Division of Imaging and Radiation Medicine

NDA Supplement Review – Clinical

NDA #	216986-S009	RPM	Sharon Thomas
Drug	Elucirem (gadopiclenol) injection	Clinical reviewer	Brenda Ye
Applicant	Guerbet	Submission date	4/22/2025
SD #	254	Goal date	2/20/2026

Background:

Elucirem is a gadolinium-based contrast agent indicated in adult and pediatric patients aged 2 years and older for use with magnetic resonance imaging (MRI) to detect and visualize lesions with abnormal vascularity in:

- the central nervous system (brain, spine, and associated tissues),
- the body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system).

The Applicant has submitted an efficacy supplement seeking to extend the Elucirem indications to pediatric patients < 2 years of age (term neonates inclusive) for contrasted MRI.

Regulatory History:

Elucirem was approved on September 21, 2022, for use in adults and pediatric patients age ≥2 years.

At the time of approval, a pediatric study in patients aged 0 to <2 years was established as a PREA postmarketing requirement:

> PMR 4341-1: Conduct a study of approximately 40 neonates and infants aged < 2 years that will receive a single dose of 0.05 mmol/kg gadopiclenol intravenously for the evaluation of the plasma pharmacokinetics profile of gadopiclenol (POP-PK analysis). Safety and imaging data will be collected as secondary endpoints.

The Final Report Submission milestone was extended twice, from 12/2023 to 12/2024 on April 7, 2023, and from 12/2024 to 4/2025 on December 2, 2024. In meeting comments dated May 10, 2024, the Agency agreed that a population pharmacokinetic approach could be used in children less than 3 months old and noted that the target enrollment of approximately 40 patients need not be interpreted as exactly 40.

This application includes the final study report for the PMR Study GDX-44-015.

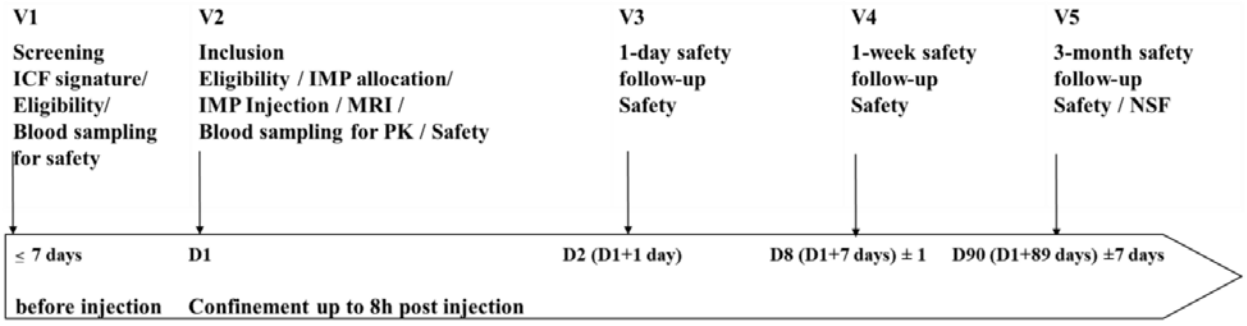
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Study GDX-44-015, entitled 'Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI", was an open-label, multicenter trial designed to investigate the pharmacokinetic (PK) profile of gadopiclenol in plasma, in pediatric patients from birth

up to 23 months of age, inclusive of term neonates or preterm infants after the neonatal period. The study design is outlined in Figure 1.

Figure 1. Schematic of Study Design



Source: GDX-44-015 clinical study report, Figure 9-1

The study was conducted in 11 centers in Europe and the US from 2022-2024, including 3 centers in Hungary (12 patients), 6 centers in Poland (19 patients), and 2 centers in the US (5 patients).

The primary objective was to evaluate the pharmacokinetic profile of gadopiclenol in plasma following a single intravenous injection of 0.05 mmol/kg body weight (BW) in pediatric patients aged up to 23 months (inclusive) scheduled for contrasted MRI of any body region, including the central nervous system (CNS).

Secondary objectives included:

- To evaluate the safety of gadopiclenol up to 3 months following a single administration.
- To evaluate the efficacy of gadopiclenol MRI by body region as assessed by on-site investigator.

The study enrolled pediatric patients with known or highly suspected abnormalities or lesions of any body region, including the CNS. Each subject received a single administration of gadopiclenol intravenously. The dose of 0.05 mmol/kg BW was the same as recommended in labeling for older children and adults.

Images were assessed by unblinded, on-site radiologists for both pre-contrast (Pre) and combined pre-contrast and post-contrast (Paired) images. Each patient's images were evaluated by a single reader. Lesion visualization parameters, including border delineation, internal morphology, and degree of contrast enhancement, for up to 3 most representative lesions or vessel abnormalities were assessed using a 4-point scale for each parameter.

The PK analyses are discussed in the Clinical Pharmacology review. The lesion visualization analyses were intended only as secondary support for the PK data. Accordingly, they are limited by multiple study design factors, including the single on-site reader, lack of reader blinding and measures to prevent recall bias, inclusion of vessel abnormalities, and relatively small sample size. These results are only briefly reviewed here.

A total of 36 patients received one injection of gadopiclenol and were analyzed in the Safety Set: 33 aged 3-23 months, 2 aged 28-89 days, and 1 aged 0-27 days. The mean age in the 3-23 months age

group was 13 months. The 2 patients included in the 28-89 day age group were 56 and 62 days old, and the patient included in the 0-28 day age group was 25 days old. There were 18 (50%) male and 18 (50%) female patients. All patients were White. One patient (3-23 months) was Hispanic or Latino. A total of 19 patients (53%) were imaged for CNS lesions and 14 (39%) for body lesions.

