CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216986Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(1) NDA
Application Number(s)	216986
Priority or Standard	Priority
Submit Date(s)	January 21, 2022
Received Date(s)	January 21, 2022
PDUFA Goal Date	September 21, 2022
Division/Office	Office of Specialty Medicine, Division of Imaging and Radiation Medicine
Review Completion Date	September 21, 2022
Established/Proper Name	Gadopiclenol
Trade Name	Elucirem
Pharmacologic Class	Gadolinium-based contrast agent
Code name	N0000183362
Applicant	Guerbet Group, France
Dosage form	Injection
Applicant proposed Dosing Regimen	0.1 mL/kg body weight (equivalent to 0.05 mmol/kg) administered as an intravenous bolus injection
Applicant Proposed Indication(s)/Population(s)	Gadopiclenol is a gadolinium-based contrast agent indicated in adults and children age 2 years and older for contrast enhanced magnetic resonance imaging (MRI) to (b) (4) lesions in: – the Central Nervous System (brain, spine and (b) (4) tissues), – the Body (head and neck, thorax (b) (4), abdomen (b) (4), pelvis (b) (4), and musculo-skeletal system).
Applicant Proposed SNOMED CT Indication Disease Term	Not applicable
Regulatory Action	Approval
Indication(s)/Population(s)	Gadopiclenol 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).
SNOMED CT Indication Disease Term	Lesion (morphologic abnormality) 52988006
Recommended Dosing Regimen	0.05 mmol/kg body weight (equivalent to 0.1 mL/kg body weight) administered intravenously at approximately 2 mL/sec

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Sharon Thomas
Nonclinical Reviewer	Olayinka Dina, PhD
Nonclinical Team Leader	Jonathan Cohen, PhD
Nonclinical Division Director	Mukesh Summan, PhD
Office of Clinical Pharmacology Reviewers	Edwin Chiu Yuen Chow, PhD, Hongshan Li, PhD (Pharmacometrics)
Office of Clinical Pharmacology Team Leaders	Christy John, PhD, Jiang Liu, PhD (Pharmacometrics)
Division Director (OCP)	Brian Booth, PhD
Clinical Reviewer	Hadi Bagheri, MD
Clinical Team Leader	Shane Masters, MD, PhD
Statistical Reviewer	Zhipeng Huang, PhD
Statistical Secondary Reviewer	Jyoti Zalkikar, PhD
Statistical Tertiary Reviewer and Division Deputy Director	Sue-Jane Wang, PhD
Cross-Disciplinary Team Leader	Shane Masters, MD, PhD
Associate Director for Labeling (DIRM)	Younsook Kim, PharmD
Deputy Division Director (DIRM)	August Hofling, MD, PhD
Division Director (DIRM)	Libero Marzella, MD, PhD
Deputy Office Director (OSM), Designated signatory authority	Alex Gorovets, MD

Additional Reviewers of Application

OPQ	Joseph Leginus, PhD, Zhengfu Wang, PhD, Dhanalakshmi (Dhana) Kasi, PhD, Danae Christodoulou, PhD, Sureshbabu (Suresh) Dadiboyena, PhD, Kamal Tiwari, PhD, Anika Lalmansingh, PhD, Eldon E. Leutzinger, PhD
Microbiology	Ash Bekele, PhD, Yeissa Chabrier-Rosello, PhD
OPDP	Nazia Fatima, PharmD, James Dvorsky, PharmD
OSI	John Lee, MD, Phillip Kronstein, MD
OSE/DMEPA	Tri Bui Nguyen, PhD, Devin Kane, PharmD, Hina Mehta, PharmD

OPQ, Office of Pharmaceutical Quality
OPDP, Office of Prescription Drug Promotion
OSI, Office of Scientific Investigations
OSE, Office of Surveillance and Epidemiology
OSM Office of Specialty Medicine
DIRM Division of Imaging and Radiation Medicine
DMEPA, Division of Medication Error Prevention and Analysis

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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CNR	contrast to noise ratio
CNS	central nervous system
CRO	contract research organization
CT	computed tomography
CV	cardiovascular
CV%	percent coefficient of variation
DART	developmental and reproductive toxicology
DCN	deep cerebellar nuclei
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	Food and Drug Administration
GBCA	gadolinium-based contrast agent
GCP	good clinical practice
Gd	gadolinium
GD	gestational day
GLP	good laboratory practice
HCC	hepatocellular carcinoma
hERG	human ether-a-go-go-related gene
ICC	Intra-class correlation
IMP	investigational medicinal product
IND	Investigational New Drug
iPSP	initial Pediatric Study Plan
IR	information request
i.v.	intravenous
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MSK	musculoskeletal
NDA	new drug application
NME	new molecular entity
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level

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NSF	nephrogenic systemic fibrosis
NZW	New Zealand White
OSI	Office of Scientific Investigation
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPK	population pharmacokinetics
PPS	per-protocol set
PTZ	pentylenetetrazole
RF	radiofrequency
RP2D	recommended phase 2 dose
SAE	serious adverse event
TEAE	treatment emergent adverse event

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1 Executive Summary

1.1. Product Introduction

Gadopiclenol injection (proprietary name Elucirem) is a gadolinium-based contrast agent (GBCA). It is a nonionic, macrocyclic gadolinium (Gd) complex that alters the relaxation rates of hydrogen nuclei in water and thereby changes signal intensity on T1-weighted magnetic resonance imaging (MRI) in a concentration dependent manner. This new molecular entity (NME) has recommended indications for use with magnetic resonance imaging to detect and visualize lesions with abnormal vascularity in the central nervous system (brain, spine, and associated tissues) and the body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system). The recommended patient population is children 2 years of age and older and adults, and the recommended dose is 0.05 mmol/kg body weight administered as an intravenous bolus.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has submitted substantial evidence of effectiveness for gadopiclenol for improving MRI visualization of lesions in the central nervous system (CNS) and elsewhere in the body. Efficacy is primarily supported by two adequate and well-controlled prospective trials conducted by the Applicant. In both trials, multiple blinded, independent readers scored three lesion visualization parameters of border delineation, internal morphology, and contrast enhancement in the absence of the drug and on paired image sets obtained before and after administration of the drug.

The first adequate and well-controlled trial evaluated the efficacy of gadopiclenol in adults with known or highly suspected lesions of the CNS. The scores for all three visualization parameters were higher for all three independent readers on paired pre-contrast and post-contrast images as compared to pre-contrast images alone. Similar results were obtained in the second adequate and well-controlled trial, which enrolled adults with known or highly suspected lesions in organs outside the CNS. These trials were considered mutually supportive for visualization claims in both anatomic regions. The Applicant also conducted a pharmacokinetic study in patients aged 2 years to 17 years that served as a basis for extrapolation of effectiveness to this population of pediatric patients.

Lesion visualization indications are shared among all previously approved macrocyclic GBCAs and are generally considered to have inherent clinical utility.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Gadopiclenol is a nonionic, macrocyclic GBCA proposed for use with MRI in adults and children aged 2 years and older to detect and visualize lesions with abnormal vascularity in the CNS and body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system). The recommended dose is 0.05 mmol/kg body weight.

MRI can provide important information regarding disease status in a large number of conditions and is considered to be standard of care in many clinical contexts. Administration of a GBCA with MRI is often necessary to obtain optimal imaging information. Currently approved macrocyclic GBCAs are distributed in the extracellular fluid and accumulate in areas with increased vascular density and permeability compared to surrounding normal tissue.

The data from two adequate and well-controlled clinical trials showed that a combination of images obtained with and without gadopiclenol improved multiple aspects of lesion visualization compared to images obtained without gadopiclenol. This is a clinically relevant comparison because in practice most contrasted MRIs also include images obtained prior to administration of contrast. Improvement in lesion visualization is generally expected to have clinical utility.

Of note, gadopiclenol was studied in patients who had lesions in the musculoskeletal system. None of the currently marketed GBCAs in the US have this approved indication, although they are often used off-label for musculoskeletal lesion visualization. Additionally, while all currently approved macrocyclic GBCAs are indicated for visualization of CNS lesions, none are broadly approved to visualize other lesions located throughout the body.

Safety of gadopiclenol was evaluated in 1047 patients, of whom 708 patients received gadopiclenol at the recommended dose of 0.05 mmol/kg. The safety profile of gadopiclenol is broadly similar to other GBCAs, and known risks associated with the class, such as hypersensitivity, nephrogenic systemic fibrosis, and gadolinium retention, can be mitigated through appropriate labeling.

As a macrocyclic GBCA, gadopiclenol is expected to result in less gadolinium retention than approved linear GBCAs. The recommended dose of all currently approved macrocyclic GBCAs and all but one currently marketed linear GBCAs is 0.1 mmol/kg body weight compared to the recommended dose of 0.05 mmol/kg body weight for gadopiclenol. A lower dose is supported by the greater relaxivity of gadopiclenol relative to other marketed GBCAs.

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In summary, the data show that gadopiclenol has a favorable benefit-risk balance for the recommended indication and patient population. Therefore, approval of this application is recommended.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• MRI is an anatomic imaging technique that is widely used for assessment of many diseases. • Distribution of contrast agents throughout the body can be affected in multiple diseases, often through changes in blood flow or vascular permeability. • Contrasted MRI has the potential to aid in distinguishing between normal and abnormal anatomy.	• MRI provides information that is important for management of many conditions, including serious conditions. • Contrast is often necessary to obtain optimal results with MRI.
Current Treatment Options	• In many cases computed tomography (CT) can be used in place of MRI. In general, the spatial resolution of CT is greater than that of MRI while the contrast among tissues is better on MRI than CT. Depending on the clinical context, one modality is often preferred over the other. • CT contrast agents are also approved and can add similar information about vascularity. • Currently, six Food and Drug Administration (FDA) approved GBCAs are marketed in the US as MRI contrast agents. • Five of these GBCAs are indicated for visualization of lesions in the CNS. • One of these GBCAs, gadoteridol (Prohance), is indicated for visualization of lesions in the head and neck in adults. Gadoteridol is a macrocyclic GBCA. • One of these GBCAs, gadodiamide (Omniscan), is indicated for visualization of lesions in the thorax, abdomen, and pelvis. Gadodiamide is a linear GBCA.	• Multiple MRI contrast agents are available for visualization of CNS lesions. • Fewer drugs are indicated for lesions outside the CNS. While several GBCAs have been used off-label to visualize lesions in the musculoskeletal system, no MRI contrast agent is currently marketed in the US for this indication. Furthermore, no macrocyclic GBCAs are currently approved broadly to visualize lesions located throughout the body. • As a macrocyclic GBCA, gadopiclenol is expected to result in less gadolinium retention than approved linear GBCAs. • The recommended dose of all currently approved macrocyclic GBCAs and all but one currently marketed linear GBCA is 0.1 mmol/kg body weight compared to the

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
		recommended dose of 0.05 mmol/kg body weight for gadopiclenol. • The lower dose of gadopiclenol is supported by its greater relaxivity relative to other marketed GBCAs.
Benefit	• The Applicant conducted two adequate and well-controlled prospective confirmatory clinical trials and submitted their results in this New Drug Application (NDA). • Trial GDX-44-010 included 256 patients with known or highly suspected CNS lesions. Three blinded readers evaluated paired pre-contrast plus post-contrast images and pre-contrast images alone for three lesion visualization criteria of border delineation, internal morphology, and degree of contrast enhancement. In the primary analysis, superiority of the paired pre-contrast plus post-contrast images with gadopiclenol over pre-contrast images alone was demonstrated for all lesion visualization criteria for all readers. • Trial GDX-44-011 included 304 patients with known or highly suspected lesions in the body including the head and neck, thorax, abdomen, pelvis, and musculoskeletal system. Paired pre-contrast plus post-contrast images and pre-contrast images alone were evaluated by three blinded readers for three lesion visualization criteria of border delineation, internal morphology, and degree of contrast enhancement. In the primary analysis, superiority of the paired pre-contrast plus post-contrast images with gadopiclenol over pre-contrast images alone was demonstrated for all lesion visualization criteria for all readers in each anatomic region except musculoskeletal, where two of the three readers demonstrated superiority.	• The primary analyses of both of the adequate and well-controlled clinical trials were successful. • In both trials, lesion visualization with gadopiclenol dosed at 0.05 mmol/kg was similar to that of gadobutrol dosed at 0.1 mmol/kg. • The ability to improve lesion visualization is a clinically relevant endpoint and the use of gadopiclenol is expected to provide meaningful additional information in multiple disease states in a similar manner to other GBCAs. • The numbers of patients with lesions in the spine, head and neck, and musculoskeletal system were small. However, given the mechanism of action, drug performance is not expected to vary substantially among different anatomic regions.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The safety population consisted of 1047 patients exposed to gadopiclenol, of whom 708 received the recommended dose of 0.05 mmol/kg. • No death related to gadopiclenol was reported. No serious adverse event related to gadopiclenol or withdrawal due to adverse event related to gadopiclenol was reported at the recommended dose. • Overall, 4.7% of patients who received gadopiclenol at the recommended dose of 0.05 mmol/kg reported one or more adverse reactions. • The most common adverse reactions were headache, nausea, dizziness, localized swelling, and various injection site related events. • Key safety issues for gadopiclenol are similar to other GBCAs and include hypersensitivity, nephrogenic systemic fibrosis (NSF), and gadolinium retention.	• No unexpected safety concerns are identified. • Available safety data indicate that GBCA class labeling will be sufficient to mitigate the potential risks of hypersensitivity and NSF. • While the recommended dose of gadopiclenol is lower than most other currently marketed GBCAs due to its high relaxivity, there is insufficient data to determine whether gadopiclenol will have similar or different retention than other macrocyclic GBCAs when administered at recommended doses.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application and was not needed.**			

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2 Therapeutic Context

2.1. Analysis of Condition

MRI is a widely used anatomic imaging modality that relies on measuring the behavior of hydrogen nuclei in a magnetic field after exposure to radiofrequency (RF) energy. After exposure to an RF pulse, the hydrogen nuclei will return to their ground state in a manner that is dependent on the local (molecular scale) environment. This return can be partially characterized by two relaxation times, longitudinal (T1) and transverse (T2). By varying the RF pulses, images can be created that are more influenced by T1 (T1-weighted), T2 (T2-weighted), or other parameters (for example, diffusion weighting). A clinical MRI scan will typically include several different RF pulse sequences to obtain multiple types of images of the same anatomic region, as different features are best shown with different image weighting.

The foundation for MRI contrast agents is the ability to alter the local environment of hydrogen nuclei, and therefore T1 and T2. While multiple paramagnetic and superparamagnetic substances, such as manganese and iron, have this ability, all approved MRI contrast agents currently marketed in the U.S. utilize gadolinium. GBCAs alter T1 and T2 in a concentration dependent manner, and the relaxivity (defined as $r = \frac{1}{\Delta T}/C$, where r is relaxivity, T is a relaxation time, and C is the concentration of contrast agent) is used to characterize the concentration dependence. In the large majority of routine clinical MRI studies, T2 changes caused by GBCAs are difficult to detect and only T1 relaxivity (r1), is relevant. Contrast is generally seen as increased signal intensity on T1-weighted images. While relaxivity measurements vary with experimental conditions, it is generally expected that at the same concentration, a GBCA with higher relaxivity will appear brighter on T1-weighted images.

Most currently available GBCAs are intravenously administered polar molecules that distribute via the circulatory system into the extracellular fluid and localize in areas of increased blood flow and vascular permeability. These vascular features are seen in a wide variety of pathologic processes, including many inflammatory and neoplastic diseases. While GBCAs accumulate in areas where there is disruption of the blood-brain barrier, a common characteristic of many lesions in the CNS, similar accumulation of GBCAs is also observed in many types of lesions located elsewhere throughout other tissues in the body. Therefore, most GBCAs can be considered relatively nonspecific and likely to have broad clinical utility. From a regulatory perspective, this justifies lesion visualization indications that are not limited to one or more specific diseases. However, it is important to note that such broad lesion visualization indications do not imply suitability of a GBCA for determining the exact diagnosis of particular diseases.

2.2. Analysis of Current Treatment Options

Currently, six FDA approved GBCAs are available in the US, as shown in Table 1. The labeled indications vary based on the data reviewed by the FDA. All of the GBCAs other than gadoxetate disodium are labeled for visualization of CNS lesions. Other lesion visualization

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claims are approved for gadodiamide in the thorax, abdomen, and pelvis and for gadoteridol in the head and neck. The remaining indications are for more specific disease diagnosis and characterization claims. Gadoxetate disodium distributes into the extracellular fluid in a similar manner as the other agents, but because a significant fraction of the drug is excreted by the hepatobiliary route, it has an indication for characterization of liver lesions.

Table 1. Currently Marketed, FDA Approved MRI Contrast Agents

Established Name	Proprietary Name	Structural Features	Indications
gadobenate dimeglumine	MultiHance	Linear, ionic	For MRI of the CNS in adults and pediatric patients (including term neonates), to visualize lesions with abnormal blood-brain barrier or abnormal vascularity of the brain, spine, and associated tissues For MRA to evaluate adults with known or suspected renal or aorto-ilio-femoral occlusive vascular disease
gadobutrol	Gadavist	Macrocyclic, nonionic	To detect and visualize areas with disrupted blood brain barrier and/or abnormal vascularity of the central nervous system in adult and pediatric patients, including term neonates To assess the presence and extent of malignant breast disease in adult patients To evaluate known or suspected supra-aortic or renal artery disease in adult and pediatric patients, including term neonates To assess myocardial perfusion (stress, rest) and late gadolinium enhancement in adult patients with known or suspected coronary artery disease
gadodiamide	Omniscan	Linear, nonionic	To visualize lesions with abnormal vascularity in the brain, spine, and associated tissues To facilitate the visualization of lesions with abnormal vascularity within the thoracic, abdominal, pelvic cavities, and the retroperitoneal space

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Established Name	Proprietary Name	Structural Features	Indications
gadoterate meglumine	Dotarem	Macrocyclic, ionic	For intravenous use with MRI in brain (intracranial), spine and associated tissues in adult and pediatric patients (including term neonates) to detect and visualize areas with disruption of the blood brain barrier and/or abnormal vascularity
gadoteridol	ProHance	Macrocyclic, nonionic	To visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues in adults and pediatric patients over 2 years of age To visualize lesions in the head and neck in adults
gadoxetate disodium	Eovist	Linear, ionic	For use in MRI of the liver to detect and characterize lesions in patients with known or suspected focal liver disease

Source: US Prescribing Information for each of the drugs
Abbreviations: CNS, central nervous system; FDA, Food and Drug Administration; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging

Aside from gadoxetate disodium, the currently marketed, FDA approved GBCAs have a recommended intravenous dose of 0.1 mmol/kg body weight. The recommended dose of gadopiclenol is 0.05 mmol/kg intravenously. As further detailed in Section 6.3.1, gadopiclenol has higher measured relaxivity than currently marketed GBCAs, which allows use of a lower dose.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Gadopiclenol is an NME that has not been approved or marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

On October 30, 2014, a pre-Investigational New Drug (IND) Type B meeting was held with the Applicant and FDA to discuss submission of an IND application for P03277, a new macrocyclic GBCA, which was later given the established name gadopiclenol. The Applicant presented the findings from phase 1 clinical research conducted in Europe and requested guidance from FDA on the path forward for the development of this product. Key issues covered at the meeting included the adequacy of the nonclinical data to support phase 2 trials, the design of dose finding studies, and data needed prior to initiation of a study in patients with renal impairment.

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IND 123673 was subsequently opened on December 17, 2015, with a protocol for a dose finding study in patients with CNS lesions.

A Type B End of Phase 2 chemistry, manufacturing, and controls meeting was held on July 10, 2017. Starting materials and isomeric characterization were discussed along with manufacturing sites and stability testing. There was also some discussion of clinical issues at this meeting, including whether the Applicant would leverage the higher relaxivity of gadopiclenol to provide greater signal intensity at similar doses as other GBCAs or to provide similar signal intensity at lower doses. FDA recommended the latter due to developing evidence regarding retention of gadolinium. FDA also encouraged the Applicant to pursue indications beyond CNS lesion visualization and indicated that it may be possible to design two phase 3 trials, one for CNS imaging and one for a different indication, such that they were mutually supportive.

A general Type B, End of Phase 2 meeting was held on August 23, 2018. FDA agreed that the completed nonclinical studies were acceptable, and that the ongoing/planned nonclinical studies were reasonable to support phase 3 clinical trials. FDA agreed that two indications could be achieved based on a single positive pivotal trial per indication and emphasized that both trials should be positive as a prerequisite for approval. FDA also recommend that for a visualization indication, where endpoints are qualitative in nature and no reference standard is available, the primary efficacy analysis should aim to demonstrate superiority of combined pre-contrast and post-contrast images over pre-contrast images. Such primary analysis was recommended over comparison of post-contrast images between gadopiclenol and another GBCA. FDA also clarified that for a general visualization claim (but not a specific diagnostic indication) it would consider a multi-organ study in support of a general body indication, where each individual organ would not need to be statistically powered.

An initial Pediatric Study Plan (iPSP) was submitted on February 14, 2017, and an initial agreement letter was issued on September 11, 2017. On October 19, 2018, the Applicant submitted an amendment to the iPSP to request a deferral of studies in patients younger than 2 years old. FDA agreed with this amendment in a letter sent January 23, 2019.

On October 16, 2018, FDA received a request for special protocol assessment of two phase 3 clinical trial protocols (GDX-44-010 and GDX-44-011). On November 30, 2018, FDA issued a special protocol agreement letter. Highlights of the negotiation included agreement that noninferiority of gadopiclenol to the comparator gadobutrol could be included as a primary objective to satisfy requirements of the European Medicines Agency but would be considered a secondary objective by FDA, agreement that gadobutrol could be used as a comparator in GDX-44-011 even though it was not approved for some of the anatomic regions targeted in the trial, and confirmation that heart lesions would not be included in GDX-44-011.

On July 27, 2021, in written responses to a Type B, pre-NDA meeting request, FDA emphasized that a lesion characterization claim would need to be validated by a reference standard rather than supported by qualitative lesion visualization ratings.

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On January 21, 2022, NDA 216986 for gadopiclenol was received by FDA. It was filed on March 22, 2022. The Applicant requested a priority review, which was granted on the basis of unmet medical need as there are currently no U.S. approved and marketed MRI contrast agents indicated for musculoskeletal lesion visualization. Furthermore, no macrocyclic GBCAs are currently approved broadly to visualize lesions located throughout the body.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

Although no specific data quality issues were suspected, because GDX-44-010 and GDX-44-011 provided the primary effectiveness and safety results for this NME application, an Office of Scientific Investigations (OSI) audit of these studies was requested. Four sites were selected for inspection, including three clinical sites and the imaging contract research organization (CRO). No significant good clinical practice (GCP) deficiencies were identified at any of the sites. OSI determined that both GDX-44-010 and GDX-44-011 appear to have been conducted in adequate compliance with GCP standards and FDA regulations.

4.2. Product Quality

Reference is made to the Office of Product Quality Integrated Quality Assessment dated August 18, 2022, which may be found in DARRTS. Briefly, the drug product Elucirem (gadopiclenol) injection contains the active ingredient rac-[(2R,2'Ξ,2''Ξ)-2,2',2''-(3,6,9-triaza-κ3N3,N6,N9-1(2,6)-333 pyridina-κN1-cyclodecaphane-3,6,9-triyl)tris(5-{[(2Ξ)-2,3-dihydroxypropyl]amino}-5-oxopentanoato-334 κ3O1,O1',O1'')(3−)]gadolinium at a concentration of 0.5 M and the excipients tetraxetan, trometamol, and if needed for pH adjustment hydrochloric acid or sodium hydroxide. The drug product is a sterile, nonpyrogenic, clear, colorless to yellow aqueous solution presented in single-dose glass vials, single-dose prefilled plastic syringes, and glass pharmacy bulk packages. The structural formula of gadopiclenol is presented in Figure 1. The chelating moiety is macrocyclic. The inclusion of a pyridine ring within the ring structure of the macrocycle is a novel feature compared to previously approved GBCAs. Due to the stability of the gadolinium interaction with the chelating moiety, gadopiclenol is considered to be the substance furnishing the pharmacologic activity in this product.

