.74 (1.53)
Basophils/Total Cells (%)	35	0.64 (0.47)	33	0.45 (0.49)	33	-0.17 (0.51)
Platelets (10^9/L)	36	352.5 (128.7)	34	390.8 (134.0)	34	33.4 (143.8)

At screening visit (baseline), the most frequent out of range values were high values for haemoglobin (38.9% of the patients), haematocrit (55.6%), and lymphocytes (45.7%) (Table 29). The number of out-of-range values was similar at screening visit and at safety visit after injection. However, a lower number of patients with out-of-range values was observed for high haemoglobin and haematocrit.

Table 29: Haematology Parameters (SI Units) – Patients with Out of Range Values- Safety Set (GDX-44-015)

	Baseline (N=36)			Day 2 (N=36)		
	n	Value < LLN	Value > ULN	n	Value < LLN	Value > ULN
Erythrocytes (10^{12}/L)	36	4 (11.1%)	15 (41.7%)	34	4 (11.8%)	4 (11.8%)
Haemoglobin (g/L)	36	5 (13.9%)	14 (38.9%)	34	5 (14.7%)	7 (20.6%)
Haematocrit (v/v)	36	2 (5.6%)	20 (55.6%)	34	1 (2.9%)	15 (44.1%)
MCV (fL)	36	4 (11.1%)	18 (50.0%)	34	4 (11.8%)	17 (50.0%)
Leukocytes (10^9/L)	36	7 (19.4%)	8 (22.2%)	34	2 (5.9%)	8 (23.5%)
Neutrophils (10^9/L)	35	10 (28.6%)	0	33	7 (21.2%)	2 (6.1%)
Lymphocytes (10^9/L)	35	2 (5.7%)	16 (45.7%)	33	1 (3.0%)	15 (45.5%)
Monocytes (10^9/L)	35	3 (8.6%)	1 (2.9%)	33	0	0
Eosinophils (10^9/L)	35	0	11 (31.4%)	33	1 (3.0%)	7 (21.2%)
Basophils (10^9/L)	35	0	0	33	0	0
Neutrophils/Total Cells (%)	35	4 (11.4%)	0	33	6 (18.2%)	0
Lymphocytes/Total Cells (%)	35	0	3 (8.6%)	33	0	4 (12.1%)
Monocytes/Total Cells (%)	35	0	5 (14.3%)	33	1 (3.0%)	1 (3.0%)
Eosinophils/Total Cells (%)	35	0	5 (14.3%)	33	1 (3.0%)	2 (6.1%)
Basophils/Total Cells (%)	35	0	0	33	0	0
Platelets (10^9/L)	36	4 (11.1%)	7 (19.4%)	34	2 (5.9%)	10 (29.4%)

Biochemistry parameters

The mean change from baseline was very close to 0 for most parameters (Table 30). There was an overall mean decrease in ferritin, and alkaline phosphatase, with a high variability between subjects.

"Ferritin decreased" associated with serum iron decreased is an ongoing signal identified during the pre-clinical study GDX-33-053. It was monitored during this paediatric study and no concerns were highlighted.

Table 30: Biochemistry Parameters - SI Units - Safety Set (GDX-44-015)

	Baseline (N=36)		Day 2 (N=36)		Change from Baseline (N=36)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Sodium (mmol/L	36	138.2 (2.4)	34	139.4 (2.4)	34	1.2 (2.3)
Potassium (mmol/L)	33	4.88 (0.50)	31	4.61 (0.52)	28	-0.22 (0.51)
Chloride (mmol/L)	36	103.0 (1.9)	34	104.0 (2.3)	34	1.0 (1.8)
Calcium (mmol/L)	36	2.625 (0.137)	33	2.629 (0.125)	33	-0.000 (0.154)
Phosphorus (mmol/L)	35	1.901 (0.249)	33	1.782 (0.248)	32	-0.102 (0.203)
Iron (µmol/L)	35	10.1 (4.0)	33	11.5 (5.2)	32	1.6 (5.3)
Ferritin (ug/L)	35	93.6 (202.3)	34	76.7 (149.7)	33	-13.2 (73.8)
Transferrin (g/L)	36	2.8 (0.5)	33	2.8 (0.5)	33	-0.0 (0.2)
Total protein (g/L)	35	62.5 (5.7)	33	62.1 (5.4)	32	-0.2 (4.4)

	Baseline (N=36)		Day 2 (N=36)		Change from Baseline (N=36)	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Serum creatinine (µmol/L)	36	20.60 (4.96)	34	21.06 (5.51)	34	0.65 (4.35)
eGFR (mL/min/1.73m²)	36	140.8 (48.6)	34	137.5 (40.0)	34	-5.1 (27.7)
BUN (mmol/L)	36	3.33 (1.53)	34	2.95 (1.35)	34	-0.42 (0.84)
AST (U/L)	33	38.3 (10.0)	33	39.5 (13.0)	30	-0.4 (8.8)
ALT (U/L)	34	22.9 (11.4)	33	24.6 (16.2)	31	0.6 (8.0)
Alkaline Phosphatase (U/L)	35	283.5 (88.1)	33	264.3 (67.5)	32	-7.3 (27.4)
Total bilirubin (µmol/L)	36	3.84 (3.13)	34	4.05 (3.53)	34	0.22 (0.87)
Conjugated bilirubin (µmol/L)	33	1.81 (1.60)	31	2.07 (1.46)	28	0.30 (0.76)
LDH (U/L)	33	281.8 (44.4)	30	283.8 (63.7)	27	1.7 (45.0)

Regarding out-of-range biochemistry values, the most frequent were high values for calcium (50%), transferrin (44.4%) and eGFR (44.4%) (Table 31). At safety visit after injection, the number of out-of-range values was similar to the one at screening visit.