Among these 36 patients, 1 patient aged 3-23 months was excluded from the Full Analysis Set, as the post-contrast images were not available. Therefore, 35 patients were analyzed for efficacy.

Efficacy Evaluation

The number of detected lesions ranged from 0 to 3. For 26/35 (74%) patients, a single lesion was detected on Pre images. The number of detected lesions was the same with Pre and Paired images except for one patient in the CNS cohort for whom 1 lesion was detected with Pre images and 2 lesions detected with Paired images.

All 3 lesion visualization parameter scores were numerically higher on average on Paired images than Pre images (Table 1).

Table 1. Mean Lesion Visualization Parameter Scores in GDX-44-015 (n=35 patients)

Lesion Visualization Parameter	Pre (n=38 lesions)	Paired (n=39 lesions)
Border delineation	2.84	3.23
Internal morphology	2.97	3.36
Degree of contrast enhancement	1	3

Source: Adapted from GDX-44-015 clinical study report, Table 11-10

Diagnostic confidence was reported as improved on Paired images compared to Pre in 13/31 (42%) patients with at least 1 lesion, unchanged in 17 (55%), and worsened in 1 (3%).

Summary of effectiveness

GDX-44-015 was intended as a PK study, and only limited effectiveness data were obtained. However, these data do not raise concern for effectiveness in patients aged 23 months or less and support use of PK data to extrapolate effectiveness to this age group from older children and adults.

Safety Evaluation

Safety assessments in GDX-44-015 consisted of the following:

- Physical examination before gadopiclenol injection and at safety follow-up visits conducted at 1 week 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 after injection, and 1 day after injection.

- Blood samples collected prior to and 1 day after gadopiclenol injection to assess biochemistry and hematology variables.

- Tolerance at the injection site assessed at 3 time points: during injection, 10-60 min after injection, and 1 day after injection.

- Clinical examination for Nephrogenic Systemic Fibrosis (NSF) at the 3-month follow-up safety visit. In case of suspicion of NSF, a deep skin biopsy was to be performed.

All 36 patients received a dose of gadopiclenol at 0.05 mmol/kg BW. 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).

Nineteen patients (53%) had 38 treatment emergent AEs (TEAEs): 17 patients out of 33 patients in the 3-23 months age group, and 2 patients out of 2 patients in the 28-89 days age group. No TEAE was reported for the 1 patient in the 0-27 days age group. Among the 38 reported TEAEs, 26 (68%) were of mild intensity, 7 (18%) were of moderate intensity, and 5 (13%) were of severe intensity. The most frequently reported TEAE was vomiting (5 patients, 14%).

A total of 8 patients experienced 11 treatment emergent serious AEs (SAEs). These events included feeding difficulties, resection of optic glioma, central fever, microcytic anemia, norovirus gastroenteritis, HPIV-3 pneumonia, upper respiratory tract infection, sella turcica cyst growth, intracranial hypertension, ventriculoperitoneal shunt dysfunction, and worsening of pre-existing renal failure. All SAEs were considered unrelated to gadopiclenol by the Applicant and investigators. SAE narratives were reviewed, and we agree with the assessment.

One patient (3%) experienced 1 TEAE considered related to gadopiclenol, erythema. The patient presented with light redness of the cheeks and tip of the nose 2h 35 min after gadopiclenol administration. The event was non-serious, considered of mild intensity, and resolved within 1 day without intervention. Other TEAEs were not considered related to gadopiclenol.

An Adverse Event of Special Interest was defined in the study as suspected NSF or symptoms suspected to be related to NSF. No suspected NSF or NSF-related symptoms were reported.

Evaluation of vital signs (blood pressure and pulse rate) did not reveal any safety concern. The changes post-contrast administration were very small and mean changes were close to 0.

Regarding clinical laboratory evaluation, the mean changes in hematology and biochemistry parameters were close to 0 and the number of patients outside the normal ranges did not increase after administration of the contrast agent.

Summary of safety

One adverse event was considered related to gadopiclenol (erythema of mild intensity). As erythema was also observed in adults and rash was observed in older children, the safety data from GDX-44-015 were considered compatible with the overall safety profile observed for gadopiclenol in adults and older children.

Conclusion:

The safety and effectiveness data provided by GDX-44-015 support extrapolation of the currently labeled indications for Elucirem to pediatric patients under two years of age. We defer to Clinical Pharmacology whether the PK data are sufficient for establishing an appropriate dose in this age group.

Appendix:

Financial disclosures

The Applicant disclosed that [redacted], who participated as the [redacted] for GDX-44-015 and as a site clinical investigator, received significant payments of other sorts made or after [redacted], from the sponsor of the covered study. Guerbet and Guerbet LLC provided [redacted] honoraria, consulting, and travel fees in [redacted] totaling approximately $90,000. The Applicant also provided approximately $15,000 in research funding to the site [redacted] was affiliated with. [redacted] patients were enrolled at that site. The Applicant stated that the site was monitored during the clinical study in accordance with study monitoring plan. They considered that [redacted] had fulfilled her obligations as clinical investigator and that there was no bias to the clinical study results.

The use of unblinded, on-site image evaluators for imaging effectiveness raises the possibility of bias, however the potential impact of any bias on the study results is assessed as very low due to the enrollment of only 8% of the study population at the site in question. We also note that the primary objective of the study was to obtain PK data, which are more objective than lesion visualization scores.

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SHANE C MASTERS
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AUGUST A HOFLING
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