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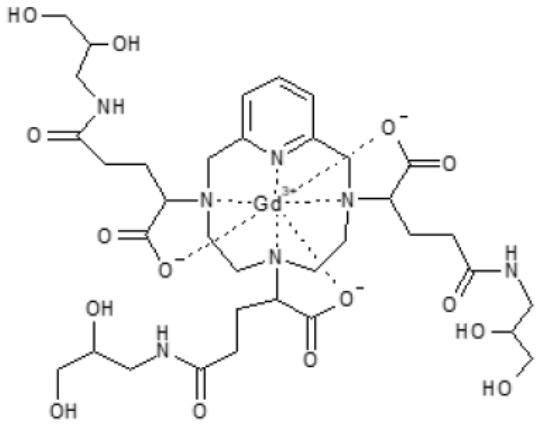
Figure 1. Structural Formula of Gadopiclenol



Source: NDA 216986 Clinical Overview Figure 2.5-2

The conditional thermodynamic stability constant for gadopiclenol is in the same range as other currently approved macrocyclic GBCAs but the kinetic stability and relaxivity are greater. Proposed shelf life of the drug product is 36 months when stored at 25°C (77°F). Excursions are permitted to 15 – 30°C (59 – 86 °F) with the caution statement of "Do not freeze" for the prefilled syringe presentations.

4.3. Clinical Microbiology

This section is not applicable to this NDA.

4.4. Devices and Companion Diagnostic Issues

One presentation of Elucirem, the prefilled plastic syringe, is a combination drug-device product. A consult was sent to the Center for Devices and Radiologic Health regarding the device constituent and no issues that would affect approvability of the NDA were identified.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

This NDA can be approved from a nonclinical perspective.

Gadopiclenol (Elucirem), is a new nonspecific, non-protein-binding, high-relaxivity, paramagnetic, macrocyclic, nonionic, GBCA for MRI (Fretellier et al. 2021). In this macrocylic pyclen-based contrast agent, the gadolinium ion (Gd^{3+}) is bound in a more thermodynamically and kinetically stable complex compared to GBCAs with linear or open-chain structures.

The Applicant conducted a comprehensive nonclinical program that supports the marketing authorization of Elucirem at the recommended dose of 0.05 mmol/kg body weight. This decision to approve is supported by the totality of nonclinical findings from pharmacology and

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toxicology studies that established imaging activity in rodent and non-rodent animal models, adequate safety margins by safety pharmacology (in vitro studies and CNS, respiratory, cardiovascular, and renal safety), general toxicology (expanded, single-dose, 14-day, and 28-day repeat-dose toxicity studies in rats and dogs), genotoxicity (in vitro and in vivo), developmental and reproductive toxicology, and other toxicology studies (Gd retention, local tolerance, and immediate hypersensitivity).

All nonclinical safety pharmacology, pharmacokinetic, and toxicology studies were conducted by or for the Applicant in accordance with Good Laboratory Practice (GLP) regulations.

In Vitro and In Vivo Pharmacology Studies

Pharmacodynamic studies included relaxivity measurements, brain tumor imaging in C6 Glioma rats, brain perfusion imaging in healthy rats and a rat brain tumor model, and pharmacokinetic (PK) biodistribution modelling by MRI.

Safety Pharmacology

In a battery of in vitro and in vivo safety pharmacology studies, significant findings were limited to a nonspecific effect in an in vitro human Ether-à-go-go-Related Gene (hERG) assay at ≥5 mmol/L (IC50>10 mmol/L, the no observed effect concentration (NOEC) was 2.5 mmol/L), a proconvulsant effect in Wistar rats at 5 mmol/kg only (the high dose, no observed adverse effect level (NOAEL) was 2.5 mmol/kg or 8-fold the clinical dose), and bronchoconstriction in anesthetized male Hartley guinea pigs at 5 mmol/kg only (the high dose, NOAEL was 2.5 mmol/kg or 10.9-fold the clinical dose). There were no significant safety findings identified for gadopiclenol for CNS safety pharmacology by functional observational battery (Irwin profile test) in Sprague Dawley rats (no observed effect level (NOEL) was 5 mmol/kg, the highest dose tested), ex vivo testing on action potential parameters in Purkinje fibers isolated from New Zealand White (NZW) female rabbits (NOEC was 10 mmol/L, the highest dose tested), cardiovascular safety pharmacology in telemetered Beagle dogs (NOEL was 2 mmol/kg, the highest dose tested or 22-fold the clinical dose), hemodynamic study in anesthetized Beagle dogs (NOEL was 2 mmol/kg, the highest dose tested or 22-fold the clinical dose), or respiratory safety and renal function pharmacology studies in Sprague Dawley rats (NOEL was 5 mmol/kg, the highest dose tested or 16-fold the clinical dose).

Pharmacokinetics/Absorption, Distribution, Metabolism, Excretion (PK/ADME)

The nonclinical PK/absorption, distribution, metabolism, excretion (ADME) program included in vitro studies of plasma protein and red blood cell binding (rat, dog, and human), in vitro metabolism by hepatic microsomes (rat, rabbit, dog, monkey, and human), and in vivo studies conducted in rats and dogs with ^{153}Gd labeled gadopiclenol. Toxicokinetics were evaluated as part of general toxicity (rats and dogs), developmental and reproductive toxicity (DART; rats and rabbits), and juvenile toxicity studies (rats). Gadopiclenol is intended for administration by the intravenous route and therefore absorption studies were limited to evaluation of oral bioavailability of gadopiclenol with respect to systemic exposure during lactation. Excretion

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(including via milk) was evaluated as part of PK studies conducted in rats and dogs. PK/ADME properties of gadopiclenol were similar between male and female animals. Gadopiclenol, following a single intravenous administration, was rapidly distributed to the vascular and extracellular compartments with low concentrations in many organs; the highest concentration of Gd was in the kidney. Gadopiclenol displayed minimal plasma protein binding (0%, 0.5%, and 1.4% in rats, humans, and dogs, respectively) and did not undergo any appreciable metabolism by in vitro studies. Gadopiclenol was excreted predominately by urinary excretion (81.7% and 78.7% in male and female rats, respectively, and 92.52% and 95.86% in male and female dogs, respectively). Oral bioavailability was low (<5%) and in DART studies, gadopiclenol displayed poor placental transfer and excretion in the milk (i.e., 0.3% of the administered dose at 6 hours).

Single and Repeat-Dose Toxicology

General toxicology and toxicokinetics of gadopiclenol by intravenous administration were evaluated in extended, single dose toxicity studies, and 14- and 28-day repeat-dose toxicity studies in mice (single dose acute toxicity study only), rats, and dogs based on their standard acceptance for non-clinical toxicology studies and the demonstrated drug exposure in these species following intravenous administration.

Overall, gadopiclenol-related findings were limited to transient, clinical observations in mice and rats which included decreased activity and swelling of extremities (fore- and hindlimbs), eyes, and face (nose and/or muzzle), generally at the high dose (12 mmol/kg in mice, ≥10 mmol/kg in rats) for single and repeat-dose studies. Clinical observations of swelling in rats were transient, occurring during the day of dosing (for single dose administration) or up to five days (for repeat-dose studies) and was not observed for the duration of the studies. Swelling of the face and ears was also observed in 2 dogs (males only) during the dosing phase of a 28-day repeat-dose toxicity study at the high dose (4 mmol/kg). Swelling was not observed consistently during the treatment phase and was not observed during the treatment-free recovery period. Gadopiclenol administration was associated with increased kidney weight in rats and dogs and correlated with microscopic findings of reversible, minimal to mild renal tubular cell vacuolation (expanded, single dose studies in rats and dogs at 10 mmol/kg and 4 mmol/kg, respectively).

In 14-day and 28-day repeat-dose toxicity studies in rats, gadopiclenol-related increases in kidney weight were correlated with microscopic findings of mild to severe renal tubular cell vacuolation, minimal to mild degeneration of the tubular epithelium (28-day study only at ≥5 mmol/kg/day), increased liver weight with centrilobular hepatocellular vacuolation (14-day study only), and macrophage accumulation that increased in severity with increasing dose. The macroscopic and histopathology findings in the kidney (increased kidney weight and moderate to severe tubular cell vacuolation) at 10 mmol/kg/day for the 14-day study were considered adverse but were partially reversible following a 14-day treatment-free recovery period (evaluated at 10 mmol/kg dose level only). Histopathology findings in the liver (vacuolation), lungs (histiocytosis), and lymph nodes (vacuolated macrophages) were partially reversible and minimal in severity. The histopathology finding of tubular epithelial degeneration in the kidneys at ≥5 mmol/kg/day for the 28-day study was considered adverse but was completely reversed

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following 28-day recovery period with partial reversibility of tubular epithelial vacuolation (evaluated at 10 mmol/kg dose level only). The NOAELs were 5 mmol/kg/day and 2.5 mmol/kg/day for 14-day and 28-day repeat-dose toxicity studies, respectively. The safety margins based on findings from 14-day and 28-day repeat-dose toxicity studies in rats were 16.1-fold and 8.1-fold, respectively, for a proposed clinical dose of 0.05 mmol/kg.

In 14-day and 28-day repeat dose toxicity studies in dogs, gadopiclenol dose-related increases in kidney weight (≥2 mmol/kg/day in males and 4 mmol/kg/day in females for 14-day studies and ≥1 mmol/kg/day in males and females and statistically significant in females only at 4 mmol/kg/day for 28-day studies) were correlated with macroscopic findings of tan discoloration of the kidney (28-day study only) and microscopic findings of minimal to mild renal tubular cell vacuolation (14-day study at all doses, and recovery animals at 4 mmol/kg/day), mild to marked renal tubular cell vacuolation (28-day study at all dose levels), and minimal to mild urothelial cell cytoplasmic vacuolation (28-day study at ≥1 mmol/kg/day). NOAELs were 4 mmol/kg/day for 14- and 28-day repeat-dose toxicity studies because the findings were reversible following treatment-free recovery period and/or considered class-related findings for contrast agents. The safety margins based on findings from 14-day and 28-day repeat-dose toxicity studies in dogs were 44.4-fold for a proposed clinical dose of 0.05 mmol/kg.

Genotoxicity, Carcinogenicity, and Reproductive Toxicity

Gadopiclenol was negative for genotoxic potential by a standard battery of in vitro and in vivo assays that included in vitro bacterial reverse mutation assay (Ames test), in vitro mammalian cell mutation assay (mouse lymphoma TK assay), and in vivo micronucleus assay in rats. Impurities that were identified in the drug substance and drug product were negative for genotoxic potential by in vitro assays. Carcinogenicity studies were not conducted and are not needed for single or infrequent use contrast agents.

In a fertility and early embryonic development study in rats, gadopiclenol at up to 10 mmol/kg/day had no effect on spermatozoa, reproductive and fertility indices, uterine implantation, or organ weights. Findings were limited to gadopiclenol-related decrease in food consumption and body weight (significant at 10 mmol/kg/day in males) and dose-dependent increase in tan discolored (3 of 11 males at 5 mmol/kg/day and 9 of 18 males at 10 mmol/kg/day) and enlarged kidneys (2 of 22 at 2.5 mmol/kg/day, 9 of 21 at 5 mmol/kg/day, and 17 of 21 at 10 mmol/kg/day) in males only that correlated with microscopic findings in repeat-dose toxicity studies. Effects on food consumption, body weight, and macroscopic findings in the kidney were considered adverse at 10 mmol/kg/day. Therefore, the NOAEL for parenteral toxicity in males and females was 5 mmol/kg/day or 16.1-fold the proposed clinical dose of 0.05 mmol/kg whereas the NOAEL for reproductive performance and fertility in males and females was 10 mmol/kg/day.

In an embryo-fetal development study in rats, findings were limited to clinical observations in the dams which included swelling (forefeet and/or nose/muzzle), tail discoloration, and lower gestational weight gain (with reduced food consumption) at 10 mmol/kg/day. There were no findings for embryo-fetal toxicity as determined by uterine implantation data, fetal sex ratios,

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fetal body weights, or fetal external, visceral, or skeletal examination. Therefore, the NOAEL for maternal toxicity was 5 mmol/kg/day or 16.1-fold the proposed clinical dose of 0.05 mmol/kg whereas the NOAEL for developmental toxicity was 10 mmol/kg/day. In an embryo-fetal development study in rabbits, clinical observations included decreased activity, aggressive behavior, reduced defecation, thin appearance, and lower gestational weight (with reduced food consumption) at 5 mmol/kg/day. There were no findings for embryo-fetal toxicity as determined by uterine implantation data, fetal sex ratios, or fetal external, visceral, or skeletal examinations; findings were limited to reduced fetal body weights at 5 mmol/kg/day. Therefore, the NOAEL for maternal and developmental toxicity was 2.5 mmol/kg/day and the drug was not considered teratogenic at ≤5 mmol/kg/day, yielding a safety margin of 16.1-fold the proposed clinical dose of 0.05 mmol/kg.

In a prenatal and postnatal development study in rats, gadopiclenol-related dose-dependent findings were limited to clinical observations in the dams and included swelling of the limbs and/or muzzle, partly closed eyes, reduced activity, irregular breathing, and redness of the extremities, which were considered adverse at 10 mmol/kg/day and considered non-adverse at ≤5 mmol/kg/day. Based on the findings, the NOAEL for maternal toxicity was 5 mmol/kg/day and the NOAEL for postnatal development (including reproductive performance) was 10 mmol/kg/day with safety margins of 16.1-fold and 32.1-fold, respectively, for a proposed clinical dose of 0.05 mmol/kg.

In a juvenile toxicity study in rats, gadopiclenol-related findings were limited to microscopic findings of cortical tubular vacuolation at all dose levels following repeat dosing that was reversible following a treatment-free recovery period. There were no gadopiclenol-related findings for postnatal development, sexual maturation, or neurobehavioral assessment. Tissue Gd levels increased with increasing dose in all tissues, with or without recovery following single or repeat-dosing; greatest levels were observed in the kidneys > liver > femur > skin > cerebellum > brain and decreased during the recovery period most quickly in the kidneys > femur > cerebellum > liver > skin. The NOAEL for juvenile toxicity was 2.5 mmol/kg/day with a safety margin of 8.1-fold for a proposed clinical dose of 0.05 mmol/kg.

Other Nonclinical Studies

The Applicant conducted other nonclinical studies which are briefly summarized below.

In a local tolerance study conducted in NZW rabbits, gadopiclenol at 0.6 mmol/kg was tolerated by the intravenous route (intended clinical route) and intra-arterial route with reversible histopathology findings. There was poor local tolerance to gadopiclenol by the perivenous route at 0.25 mmol/injection. In a study conducted to evaluate hypersensitivity reactions in the guinea pig, intravenous administration of gadopiclenol did not induce any signs of immediate hypersensitivity in sensitized animals.

Potential impurities in gadopiclenol drug substance and drug product were evaluated for genotoxic potential by in vitro bacterial reverse mutation assay (Ames test) and in vitro mammalian mutation lymphoma assay. Impurities (b) (4) and tested

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metabolites were negative for genotoxic potential. Impurity [redacted] (b) (4) was positive by Ames test only for the TA98 strain and was negative for all other tester strains.

The Applicant conducted two non-GLP studies to evaluate MRI signal enhancement and Gd retention following repeat administration of gadopiclenol or representative linear or macrocyclic GBCAs to Sprague Dawley rats. In one study, gadopiclenol was associated with 2-fold to 3-fold greater levels of total Gd compared to gadobutrol in the body (kidney, liver, bone, skin) for all timepoints at equimolar dose whereas levels of total Gd were similar in the CNS (cerebellum, cortex, brain stem, and subcortical regions). Levels of Gd associated with repeat dosing of gadodiamide were much greater than gadopiclenol or gadobutrol and paralleled T1 signal enhancement over the 12-month recovery period for cerebellum and kidney. In another study, there was no T1 signal enhancement in the deep cerebellar nuclei (DCN) following repeat dosing with gadopiclenol and treatment-free recovery period. Transient signal enhancement was observed in the choroid plexus and 4th ventricle and returned to baseline by the end of the study.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

5.3.1. Introduction

Gadopiclenol (also referred to as G02377/P03277) is a macrocyclic nonionic GBCA with high relaxivity (r_1=12.2 $mM^{-1}{\cdot}s^{-1}$ at 1.41T in water) proposed for use with MRI of the CNS and body. The recommended clinical dose of gadopiclenol for all indications is 0.05 mmol/kg body weight, equivalent to 0.1 mL/kg body weight, which is a lower dose compared to other macrocyclic GBCAs due to its higher relaxivity. Gadopiclenol will be administered as a single dose via an intravenous bolus injection [redacted] (b) (4). The chemical structure of gadopiclenol is shown below in Figure 2:

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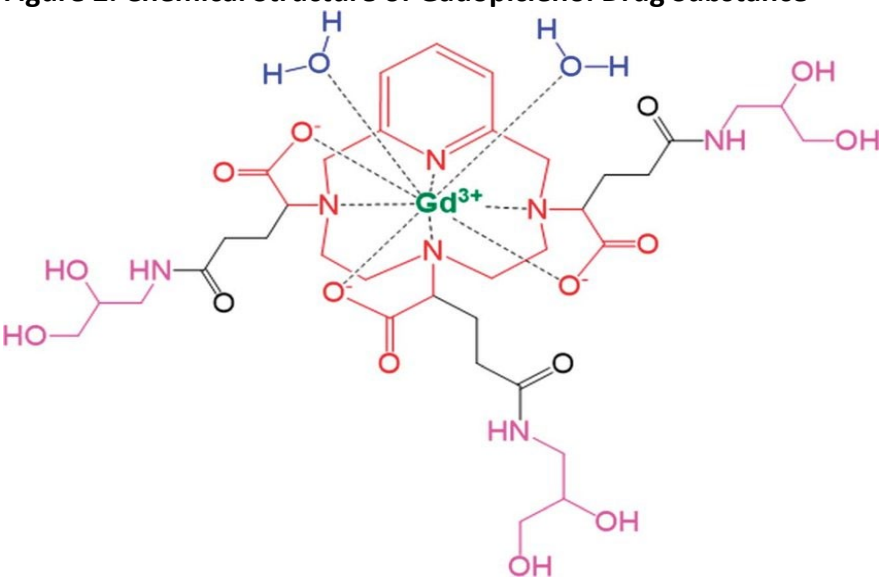
Figure 2. Chemical Structure of Gadopiclenol Drug Substance



Source: CAS # 933983-75-6 (gadopiclenol)
Molecular Formula/Molecular Weight: $C_{35}H_{54}GdN_7O_{15}$ / 970.11 g/mol

5.3.2. Mechanism of Action

The mechanism of pharmacodynamic effect of Gd on MRI signal is well documented. A Gd ion has paramagnetic properties due to its seven unpaired electrons leading to a high magnetic moment and labile water coordination properties. Gd modifies the relaxation times of water protons in blood and tissues, a mechanism also referred to as 'shortening'. Shortening results in increased signal intensity in T_1-weighted sequences.

5.3.3. Proof-of-Principle Studies

A notable and key physicochemical characteristic among the GBCA class is relaxivity. Relaxivity is the degree to which the agent can alter the longitudinal or transverse water relaxation rate constant R_1 ($1/T_1$) or R_2 ($1/T_2$), respectively, normalized to the concentration of the contrast agent. Longitudinal and transverse relaxivity are denoted as r_1 and r_2, respectively.

The Applicant conducted an in vivo proof-of-concept study to compare contrast following intravenous administration of gadopiclenol to representative GBCAs, including gadobenic acid (MultiHance), gadobutrol (Gadavist), and gadoteric acid (Dotarem) (Study No. ER-12-00029). A linear relationship was observed between dose and contrast-to-noise ratio (CNR) in rat C6 glioma tumor at gadopiclenol doses between 0.025 and 0.1 mmol Gd/kg. The results obtained in the rat glioma model were compared with the findings from representative GBCAs at their clinical dose of 0.1 mmol Gd/kg. The CNR for gadopiclenol at this dose was about twofold higher than was obtained with the other GBCA products evaluated. In this model, the 0.075 mmol Gd/kg dose of gadopiclenol was predicted to provide a 30% increase in CNR when compared to gadobenic acid, gadobutrol, or gadoteric acid administered at 0.1 mmol Gd/kg.

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5.3.4. Safety Pharmacology

Gadopiclenol was evaluated in a comprehensive battery of safety pharmacology studies which included an in vitro study to assess the electrophysiological effects of gadopiclenol on hERG current (Study No. GDX-33-024) and an ex vivo study to evaluate effects on action potential parameters in rabbit Purkinje fiber (Study No. GDX-33-034). Safety pharmacology studies conducted in rats evaluated gadopiclenol CNS safety and proconvulsant effects (Study No. GDX-33-020 and Study No. GDX-33-042), respiratory safety (Study No. GDX-33- 021) and renal safety (Study No. GDX-33-022). Cardiovascular (CV) safety pharmacology and hemodynamic studies were conducted in Beagle dogs (Study No. GDX-33-025 and GDX-33-026) and potential for bronchoconstriction was evaluated in Hartley guinea pigs (Study No. GDX-33-023).

5.3.5. Evaluation of the CNS

Study Title/Number: G03277.023 - Irwin Profile Test in the Rat After a Single Intravenous Administration / GDX-33-020

GLP Compliance: Yes

QA Statement: Yes

Study Objective

The objective of the Irwin test was to examine the potential effect of gadopiclenol (G03277.023) on a battery of behavioral and physiological parameters covering central and peripheral nervous system functions following intravenous administration of 1.25, 2.5, and 5 mmol/kg gadopiclenol and negative control (0.9% sodium chloride) in male Sprague Dawley rats (n=6/group, 8 weeks of age). Irwin test parameters (spontaneous activity, autonomic functions, gait and muscle tone, motor and sensory reflexes, physiological parameters) were evaluated prior to dosing (0 hr) and at 0.5, 1, 2, 5, and 24 hr post-dose.

Key Findings

- A single intravenous injection (slow bolus administered over 2 min) of gadopiclenol at 1.25, 2.5, or 5 mmol/kg to male Sprague Dawley rats did not significantly affect spontaneous activity, autonomic functions, gait and muscle tone, or motor and sensory reflexes.
- At a dose level of 5 mmol/kg, 0.5 hr post dose, a statistically significant change in the physiological parameter body temperature (-0.7°C) was observed relative to vehicle control (+0.2°C) but was not considered biologically relevant.
- There were no clinical signs or mortalities in the 24 hr period following a single intravenous injection of gadopiclenol at any of the dose levels evaluated.

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Conclusion

A single intravenous injection of gadopiclenol at 1.25, 2.5, or 5 mmol/kg to male Sprague Dawley rats did not affect behavioral or physiological parameters representative of main central and peripheral nervous system functions.

Study Title/Number: Evaluation of Proconvulsant Effect Following Intravenous Administration in the Rat / GDX-33-042

GLP Compliance: Yes

QA Statement: Yes

Study Objective

The objective of this GLP-compliant study was to evaluate any potential proconvulsant effect of gadopiclenol following intravenous administration at 1.25, 2.5, and 5 mmol/kg (representing 4, 8, and 16 times the clinical dose after body surface area scaling), negative control (0.9% sodium chloride), and positive control (55 mg/kg caffeine) in Wistar rats (n=6/sex/group). The proconvulsant potential of gadopiclenol was evaluated by infusion of a solution of 5.5 mg/mL pentylenetetrazole (PTZ) at a rate of 0.5 mL/kg/min beginning 5 min post-infusion of the test agent and monitoring the time of onset of PTZ-induced seizures relative to negative control (1083±48 seconds or 49.6±2.2 mg/kg PTZ) and positive control (887±36 seconds or 40.7±1.7 mg/kg PTZ). A reduction in the time of onset of seizures would indicate a proconvulsant effect.

Key Findings

- A single intravenous injection of gadopiclenol at 1.25 or 2.5 mmol/kg to Wistar rats did not induce a more rapid onset of PTZ-induced seizures (994±32 and 1018±27 sec or 45.5±1.5 and 46.6±1.3 mg/kg PTZ, respectively) compared to vehicle control.
- Gadopiclenol at 5 mmol/kg induced a statistically significant decrease in the time of onset of PTZ-induced seizures (836±40 sec or 38.3±1.8 mg/kg of PTZ, i.e. -23% from vehicle, $p<0.01$).

Conclusion

Gadopiclenol was positive for proconvulsant effects only at the high dose (5 mmol/kg) and no statistically significant effect on the time of seizure occurrence was observed at the low (1.25 mmol/kg) or mid (2.5 mmol/kg) dose level. Based on these findings, the NOAEL of intravenously administered gadopiclenol was 2.5 mmol/kg or 8-fold the proposed clinical dose of 0.05 mmol/kg.