Table 31: Biochemistry Parameters (SI Units) – Patients with Out of Range Values- Safety Set (GDX-44015)

	Baseline (N=36)			Day 2 (N=36)		
	n	Value < LLN	Value > ULN	n	Value < LLN	Value > ULN
Sodium (mmol/L	36	1 (2.8%)	5 (13.9%)	34	0	6 (17.6%)
Potassium (mmol/L)	33	0	6 (18.2%)	31	0	3 (9.7%)
Chloride (mmol/L)	36	1 (2.8%)	0	34	1 (2.9%)	0
Calcium (mmol/L)	36	0	18 (50.0%)	33	0	15 (45.5%)
Phosphorus (mmol/L)	35	1 (2.9%)	9 (25.7%)	33	0	4 (12.1%)
Iron (µmol/L)	35	4 (11.4%)	1 (2.9%)	33	4 (12.1%)	2 (6.1%)
Ferritin (ug/L)	35	24 (68.6%)	3 (8.6%)	34	25 (73.5%)	3 (8.8%)
Transferrin (g/L)	36	0	16 (44.4%)	33	0	15 (45.5%)
Total protein (g/L)	35	1 (2.9%)	0	33	3 (9.1%)	0
Serum creatinine (µmol/L)	36	9 (25.0%)	3 (8.3%)	34	8 (23.5%)	2 (5.9%)
eGFR (mL/min/1.73m²)	36	0	16 (44.4%)	34	0	14 (41.2%)
BUN (mmol/L)	36	0	10 (27.8%)	34	0	8 (23.5%)
AST (U/L)	33	0	1 (3.0%)	33	0	2 (6.1%)
ALT (U/L)	34	0	5 (14.7%)	33	0	6 (18.2%)
Alkaline Phosphatase (U/L)	35	0	6 (17.1%)	33	0	1 (3.0%)
Total bilirubin (µmol/L)	36	0	1 (2.8%)	34	0	1 (2.9%)
Conjugated bilirubin (µmol/L)	33	3 (9.1%)	1 (3.0%)	31	2 (6.5%)	1 (3.2%)
LDH (U/L)	33	1 (3.0%)	1 (3.0%)	30	1 (3.3%)	2 (6.7%)

Individual changes in laboratory values

In patients aged less than 3 months, no change in serum creatinine or eGFR of more than 15% was reported. A decrease in Blood Urea Nitrogen (BUN) between -25% and -50% was reported in the 2 patients in the 28-89 days age group while an increase in BUN between 25 and 50% was reported in the youngest patient.

In patients aged 3-23 months, an increase of creatinine of more than 25% was reported for 3 patients, including 2 patients with an increase of more than 50%. No decrease in eGFR of more than 50% was reported. Decrease between 25% and less than 50% were observed for 3 patients. No increase in BUN values of more than 50% was reported and an increase between 25% and less than 50% was observed for one patient.

No increase in serum creatinine ≥ 0.3 mg/dL was reported. Two patients (5.9%) had a serum creatinine value ≥ 1.5 times baseline at Day 2, however, in both cases, the value at Day 2 was within the normal range and the investigator considered this increase as not clinically significant.

Individually clinically significant laboratory abnormalities

Three clinically significant laboratory abnormalities were reported as adverse events after gadopiclenol administration, none being serious:

- Aspartate aminotransferase increased and serum ferritin increased in one patient in the 28-89 days age group, who underwent MRI of blood vessels. These laboratory results were observed more than 27 hours after gadopiclenol administration. They were reported as non-serious AEs, of mild intensity. To be noted, alanine aminotransferase increased and blood phosphorus increased were also reported before gadopiclenol administration for this patient.
- White blood cell count increased in one patient in the 3-23 months age group who underwent CNS MRI. This laboratory result was observed 22.5 hours after gadopiclenol administration and reported as a non-serious AE of mild intensity.

None of these laboratory abnormalities were considered related to gadopiclenol, and none led to a change in gadopiclenol administration.

Vital signs

No relevant or consistent changes in median values of blood pressure, heart rate, oxygen saturation or temperature were observed in the GDX-44-015 study (Table 32).

Physical examination at the 1-day safety follow-up showed a new abnormality in one patient at skin level. At the 1-week safety follow-up visit, a new abnormality was reported in 4 patients (on skin for 2 patients and "other" for 2 patients).

The physical examination performed at 3 months follow-up visit for NSF detection did not reveal any suspected NSF or symptoms suspected to be related to NSF.

No event at injection site was reported.

Table 32: Vital Signs Data – Safety Set

				Change from baseline		
Time-point	**Mean (SD)**	**Median**	**Min; Max**	**Mean (±SD)**	**Median**	**Min; Max**
Systolic blood pressure (mmHg)						
Baseline	93.1 (14.0)	92.0	68 ; 124			
10-60 min after injection	90.6 (16.9)	87.0	64 ; 126	-3.1 (15.7)	-1.0	-36 ; 32
Day 2	101.0 (16.4)	103.0	71 ; 141	7.6 (19.3)	3.5	-24 ; 54
Diastolic blood pressure (mmHg)						
Baseline	56.0 (16.0)	60.0	26 ; 89			

10-60 min after injection	52.5 (16.4)	54.0	22 ; 94	-3.6 (14.9)	-2.0	-33 ; 33
Day 2	60.1 (13.7)	60.0	30 ; 82	4.4 (17.6)	1.0	-22 ; 49
Pulse rate (beats/min)						
Baseline	118.9 (21.4)	120.0	70 ; 162			
10-60 min after injection	114.2 (19.8)	114.0	70 ; 163	-4.6 (24.2)	-6.5	-45 ; 79
Day 2	125.0 (16.4)	123.0	99 ; 161	5.5 (22.8)	2.0	-48 ; 60
Blood oxygen saturation						
Baseline	98.7 (1.4)	99.0	95 ; 100			
10-60 min after injection	98.4 (1.5)	99.0	95 ; 100	-0.3 (1.4)	0.0	-4 ; 2
Day 2	98.3 (1.3)	99.0	96 ; 100	-0.4 (1.8)	0.0	-4 ; 3
Temperature (°C)						
Baseline	36.52 (0.40)	36.50	35.0 ; 37.4			
10-60 min after injection	36.34 (0.41)	36.45	35.4 ; 37.2	-0.17 (0.48)	-0.10	-1.4 ; 0.8
Day 2	36.58 (0.29)	36.60	36.0 ; 37.1	0.06 (0.44)	0.10	-0.7 ; 1.8

Safety in special populations

Age

Considering the small number of patients included in the two younger age groups, it is difficult to analyse the safety according to age in the paediatric population <2 years old.

No AE was reported for the patient included in the 0-27 days age group and AEs were reported for the 2 patients in the 28-89 days age group, both of mild intensity and not related to gadopiclenol.

Among the patients aged 3 to 23 months, only one TEAE, non-serious, was considered related to gadopiclenol.

Safety results in preterm infants

The safety results for these three infants are presented in Table 33.

Table 33: Safety results for premature patients included in the study after their neonatal period

	Patient 1	**Patient 2**	**Patient 3**
Volume administered	0.9 mL	0.7 mL	0.4 mL
Occurrence of an adverse event, number of events	Yes, 1	Yes, 1	No
Adverse event description	Bronchitis, serious, severe, occurring 5 days after gadopiclenol administration, not related, resolved within 3 days.	Disfunction of ventriculoperitoneal shunt system, serious, severe, occurring 18 days after gadopiclenol administration, not related, resolved within 4 days.	

Two patients experienced a serious adverse event, which was in both cases not related to gadopiclenol and rapidly resolving.

None of these patients experienced any adverse event at the injection site.

Patient 1: Bronchitis

This 3-23 months patient was administered 0.9 ml of gadopiclenol, by intravenous route, for contrast enhanced brain MRI examination for hydrocephalus. Concomitant medication included an unknown dose of propofol.

The patient had no previous examinations with contrast agent administration.

On an unknown date, a second physical examination was performed and revealed an upper respiratory infection.

Six days after IMP administration, the patient experienced **bronchitis**. Corrective treatment included 2 ml bid of Pulmicort (budesonide) inhaler, 2ml tid of saline solution (NaCl 0.5 %) inhaler and 12 drops tid of Atrovent (ipratropium bromide) inhaler, all administered over a week.

The reaction lasted 3 days. The final outcome was Recovered/Resolved on 8 days after injection.

The investigator rated the intensity as severe, evaluated the case as serious (hospitalization) and assessed the causal relationship between the product and the adverse event upper respiratory tract infection as not Related. According to the reporter, the adverse event was not related to a trial procedure. According to the gadopiclenol IB used as reference safety information, bronchitis is unexpected. Based on the information currently available, the case was evaluated as serious (hospitalization) and the sponsor assessed that there was no reasonable possibility that bronchitis was related to gadopiclenol.

Patient 2: Device Malfunction (Disfunction of Ventriculoperitoneal Shunt System)

This 3-23 months patient was administered 0.7 mL of study product gadopiclenol, by intravenous route, for brain MRI. Concomitant medication included an unknown dose of propofol IV as anesthetic.

Nineteen days after the IMP administration, the patient experienced a **dysfunction of ventriculoperitoneal shunt system** with hydrocephalus symptoms (headache and vomiting) confirmed during the CT of patient.

The patient underwent surgery for revision of valve shunt system and exchanging of shunt drainage. Corrective treatment included 60 mg quid of paracetamol IV, 70 mg quid IV, 225 mg tid of Biofazolin (cefazolin) IV, 5 mg of Helicid (omeprazole) IV, 0.3 mg quid of morphine IV and 500 ml of Benelyte (belimumab) IV.

The reaction lasted 4 days. The final outcome was "recovered" on three days later.

The investigator rated the intensity as severe, evaluated the case as serious (hospitalization) and assessed the causal relationship between the product and the adverse event of Cardiac valve disease as not related. According to the reporter, the adverse event was not related to study procedure. Based on the information currently available, the case was evaluated as serious (hospitalization) and the sponsor assessed that there was no reasonable possibility that the event was related to gadopiclenol.

In conclusion, no specific concerns were highlighted for these patients.

<u>Sex</u>

A total of 18 male and 18 female patients aged <2 years received gadopiclenol. No analysis was performed according to sex, considering the small sample size and the fact that only one TEAE related to gadopiclenol was reported in this population.

<u>Renal impairment</u>

One patient presented a medically confirmed congenital renal failure; e-GFR and creatinine were not the only important factor of the diagnosis, as left kidney failure was considered caused by congenital urinary tract disorders with bladder anomaly, megaureter, multicystic dysplastic kidney.

This patient presented worsening of preexisting renal failure requiring surgery 47 days after gadopiclenol administration; Surgery was conducted one month later.

According to the investigator, the patient's conditions probably induced the aggravation of the preexisting renal failure leading to nephrectomy. Furthermore, the event occurred in unreasonable time sequence following the study drug administration and renal function lab values one day after gadopiclenol administration were better than values at screening visit. Therefore, the causal relationship between the event and gadopiclenol was excluded.

Hepatic impairment

One patient presented with hepatomegaly and did not experience any AE during the study.