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5.3.6. Evaluation of the Cardiovascular System

Study Title/Number: Effects of G03277.023 on hERG Channel Stably Expressed in HEK-293 Cells / GDX-33-024

GLP Compliance: Yes

QA Statement: Yes

Study Objective

The objective of the study was to examine the in vitro effects of gadopiclenol at concentrations of 1.25, 2.5, 5, and 10 mmol/L on hERG potassium channel current (a surrogate for IKr, the rapidly activating delayed rectifier cardiac potassium current) at near-physiological temperatures.

Key Findings

- Gadopiclenol produced a concentration-dependent inhibition of hERG tail current amplitude by 6.2±1.1%, 15.1±0.9%, 23.6±1.0%, and 38.8±1.6% inhibition.
- Gadopiclenol effects did not reverse after washout with vehicle.
- Gadopiclenol effects on hERG current were statistically significant at ≥5 mmol/L.

Conclusion

Gadopiclenol produced a concentration-dependent inhibition of hERG current and was statistically significant at ≥5 mmol/L, therefore the NOEC was considered to be 2.5 mmol/L. Gadopiclenol inhibition of hERG current was attributed to a nonspecific effect due to hyperosmolarity of the test article solution (also observed for other GBCAs) and not considered to be biologically relevant.

Study Title/Number: Effects of G03277.023 on the Action Potential Parameters in Isolated Rabbit Purkinje Fibers / GDX-33-034

GLP Compliance: Yes

QA Statement: Yes

Study Objective

The objective of the study was to examine the ex vivo effects of gadopiclenol at up to 10 mmol/L and negative control (2% distilled water) on action potential properties of Purkinje fibers isolated from NZW female rabbits (n=6/group); validity of the assay was demonstrated by positive control, quinidine (10 µmol/L).

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Key Findings

- Gadopiclenol at up to 10 mmol/L had no effect on action potential parameters when compared to negative control; depolarization at 1 Hz stimulation was recorded at 10 mmol/L but was not physiologically relevant.

Conclusion

Gadopiclenol was negative for effects on action potential properties at all dose levels tested in isolated rabbit Purkinje fibers. The NOEC was considered to be 10 mmol/L.

Study Title/Number: Effects of G03277.023 on Arterial Blood Pressure, Heart Rate and Electrocardiogram, Following Intravenous Administration in the Conscious Beagle Dog Monitored by Telemetry / GDX-33-025

Study Objective

This study evaluated the effects of gadopiclenol at up to 2 mmol/kg on arterial blood pressure, heart rate, electrocardiogram (ECG), and body temperature following intravenous administration in the conscious beagle dog (n=3/sex by Latin Square study design) monitored by telemetry for at least 1.5 hr pre-dose and 24 hr post-administration.

Key Findings

- Gadopiclenol, administered intravenously at the dose levels of 0.5, 1, or 2 mmol/kg (5x, 11x, and 22x the proposed clinical dose of 0.05 mmol/kg), did not affect the general health status, body weight gain, or body temperature of the animals throughout the study period.
- Gadopiclenol at up to 2 mmol/kg did not affect the heart rate, systolic, diastolic, or mean arterial blood pressure, or ECG intervals (PR, QRS, RR, QT, and QTcV).

Conclusion

A single intravenous injection of gadopiclenol at 0.5, 1, or 2 mmol/kg to Beagle dogs did not affect the cardiovascular system (heart rate and systolic, diastolic, mean arterial, and pulse pressures), ECG intervals (PR, QRS, RR, QT, and QTcV), or body temperature. Based on the absence of significant findings, the NOEL was 2 mmol/kg, the highest dose tested.

5.3.7. Evaluation of the Respiratory System

Study Title/Number: G03277.023 - Respiratory Function Evaluation in the Conscious, Freely Moving Rat by Whole Body Plethysmography Method After Single Intravenous Injection / GDX-33-021

GLP Compliance: Yes

QA Statement: Yes

Reference ID: 5048631

Study Objective

The objective of this GLP study was to examine the effects of a single 2 min intravenous injection of gadopiclenol at up to 5 mmol/kg on respiratory function parameters in the conscious, unrestrained male Sprague Dawley rat (n=8/group), using whole body barometric plethysmography for up to 240 min post-dose.

Key Findings

- No gadopiclenol-related mortality or clinical observations were observed at dose levels of 1.25, 2.5, or 5 mmol/kg (4, 8, or 16x the proposed clinical dose of 0.05 mmol/kg) throughout the study period.
- Gadopiclenol at up to 5 mmol/kg did not exert any relevant effects on respiratory system parameters (respiratory rate, inspiratory, expiratory, and relaxation times, tidal and minute volumes, peak inspiratory and expiratory flows, and the enhanced pause).

Conclusion

A single intravenous injection of gadopiclenol at 1.25, 2.5, or 5 mmol/kg to Sprague Dawley rats did not affect the respiratory system. Under the experimental conditions of the study, the NOEL was determined as 5 mmol/kg (16-fold the proposed clinical dose).

Study Title/Number: Effects of G03277.023 - Bronchoconstrictive Activity in the Anaesthetized Guinea Pig/GDX-33-023

GLP Compliance: Yes

QA Statement: Yes

Study Objective

The objective of this GLP study was to evaluate the bronchoconstrictive activity (by air overflow method) of gadopiclenol at 1.25, 2.5, and 5 mmol/kg, negative control (0.9% sodium chloride), and positive control (histamine 10 µg/kg) in the male anaesthetized Hartely guinea pig (n=6/group).

Key Findings

- Gadopiclenol administered intravenously at 1.25 mmol/kg did not induce any significant bronchoconstrictive activity in the anaesthetized guinea pig.
- Slight and transient bronchoconstriction (14% decrease in tidal volume for 30 sec) occurred 2.5 min after start of infusion of gadopiclenol intravenously at 2.5 mmol/kg.
- Gadopiclenol administered at 5 mmol/kg induced slight bronchoconstriction (14% to 19% decrease in tidal volume), reaching maximum at 3.2 min after start of infusion and lasting at least 3 min in 2/6 animals. In 1/6 animals, marked bronchoconstriction (88% decrease in tidal volume) was induced from 2 to 5 min after start of infusion and was associated with transient muscular spasms.

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Conclusion

Under the experimental conditions of the study, intravenous injection of gadopiclenol induced a slight to marked bronchoconstriction in 3/6 animals at the dose level of 5 mmol/kg and was considered biologically relevant. The NOAEL was determined as 2.5 mmol/kg (10.9-fold the proposed clinical dose).

5.3.8. Evaluation of Renal Function

Study Title/Number: G03277.023 - Renal Function Evaluation in the Rat With a Saline Overload After Single Intravenous Administration / GDX-33-022

GLP Compliance: Yes

QA Statement: Yes

Study Objective

The objective of this study was to assess any potential effects of gadopiclenol at 1.25, 2.5, and 5 mmol/kg, negative control (0.9% sodium chloride), and positive control (furosemide 40 mg/kg) on urine output, serum/urine electrolyte balance, serum and urinary biochemistry, and glomerular filtration rate (creatinine clearance) in male Sprague Dawley rats (n=8/group) with a saline overload following a single intravenous administration.

Key Findings

- No gadopiclenol-related mortality was observed at dose levels of 1.25 or 2.5 mmol/kg (4x or 8x the proposed clinical dose of 0.05 mmol/kg) throughout the study period (up to 6 hr following saline gavage).
- One death at 5 mmol/kg occurred 45 min following dosing but was determined to be unrelated to treatment or procedure.
- Gadopiclenol administered intravenously at up to 5 mmol/kg did not induce any clinical signs or any change in the serum sodium, potassium, chloride, or creatinine concentrations or in the serum osmolality. Urine sodium and chloride were decreased at the 5 mmol/kg dose level only.
- Gadopiclenol induced an increase in urine osmolality (23, 35, and 27% at 1.25, 2.5, and 5 mmol/kg, respectively) and was associated with a dose-related decrease in free water clearance that was statistically significant at ≥2.5 mmol/kg (26, 37, and 73% decrease at 1.25, 2.5, and 5 mmol/kg, respectively).

Conclusion

Under the experimental conditions of the study, intravenous injection of gadopiclenol induced an increase in urine osmolality at the tested dose levels and corresponding dose-related decreases in free water clearance that were significant at ≥2.5 mmol/kg. Glomerular filtration rate and excretion of sodium, potassium, and chloride were not affected at any dose level. The

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NOAEL was therefore considered as 1.25 mmol/kg (4-fold the proposed clinical dose) based on gadopiclenol effects on free water clearance.

5.4. ADME/PK

Table 2. ADME/PK Study Findings

Type of Study	Major Findings
Absorption	
The Pharmacokinetics of Total Radioactivity Following Single Oral Administration of [^{153}Gd]-gadopiclenol in Male Sprague Dawley Rats (GDX-33-051)	Following a single oral administration of [^{153}Gd]-gadopiclenol (0.6 mmol/kg) to male albino rats, mean T_{max} and C_{max} were 1 hr and 14.7 nmol equiv/g, respectively. Mean AUC_{0-t} was 49.0 nmol equiv.h/g. Urinary excretion and fecal elimination accounted for 0.5% and 94.0%, respectively, over a 24 hr collection period; plasma concentrations were low. Gadopiclenol was poorly absorbed when administered by the oral route.
The Disposition of [^{153}Gd]-P03277 (gadopiclenol) in the Rat Following Intravenous Administration – Pharmacokinetic Evaluation (GDX-33-071)	Systemic exposure to gadopiclenol by the intravenous route (total radioactivity estimates of geometric mean C_0 and AUC_{tlast}) increased in a proportional manner across the dose range (0.6, 1.2, and 3 mmol/kg) in male and female rats and there were no sex differences in systemic exposure. Geometric mean CL, V_d and $t_{1/2}$ values ranged from 366 to 468 mL/h/kg, 193 to 312 mL/kg, and 0.294 to 0.505 hr, respectively, and were not notably different based on administered dose. V_d indicated that gadopiclenol was distributed to the extracellular space, consistent with other GBCAs.
Distribution	
The Tissue Distribution of Total Radioactivity in the Rat Following Intravenous Administration of [^{153}Gd]-gadopiclenol. (Quantitative Whole Body Autoradiography) (GDX-33-004)	Radioactivity of [^{153}Gd]-gadopiclenol (1 mmol/kg intravenously) was widely distributed to body tissues at 10 min post-dose in Sprague Dawley rats (n=27/sex, 3/sex/time point) with greatest levels in skin > muscle > blood > kidney and liver. By 4 hr post-dose, gadopiclenol (by % injected dose) was low for all organs and tissues except excretory organs, urinary tract, and gastrointestinal tract.
The In Vitro Plasma Protein Binding and Blood Cell Partitioning of [^{153}Gd]-gadopiclenol in Rat, Dog and Human	In vitro, [^{153}Gd]-gadopiclenol was not bound to plasma proteins of rat and there was minimal binding to the plasma proteins of dog and human. [^{153}Gd]-

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Type of Study	Major Findings
(GDX-33-007)	gadopiclenol was poorly bound to RBCs in vitro, with a range of 6.0%-16.7% binding to rat RBCs, 0.0%-3.2% to dog RBCs, and no appreciable binding to human RBCs (0.0%-0.1%).
The Placental Transfer of Total Radioactivity Following Single Intravenous Administration of [^{153}Gd]-gadopiclenol in Time-Mated Sprague Dawley Rats (Quantitative Whole-Body Autoradiography) (GDX-33-049)	After a single intravenous administration of gadopiclenol (0.6 mmol/kg) to pregnant rats on gestational day 18, total radioactivity was widely distributed primarily to maternal tissues by 10 min post-dose. Mean concentrations in the amniotic fluid and fetal tissues were low relative to placenta. Concentration in fetal brain and liver were very low and unchanged over the 24 hr time course of the study, suggesting little or no placental transfer.
Metabolism	
The Comparative Metabolism of [^{153}Gd]- gadopiclenol in Rat, Dog, Rabbit, Monkey and Human Liver Microsomes (GDX-33-008)	Under the conditions of this in vitro study, [^{153}Gd]-gadopiclenol was metabolically stable (≥95% parent compound remaining) up to 2 hr and no additional components or metabolites were observed in any of the species studied.
Excretion	
The Disposition of [^{153}Gd]-gadopiclenol in the Rat Following Intravenous Administration (GDX-33-005)	After a single intravenous administration of gadopiclenol (0.6, 1.2, and 3 mmol/kg), the highest mean plasma concentration (by [^{153}Gd]-gadopiclenol) was measured at 5 min post-dose. The mean plasma concentration then decreased over time but remained above the limit of detection at 24 hr post-dose. Systemic exposure increased in a dose-proportional manner and no sex differences were reported. Renal clearance was the major route of elimination with 82% ±5% and 79% ±9% recovered via the urine by 168 hr in male and female rats, respectively. There was limited fecal excretion with 4.8% ±0.5% and 8.7% ±3% in male and female rats, respectively. Elimination half-life ranged between 0.85 and 1.43 hr. V_d was consistent with distribution of drug within the extracellular water volume.
The Disposition of [^{153}Gd]- gadopiclenol in the Dog Following Intravenous Administration	The major route of excretion for gadopiclenol was via the urine, as determined by [^{153}Gd]-gadopiclenol at a target dose of 0.2 mmol/kg by intravenous

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Type of Study	Major Findings
(GDX-33-006)	administration. Urine (at 168 hr post-dose) accounted for 93% ±2% and 96% ±7% of the administered radioactivity in male and female dogs, respectively. There was limited fecal excretion with 6.4±1.5% and 4.8% ±2.8% in male and female dogs, respectively. Near-total excretion was rapid with 95%-99% of the injected dose excreted in the first 24 hr. PK properties were comparable between male and female dogs with mean estimates of renal clearance of 80%-90% of total clearance.
The Secretion of Total Radioactivity in Milk Following Single Intravenous Administration of [^{153}Gd]-gadopiclenol in the Lactating Sprague Dawley Rat (GDX-33-050)	Following a single intravenous administration of gadopiclenol (0.6 mmol/kg) to lactating female rats, mean concentrations in milk (by [^{153}Gd]-gadopiclenol) were very low, peaking at 6 hr post-dose, with mean concentrations in milk, pups, and mammary glands decreasing at 24 hr post dose. The mean % of injected dose in the pups was 0.3% and 0.2% at 6 hr and 24 hr post-dose, respectively. Based on the findings, elimination in milk and subsequent oral bioavailability were very low.
TK Data From General Toxicology Studies	
An expanded single dose acute intravenous toxicity study in rats (GDX-33-014)	There were no significant differences in the TK parameters calculated for male and female rats. <u>Systemic Exposure:</u> Systemic exposure by combined mean $AUC_{0\text{-}inf}$, $AUC_{0\text{-}6hr}$, and C_{max} increased with increasing dose in a more than dose proportional manner (between 2.5 and 10 mmol/kg and greater between 5 and 10 mmol/kg) and was similar between sexes. The NOAEL for gadopiclenol under the conditions of the study was considered by the reviewer as 10 mmol/kg/dose. Systemic exposure by C_{max} and $AUC_{0\text{-}inf}$ (mean) at the NOAEL was 31,500 µg/mL and 35,200 µg.h/mL, respectively, for males and 29,000 µg/mL and 32,400 µg.h/mL, respectively, for females.
An expanded single dose acute intravenous toxicity study in dogs (GDX-33-016)	There were no significant differences in the TK parameters calculated for male and female dogs.

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Type of Study	Major Findings
	Systemic Exposure: Systemic exposure by combined mean $AUC_{0\text{-}inf}$, $AUC_{0\text{-}8hr}$, and C_{max} increased with increasing dose in an approximate dose proportional manner (between 1 and 4 mmol/kg) and was similar between sexes. The NOAEL for gadopiclenol under the conditions of the study was considered by the reviewer as 4 mmol/kg/dose. Systemic exposure by C_{max} and $AUC_{0\text{-}inf}$ (mean ± SD) at the NOAEL was 9,220±926 µg/mL and 14,100±2310 µg.h/mL, respectively, for males and 9,580±1,280 µg/mL and 14,300±3,230 µg.h/mL, respectively, for females.
2-week intravenous toxicity study in rats with a 2-week recovery period (GDX-33-015)	There were no significant differences in the TK parameters calculated for male and female rats. Systemic Exposure: Systemic exposure by combined mean $AUC_{0\text{-}inf}$, $AUC_{0\text{-}6hr}$, and C_{max} increased with increasing dose in an approximate dose proportional manner (between 2.5 and 10 mmol/kg) on Days 1 and 14 and was similar between sexes. There was little to no accumulation after repeat dosing for 2 weeks (combined mean accumulation ratios ranged from 0.899 to 1.38). The NOAEL for gadopiclenol under the conditions of the study was considered by the reviewer as 5 mmol/kg/dose. Systemic exposure (by C_{max} and $AUC_{0\text{-}6hr}$) at the NOAEL was 16,900 µg/mL and 9,140 µg.h/mL, respectively, for males and 17,000 µg/mL and 8,890 µg.h/mL, respectively, for females.
A 28-day intravenous toxicity study in rats with a 28-day recovery period (GDX-33-039)	There were no significant differences in the TK parameters calculated for male and female rats. Systemic Exposure: Systemic exposure by combined mean $AUC_{0\text{-}inf}$ and C_{max} increased with increasing dose in an approximate dose proportional manner (between 2.5 and 10 mmol/kg) in males and females on Days 1 and 28 and was similar between sexes. There was little to no accumulation after repeat dosing for 4 weeks (mean accumulation ratios were 1.24, 1.01, and 0.979 at 2.5, 5, and 10 mmol/kg).

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Type of Study	Major Findings
	The NOAEL for gadopiclenol under the conditions of the study was considered by the reviewer as 2.5 mmol/kg/dose. Systemic exposure by C_{max} and $AUC_{0\text{-}6hr}$ at the NOAEL was 9,090 µg/mL and 5,300 µg.h/mL, respectively, for males and 9,300 µg/mL and 4,430 µg.h/mL, respectively, for females.
2-week intravenous toxicity study in dogs with a 2-week recovery period (GDX-33-017)	There were no significant differences in the TK parameters calculated for male and female dogs. Systemic Exposure: Systemic exposure by combined mean $AUC_{0\text{-}inf}$, $AUC_{0\text{-}8hr,}$ and C_{max} increased with increasing dose in an approximate dose proportional manner (between 1 and 4 mmol/kg) in males and females on Days 1 and 14 and was similar between sexes. There was little to no accumulation after repeat dosing for 2 weeks (combined mean accumulation ratios ranged from 0.904 to 0.985). The NOAEL for gadopiclenol under the conditions of the study was considered by the reviewer as 4 mmol/kg/dose. Systemic exposure by C_{max} and $AUC_{0\text{-}8hr}$ (mean ± SD) at the NOAEL was 8,000±2,120 µg/mL and 14,500±3,980 µg.h/mL, respectively, for males and 9,300±1,210 µg/mL and 14,800±2,800 µg.h/mL, respectively, for females.
28-day intravenous toxicity study in dogs with a 28-day recovery period (GDX-33-040)	There were no significant differences in the TK parameters calculated for male and female dogs. Systemic Exposure: Systemic exposure by mean $AUC_{0\text{-}8hr}$ and C_{max} increased with increasing dose in an approximate dose proportional manner (between 1 and 4 mmol/kg) in males and females on Days 1 and 28. The increase in systemic exposure was similar between sexes. There was little to no accumulation after repeat dosing for 4 weeks (mean accumulation ratios were 0.952, 0.845, and 1.07, at 1, 2, and 4 mmol/kg). The NOAEL for gadopiclenol under the conditions of the study was considered by the reviewer as 4 mmol/kg/dose. Systemic exposure by C_{max} and $AUC_{0\text{-}8hr}$ (mean ± SD) at the NOAEL was 8,420±766 µg/mL and

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Type of Study	Major Findings
	15,900±1,750 µg.h/mL, respectively, for males and 11,000±3,890 µg/mL and 20,100±7,440 µg.h/mL, respectively, for females.
TK Data From Reproductive Toxicology Studies	
A study of fertility and early embryonic development to implantation in rats (GDX-33-038)	Systemic Exposure: Systemic exposure by $AUC_{0\text{-}6hr}$ increased with increasing dose in an approximately dose proportional manner from 2.5 to 5 mmol/kg/day and in a greater than dose proportional manner from 2.5 to 10 mmol/kg/day on Day 1. On Day 44, $AUC_{0\text{-}6hr}$ increased in an approximately dose proportional manner across the dose range. There was little to no accumulation after repeat dosing during the dosing phase of the fertility and early embryonic development study. In females, mean accumulation ratios were 1.10, 0.955, and 0.684 at 2.5, 5.0, and 10.0 mmol/kg/day, respectively. In males, accumulation ratios were 1.01, 0.986, and 0.537 at 2.5, 5.0, and 10.0 mmol/kg/day, respectively. The NOAEL for gadopiclenol under the conditions of the study was considered by the reviewer as 10 mmol/kg/dose. Systemic exposure by C_{max} and $AUC_{0\text{-}6hr}$ (mean ± SD) at the NOAEL (reproductive performance and fertility) was 50,300 µg/mL and 36,100 µg.h/mL, respectively, for males on Day 44 and 45,700±5,920 µg/mL and 35,100 µg.h/mL, respectively, for females on GD 7.
A study for effect on embryofetal development in rats with a toxicokinetic evaluation (GDX-33-035)	Systemic Exposure: Systemic exposure by C_{max} and $AUC_{0\text{-}6hr}$ increased with increasing dose on GD 6 and GD 17 in an approximately dose proportional manner and did not significantly change following repeated administration of gadopiclenol (2.5, 5, and 10 mmol/kg/day) through the gestational period (accumulation ratios were 1.39, 1.34, and 0.853 at 2.5, 5, and 10 mmol/kg, respectively). The NOAEL for gadopiclenol under the conditions of the study was considered by the reviewer as 10 mmol/kg/dose. Systemic exposure by C_{max} and $AUC_{0\text{-}6hr}$ at the NOAEL was 31,900 µg/mL and 29,500 µg.h/mL, respectively, for pregnant females on GD 17.

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Type of Study	Major Findings
A GLP Pre- and Post-Natal Development Study of Gadopiclenol by the Intravenous (5-Minute Infusion) Route in the Rat (GDX-33-056)	Systemic Exposure: Systemic exposure by mean C_{max} increased with increasing dose in an approximately dose proportional manner on GD 6 and LD 20 whereas mean AUC_{0-24hr} increased in a greater than dose proportional manner on GD 6 and an approximately dose proportional manner on LD 20. Mean accumulation ratios were 0.989, 0.437, and 0.333 at 2.5, 5, and 10 mmol/kg, respectively. The NOAEL for gadopiclenol under the conditions of the study was considered by the reviewer as 5 mmol/kg/day. Systemic exposure by C_{max} and AUC_{0-24hr} at the NOAEL was 17,600 µg/mL and 20,800 µg.h/mL, respectively, for F0 dams on GD 6 and 16,500 µg/mL and 11,000 µg.h/mL, respectively, on LD 20.
A study for the effects on embryo-fetal development in rabbits with a toxicokinetic evaluation (GDX-33-036)	Systemic Exposure: Systemic exposure by mean C_{max} and AUC_{0-6hr} values increased with increasing dose in an approximately dose proportional manner on GD 6 and 19 (mean accumulation ratios were 0.864 and 0.782 at 1 and 2.5 mmol/kg, respectively). The NOAEL for gadopiclenol under the conditions of the study was considered by the reviewer as 2.5 mmol/kg/day. Gadopiclenol was not teratogenic in the rabbit at dose levels ≤5 mmol/kg/day. Systemic exposure by C_{max} and AUC_{0-6hr} at the NOAEL (developmental toxicity) was 12,450±1,620 µg/mL and 13,500±1,040 µg.h/mL, respectively, for pregnant females on GD 19.

Abbreviations: ADME, absorption, distribution, metabolism, excretion; AUC, area under the concentration-time curve; CL, clearance; C_{max}, maximum observed plasma concentration; GBCA, gadolinium-based contrast agent; GD, gestational day; LD, lactation day; NOAEL, no observed adverse effect level; PK, pharmacokinetics; RBC, red blood cell; $t_{1/2}$, half-life; TK, toxicokinetic; T_{max}, time to maximum plasma concentration; V_d, volume of distribution

5.5. Toxicology

5.5.1. General Toxicology

Toxicological evaluation of gadopiclenol was conducted in mice, rats, rabbits, and dogs with the majority of toxicity studies conducted in rats and dogs, which were selected as the rodent and non-rodent species, respectively. The clinically relevant route of exposure (intravenous injection) was used for all in vivo toxicology studies which included acute single-dose and repeat-dose toxicology, genotoxicity studies, developmental and reproductive toxicology studies (fertility and early embryonic development, embryofetal development, and

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pre/postnatal development), juvenile toxicity studies, as well as local tolerance and hypersensitivity studies.

Acute, single-dose toxicity studies were conducted with gadopiclenol at up to 12 mmol/kg in CD1 mice (Study No. GDX-33-010) and 12 mmol/kg in Sprague Dawley rats (Study No. GDX-33-011). Expanded, single-dose toxicity studies with TK assessment were also conducted with gadopiclenol at up to 10 mmol/kg in Sprague Dawley rats (Study No. GDX-33-014) and at up to 4 mmol/kg in Beagle dogs (Study No. GDX-33-016). Pivotal, 14-day and 28-day repeat-dose toxicity studies with TK assessment were conducted with gadopiclenol at up 10 mmol/kg in rats (Study No. GDX-33-015 and Study No. GDX-33-039) and at up to 4 mmol/kg in dogs (Study No. GDX-33-017 and Study No. GDX-33-040).

5.5.2. Single-Dose Toxicity Studies

Study Title/Number: P03277 - A Single Dose Acute Intravenous Toxicity Study in Mice / GDX-33-010 (1748-016)

- A single-dose acute intravenous administration of gadopiclenol at 4, 8, or 12 mmol/kg (7x, 13x, and 20x the clinical dose) was well tolerated in male and female mice.
- There were no changes in body weight, food consumption, or macroscopic observations that were considered related to administration of gadopiclenol.
- Test article-related clinical findings included decreased activity and swelling of the face on Day 1 generally through 3 to 4 hr following dose administration.
- Based on the findings, the NOAEL was considered as 12 mmol/kg.

GLP compliance: Yes

Conducting laboratory and location: (b) (4)

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Table 3. Methods for Study No. GDX-33-010

Methods	Details
Dose and frequency of dosing	0 (vehicle), 4 (LD), 8 (MD), 12 (HD) mmol/kg gadopiclenol; single dose administration
Dose multiples of clinical dose	7x (LD), 13x (MD), 20x (HD)
Route of administration	Intravenous
Formulation/vehicle	Drug product (G03277.023) was formulated as a sterile aqueous solution for i.v. injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 11M001B, % Purity: 98.1%)/G03277.024 (Lot #: 11M002, % Purity not stated)
Species/strain	Mouse/ Crl:CD1®(ICR)
Number/sex/group	5/sex/group
Age	6 weeks (approximately) at arrival
Satellite groups/ unique design	None
Deviation from study protocol affecting interpretation of results	None

Abbreviations: HD, high dose; i.v., intravenous; LD, low dose; MD, mid dose

Table 4. Observation and Results: Changes From Control (Study No. GDX-33-010)

Parameters	Major Findings
Mortality	There were no deaths. All animals survived to scheduled necropsies.
Clinical Signs	Test article-related decrease in activity observed in 3/5, 3/5, and 5/5 males at 4, 8, and 12 mmol/kg respectively at 1 hr post-dose. Decreased activity in 5/5 and 2/5 females at the HD only at 1 hr and 2 hr post-dose, respectively. Clinical signs included swelling of the face (2/5 males) at 4 and 8 mmol/kg at 1-2 hr post-dose. Similar swelling was observed at 12 mmol/kg in 1/5 females.
Body weights	No test article-related effects
Hematology	Not evaluated
Clinical chemistry	Not evaluated
Gross pathology	No test article related macroscopic observations in male or female animals
Organ weights	Not evaluated
Histopathology Adequate battery: No	Not evaluated
Other evaluations	None

Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Study Title/Number: P03277 - A Single-Dose Acute Intravenous Toxicity Study in Rats / GDX-33-011 (1748-015)

- Gadopiclenol was associated with dose-related transient clinical findings and all rats survived to scheduled necropsies. Based on the absence of toxicologically relevant

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findings, the NOAEL was set at 12 mmol/kg (the highest dose level tested), administered as a single intravenous slow bolus injection.

- Test article-related clinical findings in males and females included observations of swelling of the face/forelimbs/hind limbs on Day 1 after treatment at 12 mmol/kg, generally through 3 hr post-administration. These findings had resolved and were no longer observed by 4 hr post-dose.

GLP compliance: Yes

Conducting laboratory and location: (b) (4)

Table 5. Methods for Study No. GDX-33-011

Methods	Details
Dose and frequency of dosing	0 (vehicle), 4 (LD), 8 (MD), 12 (HD) mmol/kg gadopiclenol; single dose administration
Dose multiples of clinical dose	13x (LD), 26x (MD), and 39x (HD)
Route of administration	Intravenous
Formulation/vehicle	Drug product (G03277.023) was formulated as a sterile aqueous solution for i.v. injection and contained 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 11M001B, % Purity: 98.1%)/G03277.024 (Lot #: 11M002, % Purity not stated)
Species/strain	Rats/ CD® [Crl:CD® (SD)]
Number/sex/group	5/sex/group
Age	Approximately 6 weeks on arrival
Satellite groups/ unique design	None
Deviation from study protocol affecting interpretation of results	None

Abbreviations: HD, high dose; i.v., intravenous; LD, low dose; MD, mid dose

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Table 6. Observations and Results: Changes From Control (Study No. GDX-33-011)

Parameters	Major Findings
Mortality	There were no deaths. All animals survived to scheduled necropsies.
Clinical signs	Test article-related swelling of the face/forelimbs/hind limbs in males and females only at 12 mmol/kg (HD)
Body weights	No test article-related effects
Clinical chemistry	Not evaluated
Gross pathology	No test article-related macroscopic findings
Organ weights	Test article-related organ weight differences were limited to the kidneys at 12 mmol/kg (HD) at Day 2 in males only where kidney weight was significantly increased compared to vehicle controls. The higher kidney weight in this dose group was likely associated with tubular cell vacuolation that was noted microscopically.
Histopathology Adequate battery: Yes	Test article-related findings of minimal (LD and MD in males and all dose levels in females) to mild (HD in males only) renal tubular cell vacuolation
Other evaluations	None

Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Study Title/Number: An Expanded Single Dose Intravenous Toxicity Study in Rats / GDX-33-014 (1748-017)

- Gadopiclenol was associated with dose-related transient clinical findings and all rats survived to scheduled necropsies. Based on the absence of toxicologically relevant findings, the NOAEL was 10 mmol/kg (the highest dose tested). Systemic exposure (C_{max} and $AUC_{0\text{-}inf}$) at the NOAEL was 31,500 µg/mL and 35,200 µg.h/mL, respectively, for males and 29,000 µg/mL and 32,400 µg.h/mL, respectively, for females.
- Test article-related clinical findings included observations of swelling of the forelimbs/hind limbs for a single male on Day 1, at 3 h post-dose (10 mmol/kg). These findings had resolved and were no longer observed by 4 hr post-dose.
- Test article-related organ weight differences were limited to the kidneys. The higher kidney weights of males at 10 mmol/kg were likely associated with the histopathology finding of renal tubular cell vacuolation which was reversible.

GLP compliance: Yes

Conducting laboratory and location: (b) (4)

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Table 7. Methods for Study No. GDX-33-014

Methods	Details
Dose and frequency of dosing	0 (vehicle), 2.5 (LD), 5 (MD), 10 (HD) mmol/kg gadopiclenol; single dose administration
Dose multiples of clinical dose	8x (LD), 16x (MD), 32x (HD)
Route of administration	Intravenous
Formulation/vehicle	Drug product (G03277.023) was formulated as a sterile aqueous solution for i.v. injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 11M001B, % Purity: 98.1%)/G03277.024 (Lot #: 11M002, % Purity not stated)
Species/strain	Rats/ CD® [Crl:CD® (SD)]
Number/sex/group	10/sex/group (main study) and 5/sex/group (recovery)
Age	6 weeks (approximately) at arrival
Satellite groups/unique design	TK satellite, n=6/sex/group for gadopiclenol and n=6/sex for negative control (0.9% sodium chloride)/no
Deviation from study protocol affecting interpretation of results:	None

Abbreviations: HD, high dose; i.v., intravenous; LD, low dose; MD, mid dose

Table 8. Observations and Results: Changes From Control (Study No. GDX-33-014)

Parameters	Major Findings
Mortality	There were no deaths. All animals survived to scheduled necropsies.
Clinical signs	Test article-related swelling of the forelimbs/hind limbs in 1 of 15 males only at 10 mmol/kg (HD) at 3 hr post-dose which resolved by 4 hr post-dose.
Body weights	No test article-related effects
Ophthalmoscopy	No test article-related effects on ophthalmoscopic parameters
Hematology	No test article-related effects on hematology parameters
Clinical chemistry	No test article-related effects on clinical chemistry analytes
Urinalysis	No test article-related effects on urinalysis
Gross pathology	No test article-related macroscopic findings
Organ weights	Test article-related organ weight differences were limited to the kidneys at 10 mmol/kg (HD) at Day 2 in males only where kidney weights (mean absolute and relative to body and brain weight) were significantly increased compared to vehicle controls.
Histopathology Adequate battery: Yes	Test article-related findings of minimal to mild renal tubular cell vacuolation at all dose levels on Day 2 and partially reversible by Day 15; no findings of cellular necrosis or inflammation.

Abbreviations: HD, high dose; LD, low dose; MD, mid dose

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Study Title/Number: An Expanded Single-Dose Acute Intravenous Toxicity Study in Dogs / GDX-33-016

- There were no mortalities during this study and no gadopiclenol-related detailed clinical observations or changes in electrocardiograms, clinical pathology, or gross necroscopic observations. Based on the absence of toxicologically relevant findings, the NOAEL was 4 mmol/kg (the highest dose tested). Systemic exposure (C_{max} and $AUC_{0\text{-}inf}$) at the NOAEL was 9,220±926 µg/mL and 14,100±2,310 µg.h/mL, respectively, for males and 9,580±1,280 µg/mL and 14,300±3,230 µg.h/mL, respectively, for females.
- Increased organ weights were observed for adrenal gland (Days 2 and 15) and kidney (Day 15) at 4 mmol/kg. No dose-dependence or microscopic correlates were identified for the modest increase in adrenal weights. There were test article-related microscopic findings of vacuolation of the tubular epithelium in the kidney which was minimal in males at ≥2 mmol/kg (Day 2) and minimal to mild in males and females at 4 mmol/kg. There were no clinical pathology correlates to the renal microscopic findings and therefore they were not considered adverse.

GLP compliance: Yes

Conducting laboratory and location (b) (4)

Table 9. Methods for Study No. GDX-33-016

Methods	Details
Dose and frequency of dosing	0 (vehicle), 1 (LD), 2 (MD), 4 (HD) mmol/kg gadopiclenol; single dose administration
Dose multiples of clinical dose	11x (LD), 22x (MD), 44x (HD)
Route of administration	Intravenous
Formulation/vehicle	Drug product (G03277.023) was formulated as a sterile aqueous solution for i.v. injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 11M001B, % Purity: 98.1%) / G03277.024 (Lot #: 11M002, % Purity not stated).
Species/strain	Dog/Beagle
Number/sex/group	3/sex/group (main study) and 2/sex/group (recovery)
Age	At least 5 months at arrival
Satellite groups/ unique design	None
Deviation from study protocol affecting interpretation of results	None

Abbreviations: HD, high dose; i.v., intravenous; LD, low dose; MD, mid dose

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Table 10. Observation and Results: Changes From Control (Study No. GDX-33-016)

Parameters	Major Findings
Mortality	There were no deaths. All animals survived to scheduled necropsies.
Clinical signs	No test article related clinical observations
Body weights	No test article-related effects
Ophthalmoscopy	Peripapillary conus in two HD males on Day 2 without microscopic correlates; relationship to test article not clear
ECG	No changes reported in ECG parameters
Hematology	No test article-related effects on hematology parameters
Clinical chemistry	No test article-related effects on clinical chemistry analytes
Urinalysis	No test article-related effects on urinalysis parameters
Gross pathology	No test article-related macroscopic findings. Minimal to moderate red discoloration at the injection site in all groups at Day 2, including the negative and vehicle control groups. Red discoloration correlated microscopically with hemorrhage and was considered non-adverse and related to the test procedure.
Organ weights	Test article-related organ differences were limited to minimal increase in adrenal gland weight in Day 2 animals and increases in kidney weight in Day 15 animals. No microscopic correlates to the adrenal gland weight increases were observed.
Histopathology Adequate battery: Yes	Test article-related findings of minimal to mild vacuolation of the renal tubular cell epithelium was observed in males and females at 4 mmol/kg and males at 1 and 2 mmol/kg on Day 2. There were no clinical pathology correlates to the microscopic change in the kidneys and this change was not considered adverse. Renal tubular cell vacuolation was not observed in the Day 15 animals.
Other evaluations	None

Abbreviations: ECG, electrocardiogram; HD, high dose; LD, low dose; MD, mid dose

5.5.3. Repeat-Dose Toxicity Studies

Study Title/Number: P03277- Two-Week Intravenous Toxicity Study in Rats With a Two-Week Recovery Period / GDX-33-015 (1748-018)

- Gadopiclenol was associated with dose-related clinical findings during the dosing period, and all rats survived to scheduled necropsies. Test article-related adverse clinical observations included swelling of the face/forelimbs/hind limbs, salivation, eyelids partially/completely closed, decreased activity, and decreases in mean group body weight gain and mean food consumption.
- Test article-related organ weight increases were observed in the kidneys (≥2.5 mmol/kg/day), liver (10 mmol/kg/day in males and ≥2.5 mmol/kg/day in females), and lungs (10 mmol/kg/day in males and ≥2.5 mmol/kg/day in females) and correlated with microscopic findings that increased in severity with increasing dose. Adverse

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microscopic findings included mild to severe renal tubular cell vacuolation, centrilobular hepatocellular vacuolation and presence of vacuolated macrophages, and minimal to moderate alveolar histiocytosis. Microscopic findings were partially reversible.

- Test article-related findings in the liver correlated with a mild dose-related decrease in triglyceride levels at ≥5 mmol/kg/day, which was reversible.
- Minimal to moderate infiltrates of macrophages with vacuolated cytoplasm in the sinuses of lymph nodes were observed in all test article-treated animals as well as infiltrates of macrophages with vacuolated cytoplasm present in the interstitial connective tissues of most of the organs (5 and/or 10 mmol/kg/day). Findings were partially reversible.
- Based on the results and the resolution of microscopic findings following a 14-day recovery period, the NOAEL was 5 mmol/kg/day. Systemic exposure by C_{max} and $AUC_{0\text{-}6hr}$ at the NOAEL was 16,900 µg/mL and 9,140 µg.h/mL, respectively, for males and 17,000 µg/mL and 8,640 µg.h/mL, respectively, for females.

GLP compliance: Yes

Conducting laboratory and location: (b) (4)

Table 11. Methods for Study No. GDX-33-015

Methods	Details
Dose and frequency of dosing	0 (negative control), 2.5 (LD), 5 (MD), 10 (HD) mmol/kg gadopiclenol once daily for 14 consecutive days
Dose multiples of clinical dose	8x (LD), 16x (MD), 32x (HD)
Route of administration	Intravenous
Formulation/vehicle	Drug product (G03277.023) was formulated as a sterile aqueous solution for i.v. injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 11M001B, % Purity: 98.1%)/0.9% Sodium Chloride for Injection, USP
Species/strain	Rats/CD® [Crl:CD® (SD)]
Number/sex/group	10/sex/group (main study) and 5/sex for negative control and HD (recovery)
Age	6 weeks (approximately) at arrival
Satellite groups/ unique design	TK satellite, n=7/sex/group for gadopiclenol and n=7/sex for negative control
Deviation from study protocol affecting interpretation of results	None

Abbreviations: HD, high dose; i.v., intravenous; LD, low dose; MD, mid dose; TK, toxicokinetic

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Table 12. Observations and Results: Changes From Control (Study No. GDX-33-015)

Parameters	Major Findings
Mortality	2 males and one female died after dosing/difficulty with dosing. Mortality was not considered related to gadopiclenol.
Clinical signs	Test article-related clinical findings included observations of swelling of the face/forelimbs/hind limbs, salivation, eyelids partially/completely closed, unkempt appearance, stereotypy (head weaving), and decreased activity. Clinical findings were observed for male and female animals at the HD during the first week of the dosing period.
Body weights	Test article-related decreases in body weight gain over the 14 day dosing and post-dose recovery period; 2% decrease in males at MD and 3%-5% and 1%-3% decrease in males and females at HD, respectively. During the recovery period, body weight gain decreased 5% in males at HD on Days 15 and 18 and 3% on Days 22 and 25. In recovery females, body weight gain decreased 7% at HD on Day 15 and further decreased on Days 18-25.
Ophthalmoscopy	No test article-related effects on ophthalmoscopic parameters
Hematology	Test article-related minimal decreases in red cell mass (erythrocytes, hemoglobin, and hematocrit; up to 8%) in male and female animals at ≥5 mmol/kg/day relative to controls. In recovery animals, decreases in red cell mass at 10 mmol/kg/day (up to 9% relative to controls) that were statistically significant but not considered to be biologically relevant.
Clinical chemistry	Test article-related decrease in triglyceride (up to 42%) relative to controls in male and female animals at ≥ MD that followed a dose response; reversible following 14-day recovery period.
Urinalysis	No test article-related alterations among urinalysis parameters in either sex at any dose level
Gross pathology	No test article-related macroscopic findings at terminal or recovery necropsies
Organ weights	Test article-related increase in organ weights for the kidneys (≥ LD), lungs (HD in males and ≥ LD in females), and liver (HD in males and ≥ LD in females). Changes in the kidneys were dose dependent. Increases in organ weights correlated with microscopic findings that increased in severity with increasing dose.

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Parameters	Major Findings
Histopathology Adequate battery: Yes	Test article-related adverse findings included mild to severe renal tubular cell vacuolation (HD), centrilobular hepatocellular vacuolation and the presence of vacuolated macrophages (HD), and minimal to moderate alveolar histiocytosis (MD and HD). Minimal to moderate infiltrates of macrophages with vacuolated cytoplasm in the sinuses of lymph nodes were observed in all test article-treated animals as well as infiltrates of macrophages with vacuolated cytoplasm present in the interstitial connective tissues of most of the organs (MD and/or HD). Microscopic findings were partially reversible following 14-day recovery period.

Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Study Title/Number: P03277: Two-Week Intravenous Toxicity Study in Dogs With a Two-Week Recovery Period / GDX-33-017 (1748-020)

- There were no mortalities during this study and no gadopiclenol-related detailed clinical observations or changes in electrocardiograms, clinical pathology, or gross necroscopic observations. Based on the absence of toxicologically relevant findings, the NOAEL was 4 mmol/kg/day (the highest dose tested). Systemic exposure by C_{max} and $AUC_{0\text{-}8hr}$ at the NOAEL was 8,000±2,120 µg/mL and 14,500±3,980 µg.h/mL, respectively, for males and 9,300±1,210 µg/mL and 14,800±2,800 µg.h/mL, respectively, for females.
- Test article-related organ weight increases were observed in the kidneys at ≥2 mmol/kg/day in males and at 4 mmol/kg/day in females which were partially reversible following treatment-free recovery period and correlated with microscopic findings.
- Test article-related findings of minimal to mild tubular cell vacuolation in renal cortex were observed at all dose levels in terminal animals and in recovery animals at the high dose. Histopathology findings were not considered adverse (class finding).

GCP compliance: Yes

Conducting laboratory and Location: (b) (4)

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Table 13. Methods for Study No. GDX-33-017

Methods	Details
Dose and frequency of dosing	0 (negative control), 1 (LD), 2 (MD), 4 (HD) mmol/kg gadopiclenol once daily for 14 consecutive days
Dose multiples of clinical dose	11x (LD), 22x (MD), 44x (HD)
Route of administration	Intravenous
Formulation/vehicle	Drug product (G03277.023) was formulated as a sterile aqueous solution for i.v. injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 11M001B, % Purity: 98.1%)/0.9% sodium chloride
Species/strain	Dogs/Beagle
Number/sex/group	3/sex/group (main study) and 2/sex/group (vehicle and HD recovery only for recovery)
Age	6-6.5 months of age at arrival
Satellite groups/ unique design	None
Deviation from study protocol affecting interpretation of results	None

Abbreviations: HD, high dose; i.v., intravenous; LD, low dose; MD, mid dose

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Table 14. Observations and Results: Changes From Control (Study No. GDX-33-017)

Parameters	Major Findings
Mortality	There were no deaths. All animals survived to scheduled necropsies.
Clinical signs	No test article-related detailed clinical observations
Body weights	No test article-related changes in body weight
Ophthalmoscopy	No test article-related effects based on the ophthalmic examination
ECG	No changes reported in ECG parameters
Hematology and coagulation	No test article-related effects on hematology parameters and coagulation at termination or recovery
Clinical chemistry	No test article-related effects on clinical chemistry analytes at termination or recovery
Urinalysis	No test article-related effects on urinalysis parameters at termination or recovery
Gross pathology	No test article-related macroscopic findings
Organ weights	Test article-related increase in organ weights was reported for the kidneys at ≥ MD in males and HD in females. Mean absolute kidney weights were increased 23.1% in males only at MD, and 19.8% and 18.8% in males and females, respectively, at HD. In recovery animals, mean absolute kidney weights were slightly increased at HD by 9.7% and 18.0% in males and females, respectively, when compared to negative controls. Increases in kidney weights correlated with microscopic findings that increased in severity with increasing dose.
Histopathology Adequate battery: Yes	There were test article-related findings of minimal to mild tubular cell vacuolation in renal cortex at all dose levels in terminal animals and in recovery animals at HD. The histopathology findings were not considered adverse.
Other Evaluations	None

Abbreviations: ECG, electrocardiogram; HD, high dose; LD, low dose; MD, mid dose

Study Title/Number: P03277: A 28-Day Intravenous Toxicity Study in Rats With a 28-Day Recovery Period / GDX-33-039

- Test article-related clinical signs included swelling of the extremities and/or nose/muzzle at 10 mmol/kg/day during the first two days of dosing. Swelling of the tail (5 and 10 mmol/kg/day), edema of the tail (10 mmol/kg/day females), and purple discoloration (10 mmol/kg/day females) were observed throughout the study. Urination was increased in animals administered test article at 10 mmol/kg/day.
- Test article-related effects on clinical chemistry parameters were limited to decreases in alanine aminotransferase activity (up to 0.61x) on Days 29 (interim) and 57 (recovery) in animals administered 10 mmol/kg/day.
- Test article-related and dose-dependent increases in the kidney weights at all dose levels were partially reversible by Day 57 (recovery) and were correlated with

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microscopic findings that increased in severity with increasing dose. Microscopic findings included mild to severe tubular epithelial vacuolation (dose-related) and minimal to mild degeneration of tubular epithelium at ≥5 mmol/kg/day associated with mononuclear infiltrates. Findings were considered adverse due to evidence for tubular epithelial degeneration but resolved following treatment-free recovery period.

- Minimal to moderate test article-related vacuolated/granular macrophages were found in most organs and tissues at ≥5 mmol/kg/day and reversible by Day 57 (recovery).
- Due to the adverse histopathology findings in both sexes in the kidney (tubular epithelial vacuolation and degeneration) at 5 and 10 mmol/kg/day, the NOAEL was 2.5 mmol/kg/day. Systemic exposure by C_{max} and $AUC_{0\text{-}6hr}$ at the NOAEL was 9,090 µg/mL and 5,300 µg.h/mL, respectively, for males and 9,300 µg/mL and 4,430 µg.h/mL, respectively, for females.