Safety related to drug-drug interactions and other interactions

Not applicable

Discontinuation due to adverse events

No AE led to discontinuation of gadopiclenol administration or of the study among the paediatric patients aged less than 2 years.

Post marketing experience

Not applicable at this stage for the paediatric population aged less than 2 years.

However, post-marketing safety data have been collected for older children and adults.

Overall, 1,379,060 patients have received an injection of gadopiclenol between 21 September 2022 and 20 September 2024. Cumulatively, 58 post-marketing ADR cases reports have been received worldwide (reporting rate=0.0042%). All but 4 of the 58 ADR reports received were non-serious. The most frequent types of ADRs are nausea and vomiting. The available data demonstrate a favourable tolerance and safety profile.

Literature review

The WSA highlighted that GBCAs are considered safe when used at doses approved for clinical use (0.1-0.3 mmol/kg), and their use in children of all ages—including preterm neonates—is standard practice when clinically indicated (ACR, 2025). However, the literature review of the WSA showed that studies have demonstrated that trace amounts of gadolinium can persist in the body and accumulate in various tissues, particularly in bone and sensitive regions such as the brain, even in patients with normal renal function (Kanda et al. 2014; Errante et al. 2014; McDonald RJ et al. 2015; Murata et al. 2015). GBCAs are classified as either macrocyclic or linear, with macrocyclic agents demonstrating greater stability and reduced propensity for gadolinium release compared with linear. Several paediatric studies compared intracranial gadolinium deposition following exposure to macrocyclic versus linear GBCAs (Murata et al. 2016; Kasper et al. 2018; Renz et al. 2018; Ryu et al. 2018; Young et al. 2018; Ozturk et al. 2021; Towbin et al. 2021). Repeated administration of macrocyclic agents – gadoteric acid and gadobutrol – did not result in increased T1 signal intensity. In contrast, elevated signal intensity was observed following repeated exposure to linear agents, specifically gadopentetate dimeglumine and gadodiamide. Currently, no human data exist on gadolinium deposition in paediatric bone tissue (Roberts and Chatterjee 2019).

2.5.1. Discussion on clinical safety

The initial MAA in support of the use of gadopiclenol in adult patients and paediatric patients aged 2 years and older contained safety data of 1097 subjects (including 80 patients aged 2 to 17 years) exposed to gadopiclenol. The majority received the approved dose of 0.05 mmol /kg.

The safety data of gadopiclenol to support the proposed extension of the indication to include the paediatric population of 0-2 years is based on the results of study GDX-44-015.

Study GDX-44-015 included 36 patients who received one injection of gadopiclenol at the dose of 0.05 mmol/kg of which 33 patients were aged 3-23 months, 2 were aged 28-89 days and 1 was aged 0-27 days. As also indicated in the efficacy section, the exposure of gadopiclenol to the age group 2 of patients aged 28-89 days and age group 3 of patients aged 0-27 days is very limited as the study was terminated early following consultation with FDA and EMA. In total, 35 patients completed the study and were followed for 3 months to evaluate the safety. No preterm neonates were included but 3 preterm infants were included in the study after their neonatal period, all in the 3-23 months age group. No new safety signals have been identified. Overall, the results of the preterm infants were consistent with the overall population.

Overall, 52.8% of the patients experienced AEs during the study, including 51.5% of the age group 3-23 months and 100% (n=2) of the age group 28-89 days The percentage of patients experiencing AEs was higher in the paediatric population under 2 years of age than in the adult population (33.5%) and the paediatric population aged 2 years and older (17.5%). No AE was reported for the patient in the 0-27 days age group. Although the frequency of AEs was higher than previously reported, only one AE was considered by the investigator related to gadopiclenol, which is reassuring. This treatment-related AE of erythema was non-serious, considered of mild intensity and resolved within 1 day without any targeted medication or other action. Furthermore, the majority of the AEs were mild (73.7%) or moderate (21.1%). The most common AE was vomiting (13.9% (n=5)), which is already included as ADR in the SmPC. All other AEs were reported for only one patient each, mainly in the SOC "infections and infestations". Serious AEs (SAEs) were reported in 8 patients (22%), none of which were considered related to gadopiclenol by the investigator and none occurred in more than 1 patient. Nevertheless, of these SAEs, one patient experienced an AE of renal failure. The WSA described that this event was not related to the administration of gadopiclenol, however the causality could not be excluded. Nevertheless, as the event was of moderate intensity and resolved within 43 days, this was not considered an important safety issue.

NSF is an adverse event of special interest (AESI) because it has been associated with the administration of a gadolinium-based contrast agent (Kanal E 2007, Kuo PH, 2007). The first symptoms appear weeks to months after the administration of a gadolinium-based contrast agent. No event of NFS has been reported in study GDX-44-015, however, the sample size and follow-up of 3 months are considered too limited to adequately evaluate the risk for NSF. Additionally, also the risks and consequences of accumulated gadolinium, other than NSF, are unknown, particularly on developing brain structures. During the initial MAA procedure, it was already concluded that due to the limited long-term follow-up, NFS should be included as 'important identified risk' and adverse effects of accumulation and retention of gadolinium in the brain along with organs and tissues other than the brain (i.e. bones and skin) should be included as an 'important potential' risk in the RMP. Further, no injection site intolerance was reported.

In the context of this procedure, the applicant conducted an evaluation on the risk of increased gadolinium deposition in children, particularly below the age of 1 year, based on two safety sets, i.e. post-marketing pharmacovigilance data and literature review.

Post-marketing pharmacovigilance data

No post-marketing reports of gadopiclenol use in children under one year of age up to 30 April 2025 were revealed from the Guerbet global pharmacovigilance database; therefore, no specific safety concern could be identified from post-marketing surveillance. The more recent safety-related data provided do not modify the overall benefit-risk balance associated to gadopiclenol intravenous administration in all the approved indications when used as recommended.

Literature review

Overall, the literature review did not reveal any histopathological evidence demonstrating toxicity directly attributable to gadolinium deposition in paediatric patients- particularly those aged one year or younger. Further, no clinical consequences have been observed from gadolinium retention in the brain or other organs, and the long-term effects remain unknown.

In this respect, it is expected that gadopiclenol may improve the safety profile compared to other macrocyclic GBCAs as it is administered at half the dose reducing exposure of patients to Gd by 50%. This is confirmed by the recent non-clinical study by Rasschaert et al. (2025) demonstrating a favourable safety profile for gadopiclenol compared to two routinely used macrocyclic GBCAs (gadoteric acid and gadobutrol)- both of which are approved for use across all age groups.

Regarding laboratory findings, haematology and biochemistry values remained stable from baseline, with mean changes close to 0 for each parameter and the number of patients outside the normal range did not increase post-administration of the contrast agent. Additionally, no clinically meaningful differences in vital signs were reported.

Overall, this study did not show any new safety concern with gadopiclenol at the dose of 0.05 mmol/kg in this paediatric population of patients under 2 years old. The paediatric safety profile is considered consistent with the adult data, however, the data is very limited, particularly for the younger age groups of 0-27 days (n=1) and 28-89 days (n=2). Nevertheless, it was already concluded in the initial MAA that the safety profile of gadopiclenol appeared similar to other authorized GBCA, including gadobutrol. For comparison, other GBCAs, including gadobutrol, are currently already registered for the paediatric population of 0-18 years (including term neonates). However, due to the high relaxivity of gadopiclenol, the recommended dose of gadopiclenol (0.05 mmol/kg body weight equivalent to 0.1 ml/kg body weight) is a half-dose of gadolinium compared to other approved GBCAs, including gadobutrol, for which a dose of 0.1 mmol/kg is recommended for the overall population, including the paediatric population. In this respect, it is expected that this lower dose reduces the risk of NSF and gadolinium deposition in the body (including the brain), which is particularly important for young children who may undergo multiple contrast-enhanced MRI procedures over their lifetime. Therefore, the safety profile of gadopiclenol is expected to be improved in comparison to other GBCAs, although data on direct comparison on long-term are currently lacking. Based on above, the safe use of gadopiclenol in the paediatric population aged 0-2 years is sufficiently justified.

2.5.2. Conclusions on clinical safety

The safety profile of gadopiclenol in the paediatric population of 0-2 years appears similar to the adult population and the paediatric population aged 2 years and older. No new safety issues have been identified, although the number of patients was very limited, particularly for the youngest age groups of 28-89 days and aged 0-27 days. Nevertheless, based on safety data submitted by the WSA, the experience with other GBCAs in the proposed population, and the fact that for Elucirem/Vueway a half-dose of gadolinium compared to other approved GBCAs is recommended, the safe use of gadopiclenol in the paediatric population aged 0-2 years is sufficiently justified.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The WSA submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plans version 0.6 for Elucirem and version 5.1 for Vueway, with a DLP of 31 October 2024 (sign off: 25 November 2025) are acceptable.

The CHMP endorsed the Risk Management Plans version 0.6 for Elucirem and version 5.1 for Vueway, with a DLP of 31 October 2024 (sign off: 25 November 2025).

Safety concerns

Module SVIII - Summary of the safety concerns

Table 34- Summary of safety concerns

Summary of safety concerns in	**Gadopiclenol**
Important identified risk	· NSF (Nephrogenic Systemic Fibrosis
Important potential risk	· Adverse clinical effects of accumulation and retention of Gd in organs and tissues other than brain tissues. · Adverse clinical effects of accumulation and retention of Gd in the brain.
Missing information	· Safety in pregnancy and lactation · Clinical significance of Gd accumulation in organs and tissues other than brain tissues. · Clinical significance of Gd retention in the brain.

Pharmacovigilance plan

The due dates for the ongoing studies ER-22-00007 (investigation of SFN after repeated administration of GBCAs in mice) and ER-21-00011 (investigation of Gd distribution and speciation in rats after repeated IV administrations of gadopiclenol) were updated.

In RMP version 0.6 for Elucirem and 5.1 for Vueway, it is now stated that gadopiclenol has been included in the ODYSSEY study (category 3). It has been corrected that this study is required by US FDA (not EMA).

Overall, the pharmacovigilance plan as agreed during marketing authorisation is still considered sufficient to identify and characterise the risks of the product.

Table 35: summary of additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concern(s) addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit risk)				
None				
Category 3 - Required additional pharmacovigilance activities (United States FDA)				
ODYSSEY - GMRA-105 (Bracco)/ DGD-44-065 (Guerbet) **Title:** Prospective Evaluation of Potential Effects of Repeated Gadolinium-based Contrast Agent (GBCA) Administrations of the Same GBCA on Motor and Cognitive Functions in Neurologically Normal Adults in Comparison to a Non- GBCA Exposed Control Group - ODYSSEY **Ongoing**	To evaluate the potential effect on motor and cognitive function	- Adverse clinical effects of accumulation and retention of gadolinium in the brain - Clinical significance of gadolinium retention in the brain	Protocol amendment finalised	July 2023
			Interim Reports	Annual for FDA
			Final report	6 months after completion
Category 3 - Required additional pharmacovigilance activities				
None				

Risk minimisation measures

Part V was updated with respect to completion of the study in mice (ER-21-00003) and in rats (ER-21-00015) as well as ongoing studies ER-22-00007 and ER-21-00015.