GCP compliance: Yes

Conducting laboratory and location (b) (4)

Table 15. Methods for Study No. GDX-33-039

Methods	Details
Dose and frequency of dosing	0 (vehicle), 2.5 (LD), 5 (MD), 10 (HD) mmol/kg gadopiclenol once daily for up to 28 days
Dose multiples of clinical dose	8x (LD), 16x (MD), 32x (HD)
Route of administration	Intravenous
Formulation/vehicle	Drug product (G03277.100) was formulated as a sterile aqueous solution for i.v. injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 17M017, % Purity: 99.4%)/0.9% Sodium Chloride for Injection, USP
Species/strain	Rats/CD® [Crl:CD® (SD)]
Number/sex/group	10/sex/group (main study) and 5/sex/group (vehicle and HD recovery only for recovery)
Age	8.5 weeks (approximately) at arrival
Satellite groups/ unique design	TK satellite, n=6/sex/group for gadopiclenol and n=3/sex for negative control (0.9% sodium chloride)
Deviation from study protocol affecting interpretation of results	None

Abbreviations: HD, high dose; i.v., intravenous; LD, low dose; MD, mid dose; TK, toxicokinetic

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Table 16. Observations and Results: Changes From Control (Study No. GDX-33-039)

Parameters	Major Findings
Mortality	One control female on Day 8; cause of death was not known. No other unscheduled deaths in vehicle control or gadopiclenol-treated groups in either sex.
Clinical signs	Test article-related clinical signs were limited to swelling of the extremities and/or nose/muzzle at the HD on Day 1 and 2 of the dosing period. Swelling of the tail (MD and HD), edema of the tail (HD females), and purple discoloration (HD females) were observed throughout the study. Urination was increased at the HD throughout the study. There were no test article-related changes in the functional observational battery.
Body weights	No clear dose-related treatment effects on group mean body weight or group mean body weight change
Ophthalmoscopy	No test article-related effects on ophthalmoscopic parameters
Hematology	Test article-related effects on hematology parameters were limited to mild and reversible decreases in reticulocyte counts at the HD and minimal decrease in red cell mass (erythrocyte count, hemoglobin concentration, and hematocrit) in HD males only. No test article-related effects on coagulation parameters.
Clinical chemistry	Test article-related effects on clinical chemistry parameters were limited to decreases in alanine aminotransferase activity (up to 0.61x) on Days 29 (interim) and 57 (recovery) at the HD only. Findings may have been related to histopathology findings in the liver.
Urinalysis	Test article-related effects were limited to minimal decreases in mean urine pH on Days 29 (interim) and 57 (recovery) at the HD only (mean range 6.00-6.30) relative to controls (mean range 6.40-7.10). Urinalysis findings were likely related to the renal tubular findings observed microscopically.
Gross pathology	Test article-related macroscopic findings were limited to kidney enlargement at the HD (two males) and related to histopathology findings of mild pelvic dilation or severe renal tubular vacuolation.
Organ weights	Test article-related and dose-dependent increases in kidney weights (mean absolute and relative to body and brain weight) at all dose levels and of greater magnitude in males compared to females. Percent increase in mean absolute weights increased in a dose-dependent manner to 10.4%, 30.6%, 60.5% for LD, MD, and HD, respectively, in males and 2.9%, 12.0%, 30.6% for LD, MD, and HD, respectively, in females. All findings were statistically significant at the MD and HD with partial recovery by Day 57 (recovery). The increased kidney weights were related to histopathology findings of renal tubular cell vacuolation.

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Parameters	Major Findings
Histopathology Adequate battery: Yes	Test article-related effects in the kidney, urothelial cells, and lymph nodes. In the kidneys, mild to severe tubular epithelial vacuolation with a dose-related increase in severity and minimal to mild degeneration of tubular epithelium at the MD and HD that was associated with mononuclear infiltrates. Findings were considered adverse due to evidence for tubular epithelial degeneration but resolved following treatment-free recovery period. Minimal to mild urothelial vacuolation at ≥ LD (not considered adverse) and not reversible following treatment-free recovery period at HD (only dose level evaluated). Minimal to moderate infiltrates of macrophages with vacuolated/granular cytoplasm present in the sinuses of lymph nodes (mesenteric and mandibular) at all dose levels; macrophages also present within gut-associated lymphoid tissue at HD (three males only); reversable with exception of mesenteric lymph nodes at HD (only dose level evaluated). Minimal to moderate test article-related vacuolated/granular macrophages in liver, adrenal glands, spleen, testes, epididymis, and uterus at MD and/or HD; reversible for all organs with exception of adrenal glands, evidenced by vacuolated/granular macrophages at the HD (three females only, only dose level evaluated).
Other Evaluations	None.

Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Study Title/Number: P03277: A 28-Day Intravenous Toxicity Study in Dogs With a 28-Day Recovery Period /GDX-33-040 (1748-040)

- Gadopiclenol-related clinical observations were limited to swelling of the face and ears (one male at 4 mmol/kg/day) and forelimbs (one male at 4 mmol/kg/day, administered an antihistamine) during the dosing period, and all dogs survived to scheduled necropsies. There were no changes in electrocardiograms, clinical pathology, or gross necroscopic observations. Based on the absence of toxicologically relevant findings, the NOAEL was 4 mmol/kg/day (the highest dose tested). Systemic exposure by C_{max} and $AUC_{0\text{-}8hr}$ at the NOAEL was 8,420±766 µg/mL and 15,900±1,750 µg.h/mL, respectively, for males and 11,000±3,890 µg/mL and 20,100±7,440 µg.h/mL, respectively, for females.

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- Test article-related and dose-dependent increases in kidney weights were observed at ≥1 mmol/kg/day (statistically significant in female animals at 4 mmol/kg/day) and reversible following treatment-free recovery period.
- There were test article-related macroscopic findings of tan discoloration of the kidney (two males and one female at 4 mmol/kg/day) and corresponding microscopic findings which included mild to marked renal tubular cell vacuolation at all dose levels in terminal animals that resolved in recovery animals. There was also minimal to mild urothelial cell cytoplasmic vacuolation at ≥1 mmol/kg/day without necrosis. Histopathology findings were not considered adverse (class finding).

GCP compliance: Yes

Conducting laboratory and location: (b) (4)

Table 17. Methods for Study No. GDX-33-040

Methods	Details
Dose and frequency of dosing	0 (negative control), 1 (LD), 2 (MD), 4 (HD) mmol/kg gadopiclenol once daily for up to 28 days
Dose multiples of clinical dose	11x (LD), 22x (MD), 44x (HD)
Route of administration	Intravenous
Formulation/vehicle	Drug product (G03277.100) was formulated as a sterile aqueous solution for i.v. injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 7M017, % Purity: 99.4%) / 0.9% sodium chloride
Species/strain	Dogs / Beagle
Number/sex/group	3/sex/group (main study) and 2/sex/group (vehicle and HD recovery only for recovery)
Age	5 months of age at arrival
Satellite groups/ unique design	None
Deviation from study protocol affecting interpretation of results	None

Abbreviations: HD, high dose; i.v., intravenous; LD, low dose; MD, mid dose

Table 18. Observations and Results: Changes From Control (Study No. GDX-33-040)

Parameters	Major Findings
Mortality	All animals survived to study termination. There was no mortality.
Clinical signs	Test article-related clinical signs in 2 HD males included swelling around the dose site or forelimb as well as swelling of the face and ears which resolved.
Body weights	No test article-related body weight changes
Ophthalmoscopy	No test article-related changes on ophthalmoscopy

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Parameters	Major Findings
ECG	No changes reported in ECG parameters
Hematology	No test article-related effects on hematology parameters and coagulation at termination or recovery
Clinical chemistry	No test article-related effects on clinical chemistry parameters at termination or recovery
Urinalysis	No test article-related effects on urinalysis parameters at termination or recovery.
Gross pathology	Test article-related macroscopic finding of tan discoloration of kidneys in two males and one female at the HD which resolved following treatment-free recovery period and was related to histopathology findings of renal tubular vacuolation. Red discoloration of the injection site in control and test article treated animals was microscopically correlated to hemorrhage from the dosing procedure.
Organ weights	Reversible, test article-related organ weight increases in kidneys in terminal males and females at all dose levels. The increased weights at all doses were due to mild to marked epithelial cell vacuolation of the cortical and medullary tubules.
Histopathology Adequate battery: Yes	Test article-related and dose-dependent mild to marked tubular cell vacuolation in the absence of cellular necrosis which was absent in recovery animals. Minimal urothelial cell cytoplasmic vacuolation in the urinary bladder at ≥ MD which was absent in recovery animals. Microscopic findings were not considered adverse.
Other evaluations	None

Abbreviations: ECG, electrocardiogram; HD, high dose; LD, low dose; MD, mid dose

5.5.4. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study Title/Number: G03277.023 – Bacterial Reverse Mutation Test (Plate Incorporation and Pre-Incubation Methods) / GDX-33-027(AB12435)

Key Study Findings:

- The results of the bacterial mutagenicity assay indicated that under the experimental conditions of the study, gadopiclenol did not cause a positive mutagenic response with any of the tester strains in either the absence or presence of S9 metabolic activation.
- No positive increase in the mean number of revertants per gadopiclenol-treated plate was observed with any of the tester strains (without or with metabolic activation). No precipitate or cytotoxicity was observed. Gadopiclenol was negative (non-mutagenic) in the bacterial reverse mutation assay.

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GLP compliance: Yes

Test system: Five histidine-dependent strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, and TA102) in the absence and presence of Aroclor-induced rat liver microsome fraction (S9).

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study Title/Number: G03277.023 – In vitro Mammalian Cell Gene Mutation Test on L5178Y Mouse Lymphoma Cells $TK^{+/-}$ (Microwell method) / GDX-33-028 (AB12434)

Key Study Findings:

- No precipitate was noted at any tested dose level in any experiment. Signs of cytotoxicity were noted only in the 24 hr treatment at ≥1600 µg/mL in the absence of metabolic activation.
- Under the test conditions used, gadopiclenol did not induce any biologically significant increase in the mutant frequency at 24 hr in the absence of metabolic activation or at 4 hr either with or without metabolic activation. Gadopiclenol was negative for genotoxic potential by in vitro mouse lymphoma assay.

GLP compliance: Yes

Test system: L5178Y mouse lymphoma cells, clone -3.7.2C, designated L5178Y TK+/-; testing conducted in the absence and presence of Aroclor-induced rat liver microsome fraction (S9).

Study is valid: Yes, based on the acceptance criteria.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study Title/Number: G03277.023 – Mammalian Erythrocyte Micronucleus Test in the Rat Bone Marrow / GDX-33-032 (AB13688)

Key Study Findings:

- Gadopiclenol at doses up to and including 10 mmol/kg did not show any genotoxic activity in this in vivo test for induction of chromosome damage (ratio of polychromatic erythrocytes to normochromatic erythrocytes and mean frequency of micronucleated polychromatic erythrocytes).
- Based on the findings, gadopiclenol was negative for genotoxic potential in the assay.

GLP compliance: Yes

Test system: Species/strain: Sprague-Dawley rat, Crl: OFA(SD), SPF

Study is valid: Yes (criteria for validity were met).

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Other Genetic Toxicity Studies

None.

5.5.5. Carcinogenicity

Studies examining the carcinogenic potential of gadopiclenol have not been conducted and are not needed because gadopiclenol will be administered as a single or infrequent dose and because of the negative findings in genotoxicity studies.

5.5.6. Reproductive and Developmental Toxicology

Reproductive and developmental toxicology studies were conducted to evaluate the potential effects of gadopiclenol on fertility and reproductive performance including a determination of whether the drug is teratogenic and any effects on perinatal/postnatal development. The key findings of these DART studies including juvenile animal toxicity are described below.

Fertility and Early Embryonic Development

Study Title/Number: P03277: A Study of Fertility and Early Embryonic Development to Implantation in Rats / GDX-33-038 (1748-037)

Study Objective:

The study was conducted to determine the potential toxic effect of gadopiclenol on female estrous cycle, tubal transport, implantation, and embryonic development, and to detect functional effects on male fertility.

Key Study Findings:

- There were no test article-related findings for sperm analysis, reproductive and fertility indices, uterine implantation data, or organ weights at any of the dose levels evaluated.
- At 10 mmol/kg/day (32-fold the clinical dose), mean cycle length was increased and the number of cycles was reduced when compared to control females. These effects did not correlate with effects on reproductive and fertility indices and were not considered adverse.
- A test article-related and dose-dependent increase in discolored/enlarged kidneys was observed in males only which correlated with microscopic findings (Study # GDX-33-0141 and GDX-33-0152) and was considered adverse at 10 mmol/kg/day.
- Based on these results, the NOAEL for parenteral toxicity in males and females was 5 mmol/kg/day (16-fold the clinical dose) based on body weight, food consumption, and macroscopic findings in the kidney (males only). The NOAEL for reproductive performance and fertility in males and females was 10 mmol/kg/day. Systemic exposure by C_{max} and $AUC_{0\text{-}6hr}$ at the NOAEL (reproductive performance and fertility) was 50,300 µg/mL and 36,100 µg.h/mL, respectively, for males on Day 44 and 45,700±5,920 µg/mL and 35,100 µg.h/mL, respectively for females on gestation day (GD) 7.

Reference ID: 5048631

GLP compliance: Yes

Conducting laboratory and location: (b) (4)

Table 19. Methods for Study No. GDX-33-038

Methods	Details
Dose and frequency of dosing	0 (negative control), 2.5 (LD), 5 (MD), 10 (HD) mmol/kg daily
Route of administration	Intravenous
Formulation/vehicle	Drug product (G03277.100) was formulated as a sterile aqueous solution for i.v. injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 17M016, % Purity: 99.48%)/0.9% Sodium Chloride for Injection, USP
Species/strain	CD® [Crl:CD® (SD)] rats (approximately 8 weeks of age)
Number/sex/group	22/sex/group
Satellite groups	TK satellite, n=6/sex/group for gadopiclenol and n=3/sex for negative control (0.9% sodium chloride)
Study design	Male rats were administered gadopiclenol by i.v. injection for 4 weeks prior to mating with females and through euthanasia. Female rats were administered gadopiclenol by i.v. injection for 2 weeks prior to and throughout mating with treated males and until GD 7. On GD 13, all females were sacrificed. Parameters of evaluation included mortality, clinical signs, body weight and food consumption, pathology including uterine examination, reproductive parameters (mating, fertility, fecundity), estrous cycle by vaginal lavage, and sperm analysis (males). TK analysis was conducted in TK animals on treatment Day 1, GD 7 (females), and last day of dosing (Days 44 or 45). The high dose of 10 mmol/kg/day was selected based on DRF study No. GDX-33-037.
Deviation from study protocol affecting interpretation of results	No

Abbreviations: DRF, dose range finding; GD, gestational day; HD, high dose; i.v., intravenous; LD, low dose; MD, mid dose

Reference ID: 5048631

Table 20. Observations and Results: Changes From Control (Study No. GDX-33-038)

Parameters	Major Findings
Mortality	Mortalities were reported in vehicle control (two males and one female) and test article treated animals (one male and one female at MD, one male and one female at HD) and were not considered related to administration of gadopiclenol.
Clinical signs	Test article-related clinical signs included decreased activity (males only), swollen fore- and hind-limbs, and swollen nose/muzzle at the HD and were transient. No test article-related clinical signs were correlated with effects on reproductive and fertility indices.
Body weight	No test article-related changes in body weight in males. Test article-related decrease in female body weight during prenatal and gestational period at the HD which correlated with reduced food intake.
Necropsy findings	No test article-related effect on sperm analysis (motility, total caudal epididymal counts, counts per gram caudal epididymal tissue, and percentage abnormal), reproductive and fertility indices, corpora lutea count, pre- and post-implantation loss, number of viable embryos, and number of resorptions. Test article-related effect on estrous cyclicity at the HD.

Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Embryo-Fetal Development

Study Title/Number: A Study for the Effect on Embryo-Fetal Development in Rats With a Toxicokinetic Evaluation / GDX-33-035 (1748-034)

Study Objective:

This study was conducted to determine the developmental toxicity, including the teratogenic potential and the toxicokinetics, of gadopiclenol in rats.

Key Study Findings:

- All females survived to the scheduled necropsy. Test article-related clinical observations were at 10 mmol/kg/day and included swelling (forefeet and/or nose/muzzle), tail discoloration (black/purple/red), and lower gestational weight gain and reduced food consumption.
- There were no test article-related findings for embryofetal toxicity by uterine implantation data, fetal sex ratios, fetal body weights, or fetal external, visceral, or skeletal examinations.
- Based on these results, the NOAEL was 5 mmol/kg/day for maternal toxicity and 10 mmol/kg/day for developmental toxicity. Systemic exposure by C_{max} and $AUC_{0\text{-}6hr}$ at the NOAEL (developmental toxicity) was 31,900 µg/mL and 29,500 µg.h/mL, respectively, for pregnant females on GD 17.

Reference ID: 5048631

GLP compliance: Yes

Conducting laboratory and location: (b) (4)

Table 21. Methods for Study No. GDX-33-035

Methods	Details
Dose and frequency of dosing	0 (negative control), 2.5 (LD), 5 (MD), 10 (HD) mmol/kg/day daily
Route of administration	Intravenous
Formulation/vehicle	Drug product (G03277.035) was formulated as a sterile aqueous solution for i.v. injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 13M001, % Purity: 98.6%)/0.9% Sodium Chloride for Injection, USP
Species/strain	Rats/CD® [Crl:CD® (SD)]
Number/sex/group	25/group
Satellite groups	TK satellite, n=9/group for gadopiclenol and n=3 for negative control (0.9% sodium chloride)
Study design	Pregnant rats were administered gadopiclenol at doses of 0 (negative control), 2.5 (LD), 5 (MD), and 10 (HD) mmol/kg/day from GD 6 to 17. Cesarean examination was performed on GD 20. Maternal parameters of evaluation included mortality, clinical signs, and body weight and food consumption. Fetal parameters included litter size, live/dead fetuses, fetal weight, sex, and external, skeletal, and visceral malformations and variations. TK analyses of gadopiclenol were conducted on GD 6 and GD 17.
Deviation from study protocol affecting interpretation of results:	No

Abbreviations: GD, gestational day; HD, high dose; i.v., intravenous; LD, low dose; MD, mid dose; TK, toxicokinetic

Reference ID: 5048631

Table 22. Observations and Results: Changes From Control (Study No. GDX-33-035)

Parameters	Major Findings
Mortality	No treatment-related death in pregnant females.
Clinical signs	Test article-related findings at the HD which included swelling of the forefeet and/or nose/muzzle, discoloration (black/purple/red) of the tail, and lower gestational weight gain and reduced food consumption.
Body weights	Test article-related reduction in gestational weight gain at the HD.
Necropsy findings Cesarean section data	No test article-related findings for gravid uterine weights, pregnancy indices, or uterine implantation data (mean number of corpora lutea, uterine implantation sites, viable fetuses, litter size, resorption sites per animal, and mean pre- and post-implantation loss).
Necropsy findings Offspring	No test article-related findings for intrauterine growth and survival (including fetal sex ratio and body weights) and fetal morphology (external, skeletal, and visceral examinations) by maternal test article administration from GD 6 through GD 17.

Abbreviations: HD, high dose; i.v., intravenous; LD, low dose; MD, mid dose; TK, toxicokinetic

Study Title/Number: A Study for the Effect on Embryo-Fetal Development in Rabbits With a Toxicokinetic Evaluation / GDX-33-036 (1748-035)

Study Objective:

This study was conducted to determine the developmental toxicity, including the teratogenic potential and the toxicokinetics, of gadopiclenol in rabbits.

Key Study Findings:

- All females administered gadopiclenol at ≤2.5 mmol/kg/day survived to the scheduled necropsy. Dose-related mortality was observed in 2 animals at 5 mmol/kg/day. Test article-related clinical observations at 5 mmol/kg/day included decreased activity, aggressive behavior, reduced defecation, thin appearance, lower gestational weight gain, and reduced food consumption.
- There were no test article-related findings for embryofetal toxicity by uterine implantation data, by fetal sex ratios, or by fetal external, visceral, or skeletal examinations. Test article-related findings were limited to reduced fetal body weights at 5 mmol/kg/day.
- Based on these results, the NOAEL for maternal and developmental toxicity with gadopiclenol was 2.5 mmol/kg/day and gadopiclenol was not teratogenic in the rabbit at a dose level ≤5 mmol/kg/day. Systemic exposure by C_{max} and $AUC_{0\text{-}6hr}$ at the NOAEL (developmental toxicity) was 12,450±1,620 µg/mL and 13,500±1,040 µg.h/mL, respectively, for pregnant females on GD 19.

GLP compliance: Yes

Reference ID: 5048631

Conducting laboratory and location: (b) (4)

Table 23. Methods for Study No. GDX-33-036

Methods	Details
Dose and frequency of dosing	0 (negative control), 1 (LD), 2.5 (MD), 5 (HD) mmol/kg/day daily
Route of administration	Intravenous
Formulation/vehicle	Drug product (G03277.035) was formulated as a sterile aqueous solution for i.v. injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 13M001, % Purity: 98.6%)/0.9% Sodium Chloride for Injection, USP
Species/strain	Rabbits/New Zealand White Hra:(NZW)SPF
Number/sex/group	23/group
Satellite groups	TK satellite, n=4/group for gadopiclenol and negative control (0.9% sodium chloride)
Study design	Pregnant rabbits were administered gadopiclenol at doses of 0 (negative control), 1 (LD), 2.5 (MD), and 5 (HD) mmol/kg/day from GD 6 to GD 19. Cesarean examination was performed on GD 29. Maternal parameters of evaluation included mortality, clinical signs, body weight, and food consumption. Fetal parameters included litter size, live/dead fetuses, fetal weight, sex, and external, skeletal, and visceral malformations and variations. TK analyses of gadopiclenol were conducted on GD 6 and GD 19.
Deviation from study protocol affecting interpretation of results	No

Abbreviations: GD, gestational day; HD, high dose; i.v., intravenous; LD, low dose; MD, mid dose; TK, toxicokinetic

Reference ID: 5048631

Table 24. Observations and Results: Changes From Control (Study No. GDX-33-036)

Parameters	Major Findings
Mortality	Treatment-related mortality during dosing at the HD (1 found dead and 1 euthanized in extremis).
Clinical signs	Test article-related findings at the HD included decreased activity (2/23 animals), aggressive behavior (4/23 animals), reduced defecation (14/23 animals), and thin appearance (6/23 animals). Purple discoloration at the injection site was observed in all groups and considered related to the dosing procedure. This resolved after cessation of treatment, except at the HD where discoloration was observed after dosing.
Body weights	Test article-related reduction in gestational weight gain at the HD.
Necropsy findings Cesarean section data	No test article-related findings for gravid uterine weights, pregnancy indices, or uterine implantation data (mean number of corpora lutea, uterine implantation sites, viable fetuses, litter size, resorption sites per animal, and mean pre- and post-implantation loss). Maternal macroscopic findings were limited to tan discoloration of the kidneys at the HD (4/21 at terminal necropsy).
Necropsy findings Offspring	Test article-related findings were limited to reduced fetal body weight (10%-12%) at the HD. No test article-related findings were described for fetal sex ratio or fetal morphology (external, skeletal, and visceral examinations) by maternal test article administration from GD 6 through GD 19.

Abbreviations: GD, gestational day; HD, high dose; LD, low dose; MD, mid dose

Prenatal and Postnatal Development

Study Title/Number: A GLP Pre- and Post-Natal Development Study of Gadopiclenol by the Intravenous (5-Minute Infusion) Route in the Rat / GDX-33-056 (20211810)

Key Study Findings:

- Test article-related and dose-dependent clinical observations included swelling of the limbs and/or muzzle, partly closed eyes, decreased activity, irregular breathing, and redness of the extremities which were adverse at 10 mmol/kg/day and considered non-adverse at ≤5 mmol/kg/day. Findings included reduced food consumption during the gestational period at ≥5 mmol/kg/day and transient reduced body weight gain at 10 mmol/kg/day.
- There was lower mean pup weight at birth for females in the 5 mmol/kg/day group and both males and females in the 10 mmol/kg/day group compared to controls. This finding was not considered adverse based on historical values and absence of any findings for development, behavior, or reproductive performance.
- Based on the findings, the NOAEL for maternal toxicity was 5 mmol/kg/day and the NOAEL for postnatal development (including reproductive performance) was 10 mmol/kg/day. Systemic exposure by C_{max} and $AUC_{0\text{-}24hr}$ at the NOAEL was 17,600 µg/mL

Reference ID: 5048631

and 20,800 µg.h/mL, respectively, for F0 dams on GD 6 and 16,500 µg/mL and 11,000 µg.h/mL, respectively, on lactation day 20. Gadopiclenol was measurable in F1 generation pups at ≥5 mmol/kg/day.