The risk minimisation measures as agreed during marketing authorisation are still considered sufficient to minimise the risks of the product in the proposed indication(s).

Table 36: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Nephrogenic Systemic Fibrosis (NSF)	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 SmPC section 4.4	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up form for collection of additional informatio

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	SmPC section 4.8 SmPC section 4.9 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	
Important potential risks		
Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up form for adverse events lasting over 4 weeks. Additional pharmacovigilance activities: None.
Adverse clinical effects of accumulation and retention of gadolinium in the brain	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up form for adverse events lasting over 4 weeks. Additional pharmacovigilance activities: ODYSSEY (GMRA-105/DGD-44-065) clinical study (post- authorisation safety study): Prospective evaluation of potential effects of repeated gadolinium-containing contrast agent administrations of the same GBCA on motor and cognitive functions in neurologically normal adults in comparison to a non-GBCA exposed control group.
Missing information		

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Safety in pregnancy and lactation	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 SmPC section 4.6 Peel-off tracking label Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Pregnancy notification forms and follow-up forms.
Clinical significance of gadolinium accumulation in organs and tissues other than brain tissue	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 Peel-off tracking label Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up form for adverse events lasting over 4 weeks. Additional pharmacovigilance activities: - Preclinical study in mice investigating the occurrence of small fiber neuropathy after repeated administration. - Preclinical study in rats investigating speciation of Gd retained after repeated injections of a half-dose of gadopiclenol vs gadobutrol.
Clinical significance of gadolinium retention in the brain	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up form for adverse events lasting over 4 weeks. Additional pharmacovigilance activities: - Preclinical study in mice investigating the occurrence of small fiber neuropathy after repeated administration.

2.7. Update of the Product information

As a result of this variation, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA and has been found acceptable for the following reasons: based on the limited impact of the variation on the package leaflet text, a readability user test is considered unnecessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Gadopiclenol is a new chemical entity discovered and developed by Guerbet. It is a non-ionic macrocyclic gadolinium (Gd) complex intended to be used in humans as a contrast agent for Magnetic Resonance Imaging (MRI).

The **final** therapeutic indication for Elucirem/Vueway 0.5 mmol/ml solution for injection is as follows:

This medicinal product is for diagnostic use only.

Elucirem/Vueway is indicated in adults and children from birth for contrast-enhanced magnetic resonance imaging (MRI) to improve detection and visualization of pathologies with disruption of the blood-brain-barrier (BBB) and/or abnormal vascularity of:

- *the brain, spine, and associated tissues of the central nervous system (CNS);*
- *the liver, kidney, pancreas, breast, lung, prostate, and musculoskeletal system.*

It should be used only when diagnostic information is essential and not available with unenhanced MRI.

3.1.2. Available therapies and unmet medical need

Contrast enhancement provides another tool to increase diagnostic confidence and accuracy as it can impact the medical management of a significant number of patients. The benefit of contrast administration is widely accepted.

Contrast-enhanced MRI utilises extracellular Gadolinium-based Contrast Agents (GBCAs) as the clinical standard for detecting and delineating lesions and associated tissues. Following the administration of a GBCA, lesions are further characterised by their temporal and spatial patterns of signal enhancement produced by the contrast agent. GBCAs are widely recognised as critical for optimal MRI visualisation of lesions and are regarded as particularly valuable for tumour detection/anatomical characterisation. The paramagnetic metal gadolinium (Gd3+) is the rare earth element responsible for the enhancement effect of GBCA in MRI.

GBCAs are classified as linear or macrocyclic agents based on the chemical structure of their ligand. Macrocyclic agents have shown a better safety profile due to higher stability, less risk of dissociation, and less release of free Gd. Associations between GBCAs and nephrogenic systemic fibrosis (NSF) and gadolinium deposition in the brain and other organs have been reported (Endrikat J et al. 2018 and Kanda T et al. 2014). In this context, it is recommended to use the minimum GBCA dose that provides

sufficient contrast enhancement for diagnosis in routine practice ((EPAR, EMEA/H/A-31/1437). Thus, the development of high-relaxivity GBCAs meets a true medical need. Such agents would allow a reduction of the injected dose with the same efficacy as the other available GBCAs.

Gadopiclenol is a macrocyclic GBCA characterised by a very high r1 relaxivity, at least two-fold higher compared to other available GBCAs, whatever the magnetic field strength.

3.1.3. Main clinical studies

The application is based on the results of the paediatric development program which was in accordance with the currently agreed PIPs (EMEA-001949-PIP01-16-M07 for CNS and EMEA-001949-PIP02-18-M05 for body). In March 2025, the PDCO adopted an opinion confirming the compliance of all studies in the agreed paediatric investigation plans as set out in the latest Agency's Decisions of 16 August 2024, P/0294/2024 and P/0293/2024, respectively.

The main evidence of efficacy and safety was based on the results of study GDX-44-015. Study GDX-44-015 is a phase 2, open-label, uncontrolled, multicentre, international study to evaluate the PK, safety, and efficacy of gadopiclenol at 0.05 mmol/kg c in paediatric patients < 2 years of age. The design of study GDX-44-015 is similar to study GDX-44-007 conducted in paediatric patients ages 2 to 17 years which was part of the initial MAA of Elucirem/Vueway to support the paediatric population of patients aged 2 to 17 years. Three age groups were defined: 1) Group 1 of patients aged 3 to 23 months (inclusive); Group 2 of patients aged 28 days to less than 3 months; and Group 3 of patients aged from birth to 27 days (term newborns) and the study included three cohorts, i.e., a CNS, blood vessel and body cohort. MRI was performed prior to and after gadopiclenol administration using the same MRI parameters before and after injection for each patient.

The primary objective was to evaluate the PK profile of gadopiclenol in plasma following a single intravenous injection of 0.05 mmol/kg BW (see pharmacology). The secondary objectives were to evaluate the safety up to 3 months following single administration of gadopiclenol and to evaluate efficacy of gadopiclenol-enhanced MRI by body region as assessed by on-site Investigator. The main efficacy endpoints were qualitative assessments (lesion visualisation assessed using 3 co-endpoints: border delineation, internal morphology and degree of contrast enhancement) and quantitative parameters (Contrast-to-Noise Ratio [CNR], Lesion-to-Background Ratio [LBR] and percentage of enhancement) for up to 3 most representative lesions or vessel abnormalities, consistent with standard endpoints for contrast agents, and similar to those assessed in the pivotal studies conducted in adults (GDX-44-010 and GDX-44-011) and those assessed in the study conducted in paediatric patients aged 2 to 17 years (GDX-44-007), and therefore considered acceptable. Additional efficacy endpoints included technical adequacy for diagnosis, overall contrast quality, number and location of lesions detected, change in diagnostic confidence and impact on patient’s treatment plan. All efficacy analyses were descriptive.

The data of this study was also used to update a popPK model, that was developed for the initial MAA submission, in order to justify the proposed dose recommendation for the paediatric population of 0-2 years of age.

3.2. Favourable effects

Efficacy assessment. Administration of gadopiclenol at 0.05 mmol/kg in paediatric subjects 0-2 years old results in enhancement of the CNS and body images in terms of the qualitative parameters (lesion visualization score) and quantitative parameters (signal intensity, percentage of lesion enhancement and LBR (only for body)). Additionally, the investigator’s confidence in diagnosis improved for most examinations (26.7% for CNS and 64.3 % for Body MRI). Consequently, the diagnosis changed

between pre-contrast and paired images for 2 patients (13.3%) in the CNS cohort and 4 patients (28.6%) in the Body cohort. In this respect, a possible change in treatment plan was reported for 7 out of 14 patients (50%) in the body cohort and none of the 15 patients in the CNS cohort.

3.3. Uncertainties and limitations about favourable effects

Efficacy. In the paediatric population of 0—2 years of age a lower effectiveness in terms of quantitative assessment compared with the adult population has been observed. Nevertheless, the investigator's confidence in diagnosis was still improved for most examinations.

CNS images. The enhancement of the CNS images of patients aged 0-2 years was limited given that 1) in terms of contrast enhancement 33% of the patients had no contrast enhancement in the CNS images and according to other parameters, no major improvement was seen compared to native images on paired assessment; 2) gadopiclenol led to change in diagnosis in only about 13% of the cases; and 3) diagnostic confidence improved in only about 28% of the cased and the therapeutic plan was not changed in any of the cases. The observed lower values of enhancement observed in the CNS paediatric population can be explained by the difference in the type of disease included in the paediatric and adult studies.

Sample size. The number of paediatric patients aged 0—2 years included in study GDX-44-015 is limited, particularly the age groups 2 (aged 28-89 days) and 3 (aged 0-27 days) are very underrepresented with only 2 and 1 patients, respectively, however, sufficient for the PK model and to achieve the study primary objective.

Type of lesion/disorder. Due to the limited number of patients included in the different cohorts, several lesion types are under- or not represented. Nevertheless, the results found in the different lesions in the adult CNS and body MRI study can be extrapolated to the paediatric population since the determinants of contrast enhancements in paediatric and adult diseases are the same and the PK profile of gadopiclenol in paediatric patients aged 0-2 years are comparable to the PK profile in adults (and the paediatric population of 2 years and older).

3.4. Unfavourable effects

Adverse events. In total, 52.8% of the patients had adverse events (AEs) during the study of which 51.5% were in the age group of 3-23 months and 100% (n=2) in the age group of 28-89 days, which was higher than the %AEs observed in the adult population (33.5%) and the paediatric population aged 2 years and older (17.5%). No AE was reported for the patients in the 0-27 days age group.

The most common AE was vomiting (13.9%), which has already been included as ADR in the SmPC. All other AEs were reported for only one patient each, which were mainly in the SOC "infections and infestations". SAEs were reported in 8 patients (22%) which none were considered by the investigator related to gadopiclenol and none occurred in more than only 1 patient.

AESI. No events of NFS and no injection site intolerance was reported.

Laboratory findings. Haematology and biochemistry values remained stable from baseline, with mean changes close to 0 for each parameter and the number of patients outside the normal range did not increase post-administration of the contrast agent.

Vital signs. No clinically meaningful differences in vital signs were reported.

3.5. Uncertainties and limitations about unfavourable effects

Follow-up. The safety follow-up of 3 months is limited in order to evaluate long term safety (including risk for NFS and AE related to accumulation and retention of gadolinium in the brain along with organs and tissues other than the brain). Clinical significance of Gd accumulation in the brain and in organs and tissues other than brain tissues is included as missing information in the RMP and will be followed up post-marketing (proactive monitoring through periodic reports and signal detection process (adverse event follow-up form for collection of additional information) and for the clinical significance of Gd accumulation in the brain, through a post- authorisation safety study (ODYSSEY (GMRA-105/DGD-44-065) clinical study)).

Sample size. The number of paediatric patients aged 0—2 years included in study GDX-44-015 is limited, particularly the age groups 2 (aged 28-89 days) and 3 (aged 0-27 days) are very underrepresented with only 2 and 1 patients, respectively. Nevertheless, no safety signals has been identified and gadopiclenol can be given at a dose corresponding to half the dose of gadolinium compared to other non-specific gadolinium-containing contrast agents, also approved for the paediatric population of < 2 years. It is expected that this lower dose of gadolinium presents a clinical safety advantage compared with these other GBCAs.