GLP compliance: Yes

Conducting laboratory and location: (b) (4)

Table 25. Methods for Study No. GDX-33-056

Methods	Details
Dose and frequency of dosing	0 (negative control), 2.5 (LD), 5 (MD), 10 (HD) mmol/kg/day daily
Route of administration	Intravenous infusion (5 min)
Formulation/vehicle	Drug product (G03277.100) was formulated as a sterile aqueous solution for i.v. injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 19M003, % Purity: 98.8%)/0.9% sodium chloride
Species/strain	Rats/Sprague-Dawley, Crl:OFA(SD)
Number/sex/group	22/group
Satellite groups	TK satellite, n=3/group for gadopiclenol and negative control (0.9% sodium chloride) + F1 generation on PND 21
Study design	Pregnant rats (F0 generation) were administered gadopiclenol at doses of 0 (negative control), 2.5 (LD), 5 (MD), and 10 (HD) mmol/kg/day from gestational day 6 to lactation day 20. F0 dams were evaluated for pregnancy and partuition (including duration of gestation, abnormalities of delivery, nesting, or nursing behavior, and number of implantation sites). F1 generation pups were evaluated by litter (live/dead pups, external abnormalities, and number, weight, and sex up to PND 21) and behavioral testing. After weaning, F1 generation animals were selected (one male and one female per litter) for post-weaning behavioral testing and mating. Post-weaning development and behavioral testing included sexual maturation, T-maze, locomotor activity, and auditory startle reflex. TK analyses of gadopiclenol were conducted on gestational day 6 and lactation day 20 in F0 generation animals and PND 20 in F1 generation animals.
Deviation from study protocol affecting interpretation of results	No

Abbreviations: HD, high dose; i.v., intravenous; LD, low dose; MD, mid dose; PND, postnatal day

Reference ID: 5048631

Table 26. Observations and Results: Changes From Control (Study No. GDX-33-056)

Generation	Major Findings
F0 Dams	Transient, test article-related findings included swelling of the limbs and/or muzzle, partly closed eyes, decreased activity, irregular breathing, and redness of the extremities. Findings were severe at HD and considered non-adverse at ≤ MD. Dose-related decrease in food consumption during the gestation period associated with reduced body weight gain from gestational day 6 to 15 at the HD, not considered adverse. No test article-related effect on parturition, gestation length, or sex ratio of offspring.
F1 Generation	Lower mean pup weight at birth for females in the MD group and both males and females in the HD group compared to controls, finding not considered adverse. No test article-related effect on pre-weaning development, post-weaning neurobehavioral tests, sexual maturation, mating or fertility performance, kidney function, or macroscopic findings.

Abbreviations: HD, high dose; MD, mid dose

Juvenile Animal Toxicity

Study Title/Number: Juvenile Toxicity Study of Gadopiclenol by Single or Repeat Intravenous (Bolus) Administration in the Rat Followed by a 9-Week Treatment-Free Period / GDX-33-053 (AB22616)

Key Study Findings:

- There were no test article-related findings for juvenile toxicity following single or repeat dosing for postnatal development, sexual maturation, or neurobehavioral assessment.
- Test article-related findings of cortical tubular vacuolation were observed at all dose levels following repeat dosing (subgroup B) and were reversible following treatment-free recovery period (subgroup C).
- Tissue Gd concentrations increased with increasing doses in all tissues after single and repeat doses, with or without recovery. The greatest levels were in the kidneys > liver > femur > skin > cerebellum > brain in male and female animals. At the end of treatment-free recovery following repeat dosing, overall exposure was kidneys > femur > brain > cerebellum > liver > skin in male and female animals. In single dose recovery animals, Gd levels were at or below the lower limit of quantification (LLOQ) except for in the kidneys.
- Based on the findings, the NOAEL for juvenile toxicity was 2.5 mmol/kg/day. Systemic exposure by C_{max} and AUC_{0-t} at the NOAEL on postnatal day 30 was 7,870 µg/mL and 4,560 µg.h/mL, respectively, in males and 7,760 µg/mL and 4,400 µg.h/mL, respectively, in females.

GLP compliance: Yes

Reference ID: 5048631

Conducting laboratory and location: (b) (4)

Table 27. Methods for Study No. GDX-33-053

Methods	Details
Dose and frequency of dosing:	0 (negative control), 0.6 (LD), 1.25 (MD), 2.5 (HD) mmol/kg as a single dose or repeated daily doses without or with 9-week recovery period
Route of administration:	Intravenous
Formulation/vehicle:	Drug product (G03277.100) was formulated as a sterile aqueous solution for i.v. injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 17M016, % Purity: 99.48%)/0.9% sodium chloride
Species/strain:	Rats/Sprague-Dawley (Crl: OFA (SD)
Number/sex/group:	15/sex/group
Satellite groups:	TK satellite, n=9/sex/group for gadopiclenol and n=9/sex for negative control (0.9% sodium chloride)
Study design:	Juvenile animals were administered control or gadopiclenol as a single (PND 10, subgroups A and D) or repeat dose (PND 10, 14, 18, 22, 26, 30; subgroups B and C), without (subgroups B and D) or with a 9-week recovery period (subgroups A and C). Scheduled euthanasia was on PND 11 (subgroup D, satellite group for TK, plasma/tissue Gd), PND 31/32 (subgroup B), PND 71/72 (subgroup A), or PND 91/92 (subgroup C). Study endpoints included evaluation of postnatal development (tibial length, gripping reflex, auditory reflex, and pupillary reflex), sexual maturation (subgroup C only with timing of vaginal opening and estrous cycle in females, timing of balano-preputial opening and sperm analysis in males), neurobehavioral assessment (subgroup C only by water maze and motor activity), and measurement of tissue and plasma levels of Gd.
Deviation from study protocol affecting interpretation of results:	No

Abbreviations: HD, high dose; i.v., intravenous; LD, low dose; MD, mid dose; PND, postnatal day; TK, toxicokinetic

Table 28. Observations and Results: Changes From Control (Study No. GDX-33-053)

Parameters	Major Findings
Mortality	1, 2, 0, 3 animals moribund or found dead in control, LD, MD, and HD groups; mortality not considered to be test article-related.
Clinical signs	Subgroups A – C: No test article-related effects on clinical signs

Reference ID: 5048631

Parameters	Major Findings
Body weights	Subgroups A – C: No test article-related body weight changes or effects on food consumption
Ophthalmoscopy	Subgroups A – C: No test article-related changes on ophthalmoscopy
Hematology	Subgroups A – C: No test article-related effects on hematology and coagulation parameters based on historical values. Non-dose-related minimal to mild increase in neutrophils, lymphocytes, and white blood cells at the HD in subgroup B.
Clinical chemistry	Subgroup A: No test article-related effects on clinical chemistry parameters Subgroup B: Test article-related decrease in ferritin at all dose levels in males and LD and HD females, decrease in serum iron at all dose levels in females, increase in urea at all dose levels in females Subgroup C: No test article-related effects on clinical chemistry parameters. Effects on serum ferritin, iron, and urea were considered reversible and not adverse
Urinalysis	Subgroup A: No test article-related effects on urinalysis parameters Subgroup B: Test article-related increase in iron urinary excretion in HD females Subgroup C: No test article-related effects on urinalysis parameters. Effect on iron urinary excretion was considered reversible and not adverse.

Reference ID: 5048631

Parameters	Major Findings
Cross pathology	Subgroups A – C: No test article-related effects on macroscopic gross pathology
Organ weights	Subgroups A – C: No test article-related effects on organ weights
Histopathology Adequate battery: Yes	Subgroup B: Test article-related finding of cortical tubular vacuolation at all dose levels following repeat dosing, reversible following 9-week recovery period and not considered adverse Subgroup C: No test article-related finding by microscopic analysis. Subgroups A – C: No test article-related effect on the myeloid to erythroid ratio (bone smear analysis)
Postnatal development	Subgroups A – C: No test article-related effect on postnatal development as determined by tibial length (left), gripping reflex, pupillary reflex, or auditory reflexes
Sexual maturation	Subgroup C only: No test article-related effect on sexual maturation
Neurobehavioral assessment	Subgroup C only: No test article-related effect on learning/memory by Morris water maze or habituation/motor activity by motor activity assessment
Tissue Gd levels	Gd concentrations increased with increasing doses in all tissues after single and repeat doses, with or without recovery. In males at the HD, Gd exposure (subgroup D/B; nmol/g) was kidneys (998/2186) > liver (98.3/108) > femur (47.1/86.3) > skin (40.5/80.7) > cerebellum (14.9/4.14) > brain (10.2/3.68). In females at the HD, Gd exposure was kidneys (998/1666) > liver (93.0/89.2) > femur (47.1/67.2) > skin (40.5/58.1) > cerebellum (14.9/3.29) > brain (10.2/3.01). At the end of 9-week recovery (subgroup C), overall exposure was kidneys > femur > brain > cerebellum > liver > skin in males and females. For single dose following 9-week recovery (subgroup A), Gd levels were at or below the LLOQ except for kidneys.

Abbreviations: Gd, gadolinium; HD, high dose; LD, low dose; LLOQ, lower limit of quantitation; MD = mid dose

Reference ID: 5048631

5.5.7. Other Toxicology Studies

Gadolinium Retention

Study Title/Number: Potential for Gadolinium Tissue Deposition/Retention in Adult and Juvenile Rats Following Intravenous Administration of Gadopiclenol / GDX-33-054

Key Study Findings:

- In both juvenile and adult animals, no unscheduled death, treatment-related clinical sign, or effect on body weight gain in any group or subgroup was reported.
- Following single or repeat dosing with gadopiclenol (0.6 mmol/kg) in both juvenile and adult animals, there were measurable levels of retained Gd in the kidney, liver, femur, skin, cerebellum, brain, and plasma.
- Following single or repeat dosing and recovery period in both juvenile and adult rats, tissue Gd levels were very low, close to or below the LLOQ, in the tissues selected for evaluation.
- Tissue Gd levels were lower following administration of 0.6 mmol/kg gadopiclenol than the reference item, 0.6 mmol/kg gadodiamide (Omniscan) at the end of the treatment period and after 8-week recovery period with either a single or repeat dose.

GLP compliance: Yes

Conducting laboratory and location: (b) (4)

Table 29. Methods for Study No. GDX-33-054

Methods	Details
Dose and frequency of dosing	0.6 mmol/kg as a single (subgroups A and C) or repeat dose (subgroup B and D) every 4 days for 8 weeks, without (subgroup A and C) or with 8-week recovery period (subgroup B and D).
Route of administration	Intravenous
Formulation/vehicle	Drug product (G03277.100) was formulated as a sterile aqueous solution for i.v. injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 17M016, % Purity: 99.48%) Reference item, gadodiamide (Omniscan), was supplied preformulated (Batch # 14110307).
Species/strain	Rat/Sprague-Dawley (Crl: OFA (SD))
Number/sex/group	6/sex/group
Satellite groups	No
Study design	Juvenile animals were administered gadopiclenol as a single or repeat dose (Days 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49,

Reference ID: 5048631

Methods	Details
	53, and 57) on PND 10 without or with an 8-week recovery period. Adult animals were administered gadopiclenol or gadodiamide as a single or repeat dose (Days 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 41, 45, 49, 53, and 57) without or with an 8-week recovery period. Study endpoints included clinical observations, body weight gains, organ weights, gross macroscopic evaluation, histopathology, and determination of plasma and tissue Gd levels (right femur, right half of brain, right half of cerebellum, right kidney, part of liver, and skin) by ICP-MS.
Deviation from study protocol affecting interpretation of results:	No

Abbreviations: Gd, gadolinium; ICP-MS, Inductively coupled plasma mass spectrometry; i.v., intravenous; PND, postnatal day

Table 30. Observations and Results (Study No. GDX-33-054)

Parameters	Major Findings
Mortality	There were no deaths. All animals survived to scheduled necropsies.
Clinical signs	No test article or reference item related effects on clinical signs in juvenile or adult animals
Body weights	No test article or reference item related body weight changes in juvenile or adult animals
Hematology	Not evaluated
Clinical chemistry	Not evaluated
Urinalysis	Not evaluated
Gross pathology	No test article or reference item related macroscopic findings in juvenile or adult animals
Organ weights	No test article or reference item related effects on organ weights in juvenile or adult animals
Histopathology Adequate battery: Yes	Histopathology findings at terminal sacrifice were limited to minimal cytoplasmic vacuolation (fine droplets) in the proximal convoluted renal tubule epithelium. Incidence was similar between single and repeat dose in adult or juvenile animals, and between gadopiclenol and gadodiamide reference item. In the absence of degenerative or necrotic changes, it was considered non-adverse.
Tissue Gd levels (juvenile)	After single/repeat dosing of gadopiclenol, the highest Gd concentrations (nmol/g) were detected in the kidney (91.8/1046, after single/repeated dosing, respectively), followed by liver

Reference ID: 5048631

Parameters	Major Findings
	(8.06/26.0) or femur (7.67/38.1), skin (5.91/17.8), cerebellum (1.46/0.692) or brain (0.984/0.735), and plasma (0.146/0.167). After single/repeat dosing of gadopiclenol with 8-week recovery period, Gd concentrations (nmol/g) were close to or below the LLOQ in all tissues, except femur (up to 0.05/17.3) and kidneys (up to 1.15/44.4). Following the recovery period, the Gd levels decreased by more than 95% compared to the end of the dosing period for animals who received a single dose. In animals receiving repeated administrations, the same decrease was observed in kidney, liver, plasma, and skin, but was less evident in brain and cerebellum (between 70% to 93%), and femur (up to 47%).
Tissue Gd levels (adult)	After single/repeat dosing of gadopiclenol, the highest Gd concentration (nmol/g) was detected in the kidney (486/1343, after single/repeated dosing, respectively), followed by liver (16.4/35.2), femur (11.9/35.8), skin (12.6/18.1), cerebellum (0.219/1.31), brain (0.365/0.742), and plasma (0.088/0.172). In rats that were administered gadodiamide as single/repeat dose, the highest Gd concentration (nmol/g) was detected in the kidney (444/1243, after single/repeat dosing, respectively) followed by the femur (16.7/163), skin (14.0/155), liver (20.1/32.7), cerebellum (0.477/4.24), brain (3.62/0.564), and plasma (0.172/0.273). After single/repeat dose and recovery period, Gd concentrations (nmol/g) were low and close to the LLOQ in all tissues, except in femur (up to 2.00/25.7) and in kidneys (up to 2.87/123). After a single dose and recovery period, these values decreased by more than 95% relative to the end of the dosing period with the exception of the femur (up to 77%). In animals receiving repeated administrations, these values decreased by more than 90% in kidneys, liver, plasma, and skin, being less evident in brain and cerebellum (up to 70%), and femur (up to 18%).

Note: Tissue Gd concentrations are presented for males only and were similar to Gd concentrations for females in juvenile and adult animals.
Abbreviations: Gd, gadolinium; LLOQ, lower limit of quantitation

Conclusions:

- After single dosing at the end of the treatment period, Gd concentrations in juvenile animals compared to adult animals were lower in kidney, higher in brain and cerebellum, and similar in other tissues. After repeated dosing with and without recovery and single dosing with recovery, these values were equivalent between juvenile and adult animals.

Reference ID: 5048631

- Overall, tissue Gd concentrations were lower following gadopiclenol treatment than gadodiamide (reference item) treatment at the end of the dosing period and after an 8-week recovery period following either a single or repeat dose administration.
- Intravenous administration of gadopiclenol or the gadodiamide reference item induced at terminal sacrifice minimal cytoplasmic vacuolation (fine droplets) in the proximal convoluted renal tubule epithelium. The incidence was similar between single and repeat dose in adult or juvenile rats from both sexes, and also between gadopiclenol and the gadodiamide reference item. In the absence of degenerative or necrotic changes, it was considered non-adverse.
- After an 8-week treatment-free recovery period, the reversibility of this finding in single dose recovery animals and repeat-dose recovery animals was complete in all adult and juvenile groups.

Local Tolerance

Nonclinical local tolerance testing was conducted to evaluate and provide support for human exposure to a drug product both as an active drug substance and excipients at contact sites after intended clinical use and after unintentional administration.

Study Title/Number: G03277.023 - Local Tolerance in the rabbit by Intravenous, Perivenous and Intra-Arterial Routes / GDX-33-018 (AB11950)

Study Objective:

This study was conducted to evaluate the local tolerance of gadopiclenol (G03277.023) in NZW rabbits after a single intravenous, perivenous, or intra-arterial administration.

Key Study Findings:

- There were no deaths or systemic treatment-related clinical signs throughout the study and there was no effect on body weight in the gadopiclenol-treated group.
- Following intravenous or intra-arterial administration, slight-to-moderate erythema was observed at the injection site which did not persist after day 2. Histopathologically, moderate vascular intimal necrosis of the arterial wall or minimal erosion of the vascular intima was observed 24 hr after intra-arterial injection but the changes were not observed 96 hr post-dose.
- After a perivenous injection, very slight to moderate erythema and very slight-to-slight edema were noted at the injection site which correlated with histological changes observed in the dermis and epidermis (dermal hemorrhage, edema, inflammation, necrosis; epidermal necrosis, crusts, and acanthosis) at 96 hr post-dose. Based on the macroscopic and histopathology findings, there was poor local tolerance for gadopiclenol by the perivenous route at 0.25 mmol/injection.

GLP compliance: Yes

Reference ID: 5048631

Conducting laboratory and location (b) (4)

Table 31. Methods for Study No. GDX-33-018

Methods	Details
Dose and frequency of dosing	0 (negative control), 0.25 mmol, or 0.6 mmol/kg as a single dose
Route of administration	Intravenous, perivenous, intra-arterial
Formulation/vehicle	Drug product (G03277.023) was formulated as a sterile aqueous solution for intravenous, perivenous, or intra-arterial injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 11M001B, % Purity: 98.1%)/0.9% sodium chloride
Species/strain	Rabbits/New Zealand White rabbit, LAGO: INR (NZW) EOPS
Number/sex/group	5/sex/group
Satellite groups	No
Study design	Gadopiclenol or negative control were administered by intravenous (0.6 mmol/kg; left ear), perivenous (0.25 mmol; left ear), or intra-arterial (0.6 mmol/kg; right ear) route. Animals were evaluated for morbidity, mortality, clinical signs, and body weight, and were subjected to macroscopic and histopathologic examination from 24 hr to 96 hr post-dose.
Deviation from study protocol affecting interpretation of results	No

Reference ID: 5048631

Table 32. Observations and Results: Changes From Control (Study No. GDX-33-018)

Parameters	Major Findings
Mortality	There were no deaths. All animals survived to scheduled necropsies.
Clinical signs	No test article-related effects on clinical signs by i.v., PV, or IA route
Injection site observations	i.v. route: Very slight to well defined erythema (grades 1 and 2) in 4/10 animals (Day 1), 2/5 animals (Day 2). Mean irritation index up to 0.7. Finding not considered to be adverse. PV route: Very slight to moderate erythema (grades 1 to 3) in 9/10 animals (Day 1), 3/5 animals (Day 4). Very slight or slight edema (grade 1 or 2) in 3/5 animals (Days 1 to 4). Mean irritation index up to 2.3. IA route: Very slight to moderate erythema (grades 1 to 3) in 5/10 animals on Day 1 and very slight to well defined erythema on Day 2. Reaction was not observed on Day 3 and Day 4. Induration observed in 1/5 animals on Day 3 and Day 4. Mean irritation index up to 1.8.
Body weights	No test article-related body weight changes by i.v., PV, or IA route
Histopathology Adequate battery: Yes	i.v. route: No test article-related findings at 0.6 mmol/kg (4-fold dose multiples) PV route: Histological changes in the dermis and epidermis (dermal hemorrhage, edema, inflammation, necrosis, crusts, acanthosis); poor local tolerance at 0.25 mmol IA route: Moderate vascular necrosis of the arterial wall or minimal intimal erosion in 2/5 animals at 24 hr, reversible by 96 hr post-dose

Abbreviations: IA, intra-arterial; i.v., intravenous; PV, perivenous

Immediate Hypersensitivity

Study Title/Number: Evaluation of the Potential to Induce Immediate Hypersensitivity in the Guinea Pig / GDX-33-019 (AB12425)

Study Objective:

The study was conducted to evaluate the potential to induce immediate type hypersensitivity in the guinea pig.

Reference ID: 5048631

Key Study Findings:

- No clinical signs were observed after intravenous challenge injection of gadopiclenol (Day 21) to animals sensitized to negative control or gadopiclenol on Days 0 and 7.
- Intravenous challenge injection of ovalbumin (positive control) to animals sensitized to positive control on Days 0 and 7 resulted in anaphylaxis, demonstrating validity of the assay.
- Under the experimental conditions of this study, intravenous injection of gadopiclenol did not induce any signs of immediate hypersensitivity in guinea pigs sensitized to gadopiclenol.

GLP compliance: Yes

Conducting laboratory and location (b) (4)

Table 33. Methods for Study No. GDX-33-019

Methods	Details
Dose and frequency of dosing	0 (negative control), 0.25 mmol/0.5 mmol gadopiclenol, 4 µg/mL ovalbumin (positive control); dosing on Days 0, 7, and 21
Route of administration	Subcutaneous for induction phase and intravenous for challenge phase
Formulation/vehicle	Drug product (G03277.100) was formulated as a sterile aqueous solution for intravenous, perivenous, or intra-arterial injection containing 0.5 mmol/mL of the drug substance gadopiclenol (Lot #: 11M001B, % Purity: 98.1%)/0.9% sodium chloride Positive control: 4 µg/mL ovalbumin
Species/strain	Guinea pig / Hartley (Crl:HA)
Number/sex/group	5 males/group for negative and positive control and 10 males/group for test item
Satellite groups	No
Study design	Animals were administered negative control (Group 1, 0.9% sodium chloride), gadopiclenol (Group 2), or positive control (Group 3, ovalbumin) by subcutaneous injection on Day 0 and Day 7. Adjuvant (5 mg aluminum hydroxide in 0.4 mL volume) was injected on Day 0 only. Gadopiclenol or positive control was administered by intravenous injection on Day 21 (challenge phase).
Deviation from study protocol affecting interpretation of results	No

Reference ID: 5048631

Table 34. Observations and Results: Changes From Control (Study No. GDX-33-019)

Parameters	Major Findings
Mortality	There were no deaths in Group 1 or Group 2 animals.
Clinical signs	No test article-related effects on clinical signs after intravenous challenge with gadopiclenol in Group 1 or Group 2 animals. Anaphylactic reaction in the first Group 3 animal (positive control, ovalbumin) within 1 min following injection. Clinical signs included chewing, difficulty breathing, convulsions, and death. Challenge injection was not administered to remaining 4 animals.
Body weights	No test article-related effects on body weight.

Genotoxicity Evaluation of Impurities

The Applicant assessed the genotoxicity of potential impurities for gadopiclenol, including compounds from the drug substance, (b) (4), by-products, and degradation products according to ICH M7 and by quantitative structure-activity relationship. One potential impurity was identified in the drug substance and drug product ((b) (4); Figure 3) and one impurity ((b) (4); Figure 4) at higher levels than qualified. (b) (4) Genotoxic potential of impurities (b) (4) were evaluated by in vitro Ames test and in vitro mammalian mutation lymphoma assay.

Figure 3. Chemical Structure of (b) (4)

Figure 4. Chemical Structure of (b) (4)

In vitro Ames test was also conducted for (b) (4); Figure 5 shows (b) (4) and (b) (4) Figure 6).