3.6. Effects Table

Not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In 2023, the use of gadopiclenol was approved in adults and children aged 2 years and older for contrast-enhanced magnetic resonance imaging (MRI) to improve detection and visualization of pathologies with disruption of the blood-brain-barrier (BBB) and/or abnormal vascularity of the CNS and other body regions (liver, kidney, pancreas, breast, lung, prostate and musculoskeletal system).

In the current application, an extension of the indication is proposed to include paediatric patients < 2 years of age based on the results of the completed paediatric study GDX-44-015, in line with the approved EU PIPs EMEA-001949-PIP01-16-M07 for CNS and EMEA-001949-PIP02-18-M05 for body, and with the completed full compliance checks (P/0294/2024 and P/0293/2024, respectively).

The primary objective of Study GDX-44-015 was to evaluate the PK profile in this young paediatric population. The pop PK model that was developed for the original MAA submission, was updated with the data of the paediatric population aged < 2 years. Two adjustments were made to the model to achieve a better fit for the paediatric patients from study GDX-44-015: a renal maturation factor was introduced in the formula describing clearance and the exponent for weight effect on the central volume of distribution was estimated instead of using the standard factor 1. After these adjustments, the model described the PK data in paediatric patients aged < 2 years adequately. Since there were only 2 children aged 28 days to 3 months and none younger than 27 days, estimation in these groups relied (largely) on simulation. However, the extrapolation of the data to the paediatric population < 3 months of age can be considered sufficiently reliable, because the fit of the final model is adequate and there are sufficient data (n=33) in the paediatric population aged 3-23 months. The population PK analysis showed a similar PK profile between adults and the paediatric population and adequacy of body weight-based dosing for all age groups. Therefore, it is agreed that based on these data no adjustment to the dosing regimen is considered necessary for the paediatric population < 2 years of

age and that the dose of 0.05 mmol/kg applies to the adult population as well as the entire paediatric population of 0-17 years of age.

Administration of gadopiclenol at 0.05 mmol/kg in paediatric subjects 0-2 years old results in enhancement of the CNS and body images in terms of the qualitative parameters (lesion visualization score) and quantitative parameters (signal intensity, percentage of lesion enhancement and LBR (only for body)), although the sample size was very limited, especially for the lower age groups of 0-27 days and 28-89 days. Nevertheless, similar as already concluded in the initial MAA to support the paediatric population of 2 years and older, the results found in the adult CNS and body MRI studies can be extrapolated to the paediatric population since the determinants of contrast enhancements in paediatric and adult diseases are the same and the PK profile of gadopiclenol in paediatric patients aged 0-2 years are comparable to the PK profile in adults and the paediatric population of 2 years and older.

Regarding safety, the study did not show any new safety concern with gadopiclenol at the dose of 0.05 mmol/kg in this pediatric population of patients under 2 years old. The paediatric safety profile is considered consistent with the adult data, however, the data is very limited, particularly for the younger age groups of 0-27 days (n=1) and 28-89 days (n=2). Nevertheless, it was already concluded in the initial MAA that the safety profile of gadopiclenol appeared similar to other authorized GBCA, including gadobutrol. However, due to the high relaxivity of gadopiclenol, the recommended dose of gadopiclenol (0.05 mmol/kg body weight equivalent to 0.1 ml/kg body weight) is a half-dose of gadolinium compared to other approved GBCAs, including gadobutrol, for which a dose of 0.1 mmol/kg is recommended for the overall population, including the paediatric population. Associations have been reported between gadolinium-based contrast agents (GBCAs) and nephrogenic systemic fibrosis (NSF) and gadolinium deposition in the brain and other organs (Endrikat J et al. 2018 and Kanda T et al. 2014). In this context, it is recommended to use the minimum GBCA dose that provides sufficient contrast enhancement for diagnosis in routine practice (EPAR, EMEA/H/A-31/1437). In this respect, the lower dose for gadopiclenol is expected to reduce the risk of NSF and gadolinium deposition in the body (including the brain), which is particularly important for young children who may undergo multiple contrast-enhanced MRI procedures over their lifetime. Based on above, the safe use of gadopiclenol in the paediatric population aged 0-2 years is sufficiently justified.

3.7.2. Balance of benefits and risks

Administration of gadopiclenol at 0.05 mmol/kg in paediatric subjects 0-2 years old resulted in enhancement of the CNS and body images in terms of the qualitative parameters (lesion visualization score) and quantitative parameters (signal intensity, percentage of lesion enhancement and LBR (only for body)), which was accompanied with an acceptable safety profile comparable to that observed in the adult population and paediatric population of 2 years and older.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Elucirem/Vueway (gadopiclenol) for the paediatric population aged <2 years old is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisations, concerning the following changes:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I, IIIB and IV

Extension of indication to include treatment of new population (0 to 2 years of age patients) for ELUCIREM / VUEWAY, based on final results from study GDX-44-015; this is a phase ii clinical study concerning gadopiclenol pharmacokinetics, safety and efficacy in pediatric patients < 2 years of age undergoing contrast-enhanced MRI; extension of indication is also supported with the non-clinical data. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 0.5 of the RMP has also been submitted. As part of the application, the MAH requested a 1-year extension of the market protection.

The variation worksharing procedure leads to amendments to the annex(es) I, IIIB, and IV and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the worksharing procedure, amendments to Annex(es) I, IIIB and IV and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAHs shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0294/2024 and P/0293/2024 for Elucirem & Vueway and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the WSA, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers, by consensus, that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.