Figure 5. Chemical Structure of (b) (4)

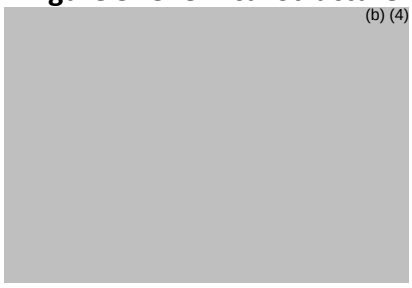
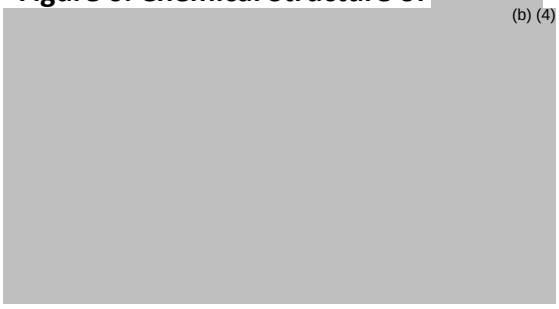


Figure 6. Chemical Structure of (b) (4)



Study Title/Number: Evaluation of the Mutagenic Activity of (b) (4) in the *Salmonella typhimurium* Reverse Mutation Assay and the *Escherichia coli* Reverse Mutation Assay / GDX-33-057 (20247993)

Study Objective:

This study was conducted to determine the potential of impurity (b) (4) and/or its metabolites to induce reverse mutations at the histidine locus in strains of *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) and at the tryptophan locus of *Escherichia coli* strain WP2uvrA in the presence or absence of an exogenous mammalian metabolic activation system (S9).

Reference ID: 5048631

Key Study Findings:

- The results of the bacterial mutagenicity assay indicated that under the experimental conditions of the study, impurity (b) (4) did not cause a positive mutagenic response with any of the tester strains in either the absence or presence of S9 metabolic activation.
- No positive increase in the mean number of revertants per (b) (4)-treated plate was observed with any of the tester strains (without or with metabolic activation). No precipitate or cytotoxicity was observed. (b) (4) was negative (non-mutagenic) in the bacterial reverse mutation assay.

GLP compliance: Yes

Test system: Four histidine-dependent strains of *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) and one *Escherichia coli* tester strain WP2uvrA in the absence and presence of Aroclor-induced rat liver microsome fraction (S9).

Study is valid: Yes

Study Title/Number: Evaluation of the Mutagenic Activity of (b) (4) in the *Salmonella typhimurium* Reverse Mutation Assay and the *Escherichia coli* Reverse Mutation Assay / GDX-33-058 (20247990)

Study Objective:

This study was conducted to determine the potential of (b) (4) and/or its metabolites to induce reverse mutations at the histidine locus in strains of *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) and at the tryptophan locus of *Escherichia coli* strain WP2uvrA in the presence or absence of an exogenous mammalian metabolic activation system (S9).

Key Study Findings:

- The results of the bacterial mutagenicity assay indicated that under the experimental conditions of the study, impurity (b) (4) did not cause a positive mutagenic response with any of the tester strains in either the absence or presence of S9 metabolic activation.
- No positive increase in the mean number of revertants per (b) (4)-treated plate was observed with any of the tester strains (without or with metabolic activation). No precipitate or cytotoxicity was observed. (b) (4) was negative (non-mutagenic) in the bacterial reverse mutation assay.

GLP compliance: Yes

Test system: Four histidine-dependent strains of *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) and one *Escherichia coli* tester strain WP2uvrA in the absence and presence of Aroclor-induced rat liver microsome fraction (S9).

Reference ID: 5048631

Study is valid: Yes

Study Title/Number: (b) (4) Bacterial Reverse Mutation Test / FSR-IPL 191012

Study Objective:

This study was conducted to determine the potential of (b) (4) to induce reverse mutations at the histidine locus in strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, and TA102) in the presence or absence of an exogenous mammalian metabolic activation system (S9).

Key Study Findings:

- The results of the bacterial mutagenicity assay indicated that under the experimental conditions of the study, (b) (4) did not cause a positive mutagenic response with the TA100, TA1535, TA1537, and TA102 tester strains in either the absence or presence of S9 metabolic activation. A positive mutagenic response was observed with the TA98 tester strain in the absence (slightly mutagenic) and presence of metabolic activation (mutagenic).
- Strong toxicity was observed in the TA102 tester strain at 5000 µg/plate and slight to moderate toxicity at 500 and 1500 µg/plate in the presence of metabolic activation. Slight toxicity was observed in TA1535, TA1537, TA98, and TA100 at >500 µg/plate.
- No positive increase in the mean number of revertants per (b) (4)-treated plate was observed with TA100, TA1535, TA1537, and TA102 tester strains (without or with metabolic activation).
- (b) (4) was positive (mutagenic) in the bacterial reverse mutation assay for only the TA98 strain.

GLP compliance: Yes

Test system: Five histidine-dependent strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA102) in the absence and presence of Aroclor-induced rat liver microsome fraction (S9).

Study is valid: Yes

Study title / number: Evaluation of the Mutagenic Activity of (b) (4) in the Salmonella Typhimurium Reverse Mutation Assay and the Escherichia coli Reverse Mutation Assay (Plate Incorporation and Pre-Incubation Methods) / 20200824

Study Objective:

This study was conducted to determine the potential of impurity (b) (4) and/or its metabolites to induce reverse mutations at the histidine locus in strains of *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) and at the tryptophan locus of *Escherichia coli (E. coli)* strain WP2uvrA in the presence or absence of an exogenous mammalian metabolic activation system (S9).

Reference ID: 5048631

Key Study Findings:

- The results of the bacterial mutagenicity assay indicated that under the experimental conditions of the study, impurity (b) (4) did not cause a positive mutagenic response with any of the tester strains in either the absence or presence of S9 metabolic activation.
- No positive increase in the mean number of revertants per (b) (4)-treated plate was observed with any of the tester strains (without or with metabolic activation). No precipitate or cytotoxicity was observed. (b) (4) was negative (non-mutagenic) in the bacterial reverse mutation assay.

GLP compliance: Yes

Test system: Four histidine-dependent strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537) and one *Escherichia coli* tester strain WP2uvrA in the absence and presence of Aroclor-induced rat liver microsome fraction (S9).

Study is valid: Yes

Study Title/Number: Evaluation of the Mutagenic Activity of (b) (4) in an In Vitro Mammalian Cell Gene Mutation Test With L5178Y Mouse Lymphoma Cells / GDX-33-059 (20247994)

Key Study Findings:

- No precipitate was noted at any tested dose level and in any experiment. No signs of cytotoxicity were noted in the study at up to 5000 µg/mL in the absence or presence of metabolic activation.
- Under the test conditions used, impurity (b) (4) did not induce any biologically significant increase in the mutant frequency at 24 hr in the absence of metabolic activation or at 4 hr either with or without metabolic activation. Impurity (b) (4) was negative for genotoxic potential by in vitro mouse lymphoma assay.

GLP compliance: Yes

Test system: L5178Y mouse lymphoma cells, clone -3.7.2C, designated L5178Y TK+/-; testing conducted in the absence and presence of Aroclor-induced rat liver microsome fraction (S9).

Study is valid: Yes, based on the acceptance criteria.

Study Title/Number: Evaluation of the Mutagenic Activity of (b) (4) in an In Vitro Mammalian Cell Gene Mutation Test With L5178Y Mouse Lymphoma Cells / GDX-33-060 (20247991)

Key Study Findings:

- No precipitate was noted at any tested dose level and in any experiment. No signs of cytotoxicity were noted in the study at up to 5000 µg/mL in the absence or presence of metabolic activation.

Reference ID: 5048631

- Under the test conditions used, impurity (b) (4) did not induce any biologically significant increase in the mutant frequency at 24 hr in the absence of metabolic activation or at 4 hr either with or without metabolic activation. Impurity (b) (4) was negative for genotoxic potential by in vitro mouse lymphoma assay.

GLP compliance: Yes

Test system: L5178Y mouse lymphoma cells, clone -3.7.2C, designated L5178Y TK+/-; testing conducted in the absence and presence of Aroclor-induced rat liver microsome fraction (S9).

Study is valid: Yes, based on the acceptance criteria.

Other Studies

The Applicant conducted a series of non-GLP studies to evaluate MRI signal and Gd retention following administration of gadopiclenol or representative linear and macrocylic GBCAs. The results of Study No. ER-15-00022 and Study No. ER-18-00010 are described below.

Study Title/Number: One-Year Follow-Up of the Systemic Retention of Gadolinium in Rats After Repeated Injections of Gadopiclenol, Gadobutrol or Gadodiamide: Distribution, Kinetics, Speciation and Safety / ER-18-00010

Study Objective:

This non-GLP comparative study was conducted to evaluate Gd retention, biodistribution and kinetics, and safety following repeat intravenous administration of gadopiclenol, gadodiamide (as a representative linear agent) or gadobutrol (as a representative macrocyclic agent) at equimolar doses (2.4 mmol/kg/dose, once per week for 5 weeks) in Sprague Dawley rats. In one sub-study, T1-weighted MRI (cerebellum and kidney) was conducted after a 12-month treatment-free recovery period and animals were sacrificed for histological evaluation, Gd speciation, and blood sampling for TK analysis and kidney function. In another sub-study, T1-weighted MRI (cerebellum and kidney) was conducted after 1, 5, and 12-month treatment-free recovery periods and animals were sacrificed for quantitation of total Gd levels in CNS, bone, kidney, liver, and muscle.

Key Study Findings:

- Minimal effect on T1-weighted signal intensity relative to brainstem was observed at 1 month in the deep cerebellar nuclei for gadopiclenol whereas no effect was observed for gadobutrol and an increase was observed throughout 12 months for gadodiamide.
- Increased CNR on MRI in the kidney cortex (compared to muscle) was observed until 12 months for gadopiclenol, gadobutrol, and gadodiamide. Increased CNR (compared to muscle) was observed in the kidney medulla until 12 months for gadopiclenol and gadobutrol and until 5 months for gadodiamide.
- Gd retention from gadopiclenol administration was increased by 2 to 3-fold compared to gadobutrol in all organs and timepoints except for CNS which had similar levels near

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the lower limit of quantification. Gd retention from gadodiamide was greater than from gadopiclenol for all tissues with poor washout over 12 months. Note that these results were also evaluated by the Statistics team.

- At 1-month post dose for gadopiclenol, all detected Gd (soluble fractions) was present as intact GBCA and chromatograms were similar to those of gadobutrol. At 12-months post dose for gadopiclenol, more than 95% of detected Gd (soluble fractions) was present as intact GBCA. Speciation analyses for cerebellum and kidney were similar for gadopiclenol and gadobutrol.
- Repeat administration of gadopiclenol was not associated with any definitive histopathology findings.

Conclusion:

Gadopiclenol was associated with 2-fold to 3-fold greater levels of Gd compared to gadobutrol in the kidney, liver, bone, and skin for all time points when administered at equimolar dose. Levels of retained Gd were similar and close to the lower limit of quantification in the CNS (cerebellum, cortex, brain stem, and subcortical regions). Levels of Gd associated with repeat administration of gadodiamide were much greater than gadopiclenol or gadobutrol, as expected based on relative lower stability of linear versus macrocyclic GBCAs. These findings paralleled T1 signal metrics over the 12-month recovery period for cerebellum and kidney.

The clinical dose of gadopiclenol will be 0.05 mmol/kg, which is half the clinical dose of 0.1 mmol/kg for gadobutrol. Therefore, based on the study design, which compared GBCAs at equimolar dose (2.4 mmol/kg/dose), it is not known whether the recommended dose of gadopiclenol would result in similar levels of Gd retention when compared to other approved macrocyclic GBCAs at their recommended doses. Despite the uncertainty based on the administered dose, T1 signal metrics in the cerebellum and Gd retention in the CNS were similar for gadopiclenol and gadobutrol in this study and would not be of greater safety concern at the lower recommended dose level.

Study title / number: P03277 - MRI follow up (2.35 and 4.7T) of Deep Cerebellar Nuclei (DCN) enhancement after multiple injections in healthy rats. Comparison of P03277 (G03277.035), gadodiamide and gadobenate dimeglumine to saline / ER-15-00022

Study Objective:

This non-GLP study was conducted to evaluate MRI signal of the DCN following repeat administration (0.6 mmol/kg/day, 4 doses per week) for 5 weeks of gadopiclenol, gadodiamide, gadobenate meglumine, or negative control (saline), in Sprague Dawley rats. T1-weighted MRI (4.7T) was conducted prior to dosing (Week 1), 3 days after the last injection (Week 6), and after the treatment-free period (Week 10). Total Gd levels were measured by inductively coupled plasma mass spectrometry (ICP-MS) at the end of study.

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Key Study Findings:

- T1-weighted hypersignal in the DCN was observed by visual qualitative scoring for gadodiamide and gadobenate meglumine, but not gadopiclenol. The increase in the DCN/brainstem T1-weighted signal ratio (end of treatment-free recovery period) was 13% and 7% for the gadodiamide and gadobenate dimeglumine groups, respectively.
- Increased T1-weighted signal of the choroid plexus and 4th ventricle was observed for gadopiclenol-treated animals only. The 4th ventricle to cerebellum ratio was 20% at Week 6 (end of treatment period) and decreased during the 4-week treatment-free recovery period to baseline at Week 10.
- Gd levels from gadodiamide (2.3 to 3.6 nmol/g tissue) and gadobenate dimeglumine (1.1 to 2.2 nmol/g tissue) in selected tissues (cerebellum + pons, cortical brain, subcortical brain, and tracheal muscle) were significantly higher compared to Gd levels from gadopiclenol (0.3 to 1.3 nmol/g tissue). Gd levels from gadopiclenol ranged from 2-fold to 10-fold lower compared to gadodiamide or gadobenate dimeglumine.

Conclusion:

Increased T1-weighted signal in the DCN was not observed following repeat dosing (20 total doses) with gadopiclenol (0.6 mmol/kg) for 5 weeks. Increased T1-weighted signal related to administration of gadopiclenol was observed in the choroid plexus and the 4th ventricle, a finding not reported for other macrocyclic agents. The signal in these brain regions was transient and returned to baseline at the end of the treatment-free recovery period. Gd retention was observed for all administered GBCAs but levels associated with gadopiclenol were 2 to 10-fold lower compared to less stable linear GBCAs. Comparisons in this study are potentially limited in that gadopiclenol was administered at the same dose level as gadodiamide and gadobenate dimeglumine, whereas gadopiclenol will be administered clinically at 0.05 mmol/kg compared to gadodiamide and gadobenate dimeglumine which are administered at 0.1 mmol/kg.

6 Clinical Pharmacology

6.1. Executive Summary

Gadopiclenol is a GBCA proposed for use with MRI in adult and pediatric patients aged 2 years and older 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 proposed gadopiclenol dose for adult and pediatric patients aged 2 years and older is a single dose of 0.05 mmol/kg body weight (0.1 mL/kg body weight) administered intravenously at approximately 2 mL/sec.

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The clinical pharmacology review focused on dose selection in adult and pediatric patients and patients with renal impairment.

6.2. Summary of Clinical Pharmacology Assessment

Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted in NDA 216986. This NDA contains sufficient data to support approval from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Table 35. Clinical Pharmacology Review Issues and Recommendations

Review Issue	Recommendations and Comments
Substantial evidence of effectiveness	Substantial evidence of effectiveness comes from two Phase 3 studies (GDX-44-010 and GDX-44-011) which evaluated efficacy and safety of a single dose of 0.05 mmol/kg gadopiclenol in patients with brain or spine lesions and in patients with lesions in other body organs. The results from both studies supported conclusions that gadopiclenol is effective for lesion visualization and has an acceptable safety profile.
General dosing instructions	The proposed gadopiclenol dose is a single dose of 0.05 mmol/kg body weight (0.1 mL/kg body weight) administered intravenously at approximately 2 mL/sec. In the Phase 2b dose finding study (Study GDX-44-004) across a dose range of 0.025 mmol/kg to 0.2 mmol/kg gadopiclenol, a dose of 0.05 mmol/kg gadopiclenol had similar CNR in CNS lesions as compared to 0.1 mmol/kg gadobenate dimeglumine (MultiHance). The efficacy and safety results from two Phase 3 studies supported that a dose of 0.05 mmol/kg gadopiclenol is effective for lesion visualization and has an acceptable safety profile.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The pharmacokinetics of gadopiclenol for pediatric patients (2 to 17 years of age) from C10 to C30 (plasma concentration from 10 min to 30 min) were within the PK range of adults (>18 years of age). No dose adjustment is needed for pediatric patients aged 2 years or older. The pharmacokinetics of gadopiclenol for patients with varying degrees of renal impairment (mild, moderate, and severe) from C10 to C30 were higher as compared to those of

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Review Issue	Recommendations and Comments
	patients with normal renal function. The overall exposure (AUC_{inf}), based on the PK results in the renal impairment study (Study GDX-44-005), showed increased gadopiclenol exposure with increased degree of renal impairment (from 1.5-fold to 8.7-fold for mild to severe renal impairment). Simulated PK data from modeling indicate that decreasing the dose of gadopiclenol in patients with moderate or severe renal impairment to match PK concentrations (C10 to C30) would not decrease overall exposure without compromising efficacy. Thus, we recommend that the use of gadopiclenol in patients with renal impairment is avoided unless diagnostic information is essential, due to possible risks such as nephrogenic systemic fibrosis (NSF). If the use of gadopiclenol is necessary, no dose adjustment is recommended in patients with renal impairment.
Labeling	Overall, the proposed labeling is acceptable upon the Applicant's agreement to the FDA revisions to the prescribing information to increase clarity. Clinical pharmacology labeling recommendations are detailed in Section 8.6, 12.2, and 12.3 of the prescribing information.

Abbreviations: AUC, area under the concentration-time curve; CNR, contrast to noise ratio; CSR, clinical study report; FDA, Food and Drug Administration; NSF, nephrogenic systemic fibrosis; PK, pharmacokinetics

Post-Marketing Requirements and Commitments

No Clinical Pharmacology PMR/PMC is requested at this time.

6.2.1. Pharmacology and Clinical Pharmacokinetics

The C_{max} and AUC_{inf} of gadopiclenol increased proportionally over a dose range from 0.025 mmol/kg to 0.3 mmol/kg (0.5 times to 6 times the recommended dose). At the recommended dose, the mean (CV%) C_{max} and AUC_{inf} were 525 (13%) µg/mL and 569 (18%) µg·h/mL, respectively.

Distribution

After intravenous administration of Elucirem, gadopiclenol is distributed in the extracellular fluids.

The mean (CV%) volume of distribution of gadopiclenol at steady state is 13 (13%) L.

Protein binding of gadopiclenol is ≤1.8% at clinically relevant concentrations.

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Following GBCA administration, gadolinium is present for months or years in brain, bone, skin, and other organs.

Elimination

The mean (CV%) elimination half-life ($t_{1/2}$) of gadopiclenol is 1.5 (14%) h.

The mean (CV%) total body clearance (CL) and renal clearance (CL_r) of gadopiclenol are 100 (9.5%) mL/min and 81 (35%) mL/min, respectively.

Metabolism

Gadopiclenol is not metabolized.

Excretion

Gadopiclenol is mainly eliminated through the kidneys by glomerular filtration. Approximately 98% of the dose was recovered in urine within 48 hours after administration.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed gadopiclenol dose for adult and pediatric patients aged 2 years and older is a single dose of 0.05 mmol/kg body weight (0.1 mL/kg body weight) administered intravenously at approximately 2 mL/sec. The recommended dose was selected based on results in the Phase 2b dose finding trial that showed a dose of 0.05 mmol/kg gadopiclenol had similar CNR in CNS lesions as compared to 0.1 mmol/kg gadobenate dimeglumine (MultiHance), an FDA approved agent for MRI of the central nervous system (Table 39). GBCAs approved for lesion visualization indications share a recommended dose of 0.1 mmol/kg. A lower GBCA dose might theoretically result in decreased retention of gadolinium, depending on stability of the chelated Gd and other chemical features. Thus, the Applicant selected 0.05 mmol/kg gadopiclenol as the recommended phase 2 dose (RP2D). The efficacy and safety of the 0.05 mg/kg dose was further supported by two Phase 3 trials, which evaluated gadopiclenol in patients with brain or spine lesions and in patients with lesions in other body regions.

Therapeutic Individualization

Specific Populations

No clinically significant differences in the pharmacokinetics of gadopiclenol were observed based on sex. Gadopiclenol is not metabolized. No effect of hepatic impairment on the PK of gadopiclenol is expected as the drug is predominantly eliminated through the kidneys. Gadopiclenol AUC_{inf} is increased with increasing impairment of renal function.

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Drug-Drug Interactions

Gadopiclenol is not metabolized. No interaction with cytochrome P450 modulators or substrates is expected.

Outstanding Issues

There is no outstanding issue from a clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The general overview of gadopiclenol ADME and clinical PK information are presented below.

Table 36. Overview of Gadopiclenol ADME and Clinical PK Information

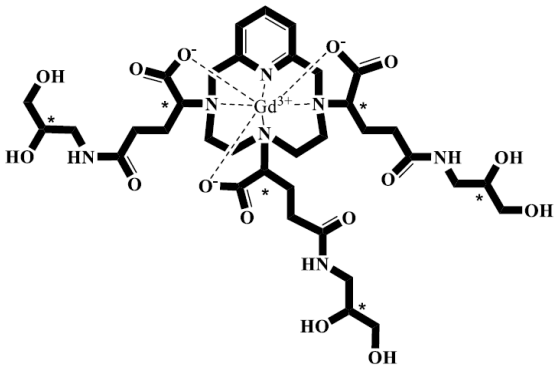
Physiochemical Properties	
Chemical structure and molecular weight	**Figure 7. Chemical Structure of Gadopiclenol**  Molecular weight: 970.11 g/mol Source: NDA216986, Module 3.2.S.1.2
Pharmacology	
Mechanism of action	Gadopiclenol is a paramagnetic, macrocyclic, nonionic complex of gadolinium that develops a magnetic moment when placed in a magnetic field. The magnetic moment allows alteration of the relaxation rates of body water protons in the vicinity, leading to an increase in signal intensity (brightness) of tissues on T1-weighted sequences. The relaxivity of gadopiclenol and other approved GBCAs is presented in Table 37.

Table 37. Relaxivity (r1) of GBCAs in Human Plasma/Serum at 1.5 T and 37°C

Gadolinium Chelate	r_1 (L.mmol^{-1}.s^{-1})
Gadobenic acid	3.8
Gadobutrol	3.3
Gadodiamide	3.3
Gadopentetic acid	3.3

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	Gadopiclenol	12.8
	Gadoteric acid	3.0
	Gadoteridol	2.9
	Gadoxetic acid	4.6
	Source: (Rohrer et al. 2005; Robic et al. 2019)	
Active moieties	Gadopiclenol is the only active moiety in plasma.	
QT/QTc prolongation	A single center, randomized, crossover, double-blind, placebo-controlled, positive-controlled (open-label), thorough QT study in healthy subjects (Study GDX-44-006) was conducted. The study utilized a crossover (4 period × 4 sequence) design with four treatment arms: 1) single dose, 0.1 mmol/kg; i.v. bolus 2 mL/s, 2) supra-therapeutic single dose, 0.3 mmol/kg; i.v. bolus 2 mL/s, 3) placebo (single dose, NaCl 0.9%; i.v. bolus 2 mL/s), and 4) moxifloxacin (single dose, 400 mg film-coated tablets by mouth), and four sequences (n=48; 12/sequence) according to a Williams design. No significant QTc prolongation effect of gadopiclenol (0.1 mmol/kg i.v. and 0.3 mmol/kg i.v.) was detected in this study. The highest dose evaluated covers the clinically relevant worst-case exposure scenario of renal impairment. The primary data analysis was a central tendency analysis, which did not suggest that gadopiclenol is associated with a significant QTc prolonging effect. The Applicant's exposure-response analysis indicated a concentration dependent increase in ΔQTcF with a slight positive slope of 0.0011 msec/µg/mL. The model predicted ΔΔQTcF (upper confidence interval) values of 2.23 (3.26) msec at the mean peak concentrations for the highest dose studied (0.3 mmol/kg of gadopiclenol: geometric mean C_{max} ~2491 µg/mL) following a single i.v. administration.	
General Information		
Bioanalysis	Gadopiclenol concentrations in plasma and urine were measured using validated LC-MS/MS methods. A summary of the method validation reports is included as an appendix (Section 16.3.1).	

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Healthy volunteers vs. patients	The PK in healthy subjects and patients appeared to be similar from a cross-study comparison.

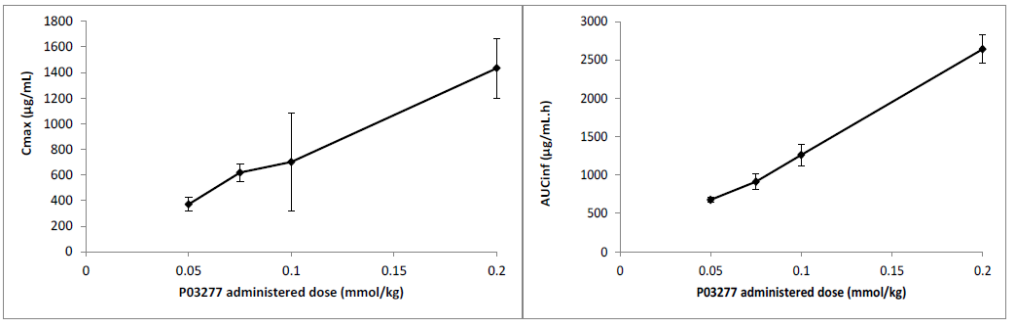
Table 38. Gadopiclenol Exposure in Healthy Subjects and Patients by Cross Study Comparison

	AUC_{inf} (µg/mL*h)	
Dose (mmol/kg)	**Healthy Subjects (n=6)**	**Patients With Brain Lesions (n=6)**
0.05	569±102	676±72
0.075	805±142	913±74
0.1	1288±184	1262±7
0.2	2368±249	2640±320

Source: Tables 9 and 11 in GDX-44-003-Appendix 16.1.13-Pharmacokinetic Report in Module 5.3.3.1
Values for AUC_{inf} are presented as mean ± standard deviation.

Drug exposure at steady state following the therapeutic dosing regimen	Not applicable. This drug is to be given as a single i.v. dose.
Minimal effective dose or exposure	In the Phase 2b dose finding study across a dose range of 0.025 mmol/kg to 0.2 mmol/kg gadopiclenol, a positive dose-response relationship for CNR was observed. However, a dose of 0.05 mmol/kg gadopiclenol had similar CNR as compared to 0.1 mmol/kg gadobenate dimeglumine and was selected for the Phase 3 trials.
Maximal tolerated dose or exposure	Single doses between 0.025 to 0.3 mmol/kg were investigated. No maximum tolerated dose has been identified.
Dose proportionality	Gadopiclenol showed dose-proportional increases in both C_{max} and AUC_{inf} across the dose range of 0.05 to 0.2 mg following a single dose.

Figure 8. Relationship of Gadopiclenol Dose to Cmax and AUC



Source: Figures 12 and 16 in GDX-44-003-Appendix 16.1.13-Pharmacokinetic Report in Module 5.3.3.1

Accumulation	Not applicable since this is a single dose drug.
Variability	Following a single dose of 0.05 mmol/kg, the inter-subject variability (CV%) of AUC_{inf} and C_{max} was 18% and 13%, respectively.

Absorption	
Bioavailability	Not applicable.
Distribution	
Volume of distribution	Following a single dose of 0.05 mmol/kg, the mean (CV%) volume of distribution of gadopiclenol at steady state is 13 (13%) L.
Plasma protein binding	Protein binding of gadopiclenol is ≤1.8% at clinically relevant concentrations.
Blood to plasma ratio	The mean blood-to-plasma ratio is ≤0.001.
Elimination	
Half-life	The mean (CV%) elimination half-life ($t_{1/2}$) of gadopiclenol is 1.5 (14%) h.
Clearance	The mean (CV%) total body CL and renal clearance of gadopiclenol are 100 (9.5%) mL/min and 81 (35%) mL/min, respectively.
Metabolism	
Primary metabolic pathway(s)	Gadopiclenol is not metabolized. Over a 2-hour incubation in human liver microsomes, the recovery of radioactivity of gadopiclenol is 74.4% with NADPH as compared to 73.3% without NADPH, which suggests the drug is not metabolized by major cytochrome P450 enzymes.
Excretion	
Primary excretion pathways (% dose) ±SD	Gadopiclenol is mainly eliminated through the kidneys by glomerular filtration. Approximately 98% of the dose was recovered in urine within 48 hours after administration. The renal clearance of gadopiclenol (~93 mL/min) is similar to glomerular filtration rate (~90 mL/min).

Abbreviations: ADME, absorption, distribution, metabolism, excretion; AUC, area under the concentration-time curve; CL, clearance; C_{max}, maximum observed plasma concentration; CNR, contrast to noise ratio; CV%, coefficient of variation; GBCA, gadolinium-based contrast agent; i.v. intravenous; LC-MS/MS, liquid chromatography – tandem mass spectrometry; NADPH, nicotinamide adenine dinucleotide phosphate; PK, pharmacokinetics; QTcF, corrected QT interval by Fredericia; SD, standard deviation; $t_{1/2}$, half-life

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The Applicant has conducted a dose finding Phase 2 trial (Study GDX-44-004) in patients with brain or spine lesions to select the RP2D and two Phase 3 trials (GDX-44-010 and GDX-44-011) in patients with brain or spine lesions or patients with lesions in other body regions to confirm efficacy and safety of gadopiclenol.

In the Phase 2 trial, the Applicant evaluated the CNR of CNS lesions for gadopiclenol at doses of 0.025, 0.05, 0.1, and 0.2 mmol/kg as compared to gadobenate dimeglumine (MultiHance) at 0.1 mmol/kg, the dose approved for MRI of the CNS, with three readers scoring the scans (Table 39). The results showed a similar CNR between 0.05 mmol/kg gadopiclenol and 0.1 mmol/kg gadobenate dimeglumine. This implies that a 0.05 mmol/kg dose of gadopiclenol may be effective in imaging.

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Table 39. Phase 2 Dose Finding: Primary Contrast to Noise Ratio Data for Off-Site Readings Using Mixed Models Holm's Step-Down Method in the Per Protocol Set (N=207)

		Least Square Mean (SE) of CNR			
Gadopiclenol Dose	n	Gadopiclenol	Gadobenate Dimeglumine	Difference	95% CI Difference
Reader 1					
0.025 mmol/kg	54	21.13 (2.65)	31.72 (2.65)	-10.59 (2.00)	[-14.59; -6.58]
0.050 mmol/kg	56	31.78 (3.58)	29.60 (3.58)	2.18 (2.42)	[-2.67; 7.03]
0.100 mmol/kg	51	35.94 (2.71)	27.28 (2.71)	8.66 (2.55)	[3.52; 13.79]
0.200 mmol/kg	44	49.99 (7.96)	35.55 (7.96)	14.45 (3.37)	[7.64; 21.25]
Reader 2					
0.025 mmol/kg	44	43.15 (7.57)	57.29 (7.57)	-14.14 (4.55)	[-23.33; 4.95]
0.050 mmol/kg	47	51.02 (5.09)	49.11 (5.09)	1.91 (4.56)	[-7.28; 11.10]
0.100 mmol/kg	43	72.17 (6.29)	52.79 (6.29)	19.38 (3.94)	[11.42; 27.34]
0.200 mmol/kg	41	103.18 (10.94)	64.81 (10.94)	38.37 (9.76)	[18.62; 58.12]
Reader 3					
0.025 mmol/kg	49	46.74 (10.04)	70.70 (10.04)	-23.96 (4.88)	[-33.78; -14.13]
0.050 mmol/kg	51	67.05 (6.43)	64.58 (6.43)	2.47 (5.40)	[-8.39; 13.32]
0.100 mmol/kg	45	94.17 (7.99)	64.94 (7.99)	29.23 (6.53)	[16.05; 42.41]
0.200 mmol/kg	42	125.08 (14.08)	73.12 (14.08)	51.96 (10.68)	[30.36; 73.55]

Source: Table 11-8 in GDX-44-004-CSR Synopsis and Body in Module 5.3.3.1
Abbreviations: CI, confidence interval; CNR, contrast to noise ratio; SE, standard error of the mean

The primary evidence of effectiveness comes from two Phase 3 studies which evaluated efficacy and safety of a single dose of 0.05 mmol/kg gadopiclenol in patients with brain or spine lesions and in patients with lesions in other body regions (see **Statistical and Clinical Evaluation**).

The imaging window for GBCAs is usually immediately after injection up to 30 min post-injection. Gadopiclenol has similar $t_{1/2}$ as compared to other GBCAs and the proposed imaging window post-injection of gadopiclenol is acceptable.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No.

Pediatric Patients Aged 2 to 17 Years Old

The Applicant has conducted a pharmacokinetic study (GDX-44-007) in pediatric patients from 2 to 17 years of age undergoing contrasted MRI. Due to high intersubject variability, the differences in PK parameters between different age groups are not considered clinically meaningful (Table 40). Based on population PK analysis, the plasma concentrations of gadopiclenol between 10 min and 30 min post-injection (C10 to C30) are comparable for all pediatric patient age groups (between 2 to 17 years old) and adult patients (Figure 9). Body

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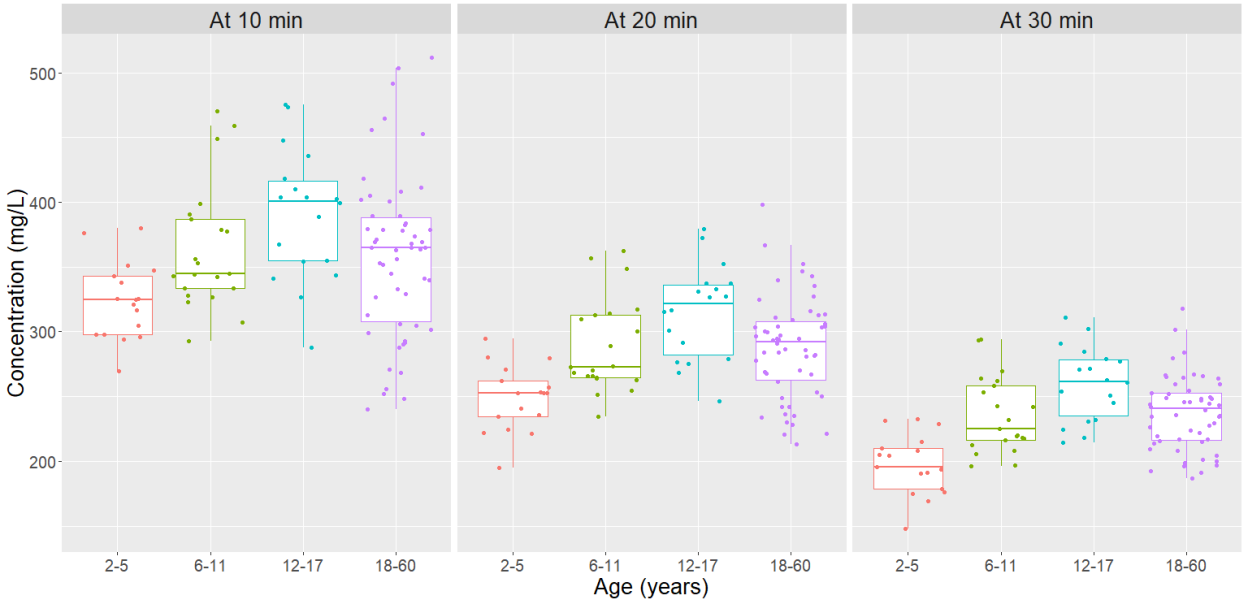
weight also did not impact the PK of gadopiclenol (See OCP Appendices, Section 16.3). Thus, no dose change is needed for pediatric patients between 2 to 17 years old.

Table 40. Pharmacokinetics Parameters Median [Range] According to Age Classes

	Age			
Parameter	**2-6 Years (n=19)**	**7-11 Years (n=19)**	**12-17 Years (n=19)**	**>18 Years (n=46)**
CL (L/h/kg)	0.12 [0.05; 0.28]	0.10 [0.04; 0.24]	0.08 [0.04; 0.20]	0.08 [0.05; 0.14]
$t_{1/2}$ (h)	1.29 [0.69; 3.38]	1.48 [0.83; 3.20]	1.77 [1.00; 3.57]	1.82 [0.93; 3.68]
AUC_{inf} (µg.h/mL)	403 [169; 964]	478 [183; 1077]	582 [267; 1291]	590 [353; 937]

Source: Table 8 of Population Pharmacokinetic Analysis Report in GDX-44-007-Appendix 16.1.13-Pharmacokinetic Report in Module 5.3.3.5. Results are reported for the recommended dosage.
Abbreviations: AUC, area under the concentration-time curve from time 0 to infinity; CL, clearance; $t_{1/2}$, half-life

Figure 9. Gadopiclenol Plasma Concentration at 10, 20, and 30 min in Patients With Normal Renal Function After Intravenous Injection of 0.05 mmol/kg Dose by Age Group



Source: FDA's analysis

Renal Impairment

The Applicant has conducted a pharmacokinetic study (GDX-44-005) in patients with renal impairment. Based on population PK analysis (Figure 10), the plasma concentrations of gadopiclenol between 10 min and 30 min post-injection (C10 to C30) are relatively higher for patients with renal impairment as compared to those in healthy volunteers with normal renal function. Given that imaging can occur immediately after injection up to about 30 min, image quality for patients with renal impairment as compared to patients with normal renal function is predicted to be similar. However, significantly higher AUC_{inf}, longer $t_{1/2}$, and lower renal clearance (CL_r) are observed in patients with renal impairment, particularly in patients with severe renal impairment (Table 41).

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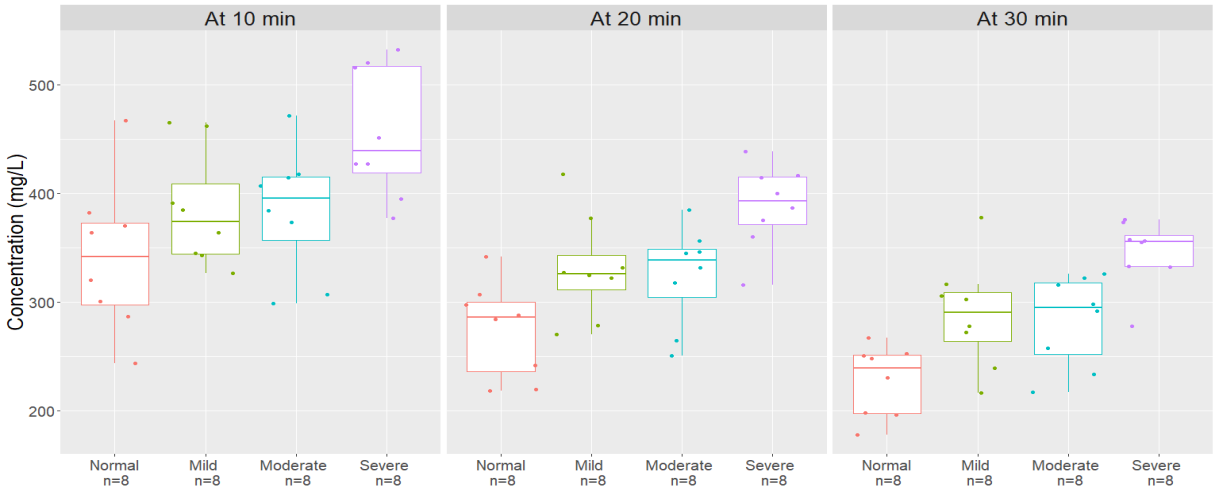
Figure 10. Gadopiclenol Plasma Concentration at 10, 20, and 30 min After Intravenous Injection of 0.05 mmol/kg Dose in Subjects With Normal and Impaired Renal Function



Source: FDA's analysis

Table 41. Effect of Renal Impairment on the Pharmacokinetics of Gadopiclenol

Parameter	Normal (eGFR ≥90 mL/min) (n=8)	Mild (eGFR 60 to <90 mL/min) (n=8)	Moderate (eGFR 30 to <60 mL/min) (n=8)	Severe (eGFR 15 to <30 mL/min) (n=8)
AUC_{inf} (µg·h/mL)	1113 (24%)	1711 (31%)	2759 (28%)	9671 (18%)
CL_r (mL/min)	96 (10%)	76 (23%)	44 (25%)	14 (26%)
$t_{1/2}$ (h)	1.9	3.3	3.8	11.7

Source: Table 20 in GDX-44-005-Appendix 16.1.13-Pharmacokinetic Report in Module 5.3.3.3
Notes: Values were obtained following administration of a single gadopiclenol 0.1 mmol/kg dose (2 times the recommended dosage) and are presented as mean (% coefficient of variation). eGFR is the estimate of GFR based on an estimation equation and expressed in mL/min. To convert mL/min/1.73 m2 to mL/min, multiply by the individual's BSA and divide by 1.73.
Abbreviations: AUC_{inf}, area under the concentration-time curve from time 0 to infinity; BSA, body surface area; CLr, renal clearance; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; $t_{1/2}$, half-life

GBCAs are known to have a risk for NSF in patients with renal impairment. The higher exposure of gadopiclenol may increase the risk of adverse reactions such as NSF. Modeling and simulation were conducted to evaluate whether decreasing the gadopiclenol dose for patients with renal impairment could provide comparable AUC_{inf} to that of patients with normal renal function without comprising efficacy. The simulated PK data indicated that decreasing the gadopiclenol dose in patients with moderate or severe renal impairment was not adequate to decrease AUC_{inf} to a clinically meaningful extent (Table 42) without compromising the C10 to C30 concentrations for these patients (Figure 11). As a result, a dose adjustment for patients with renal impairment is not advisable. Thus, due to the potentially increased risk of adverse reactions such as NSF, the use of gadopiclenol should be avoided among these patients unless the diagnostic information is essential and not available with non-contrast MRI or other imaging modalities. If use is necessary, no dose adjustment of gadopiclenol is recommended for patients with renal impairment.

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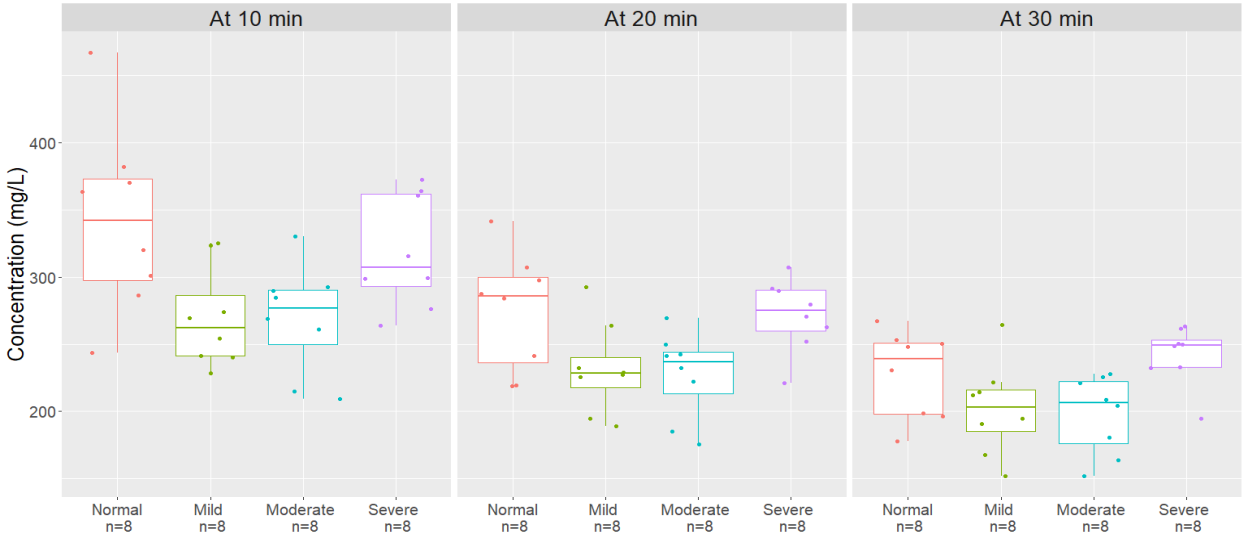
Figure 11. Simulated Gadopiclenol Plasma Concentration at 10, 20, and 30 min After Intravenous Injection of 0.05 mmol/kg Dose in Patients With Normal Renal Function and 0.035 mmol/kg Dose (↓30% in Recommended Dose) in Patients With Mild, Moderate, and Severe Renal Impairment



Source: FDA analysis

Table 42. Simulated Change in Exposure (AUC_{inf}) in Patients With Renal Impairment Receiving 0.035 or 0.05 nmol/kg Gadopiclenol as Compared to Patients With Normal Renal Function Receiving 0.05 nmol/kg Gadopiclenol

	Mild (eGFR 60 to <90 mL/min)	Moderate (eGFR 30 to <60 mL/min)	Severe (eGFR 15 to <30 mL/min)
Fold change in AUC_{inf} with 0.05 mmol/kg as compared to 0.05 mmol/kg in patients with normal renal function	↑1.5-fold	↑2.5-fold	↑8.7-fold
Fold change in AUC_{inf} with 0.035 mmol/kg (↓30% from recommended dose) as compared to 0.05 mmol/kg in patients with normal renal function	↑1.1-fold	↑1.7-fold	↑6.1-fold

Source: FDA's analysis
Abbreviations: AUC_{inf}, area under the concentration-time curve from time 0 to infinity; eGFR, estimated glomerular filtration rate

The Applicant has also evaluated gadopiclenol administration in patients with estimated glomerular filtration rate (eGFR) <15 mL/min in Study GDX-44-005. Since these patients were on hemodialysis, no plasma PK was measured. The hemodialysis removed gadopiclenol from plasma and the percentage decrease in blood concentration was 95 to 98% at the end of the first hemodialysis session and 100% after a subsequent hemodialysis session.

Reference ID: 5048631

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The interaction of gadopiclenol with other comedications is not expected as gadopiclenol is not a substrate of major CYP isozymes. As gadopiclenol is administered as a single intravenous dose and has a short elimination half-life (~1.8 hr), if gadopiclenol mediates any CYP P450 inhibition or induction or interacts with drug transporters, these actions would not be anticipated to have any clinically meaningful effect.

Reference ID: 5048631

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 43. Listing of Clinical Trials

Trial Identity	NCT No.	Study Design	Regimen/ Schedule/ Dose	Study Endpoints	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Phase 3 studies to support efficacy and safety							
GDX-44-010	NCT03996447	Randomized, double-blind, crossover	0.05 mmol/kg i.v.	Lesion visualization scores of paired gadopiclenol MRI + noncontrast MRI compared to noncontrast MRI in terms of 3 lesion visualization co-primary criteria (border delineation, internal morphology, and degree of contrast enhancement)	256	Patients presenting with known or highly suspected CNS lesion(s) based on results of a previous imaging procedure	33 centers in Belgium, France, Germany, Hungary, Italy, Republic of Korea, Poland, Spain, Taiwan, United States of America, and Mexico

Reference ID: 5048631

Trial Identity	NCT No.	Study Design	Regimen/ Schedule/ Dose	Study Endpoints	No. of Patients Enrolled	Study Population	No. of Centers and Countries
GDX-44-011	NCT03986138	Randomized, double-blind, crossover	0.05 mmol/kg i.v.	Lesion visualization scores of paired gadopiclenol MRI + noncontrast MRI compared to noncontrast MRI in terms of 3 lesion visualization co-primary criteria (border delineation, internal morphology, and degree of contrast enhancement)	304	Patients presenting with known or suspected enhancing lesion(s) in at least one body region based on a previous imaging procedure	33 centers in Bulgaria, Germany, Spain, France, Hungary, Ukraine, Italy, Republic of Korea, Poland, United States of America, and Mexico
Other studies pertinent to the review of efficacy and safety							
GDX-44-007	NCT03749252	Non-randomized, open-label, prospective	0.05 mmol/kg i.v.	Population pharmacokinetic parameters	80	Patients 2-17 years with known or suspected lesion(s) of CNS or body including head and neck and musculoskeletal system	16 centers in Poland, Bulgaria, Hungary, Slovakia, and Ukraine

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Trial Identity	NCT No.	Study Design	Regimen/ Schedule/ Dose	Study Endpoints	No. of Patients Enrolled	Study Population	No. of Centers and Countries
GDX-44-008	NCT02973516	Non-randomized, open-label, prospective	0.1 and 0.05 mmol/kg i.v.	Sensitivity and specificity for detection of hepatocellular carcinoma	40	Patients with liver cirrhosis or chronic liver disease who have hepatic nodules confirmed as hepatocellular carcinoma or not	2 centers in France
Other studies pertinent to the review of safety							
GDX-44-003	NCT03603106	Part 1: Randomized, double-blind, placebo control Part 2: Non-randomized, open-label, prospective	0.025 to 0.3 mmol/kg i.v.	Safety and pharmacokinetic profile	66 Part 1: 54 Part 2: 12	Part 1: Healthy volunteers Part 2: Patients with brain lesions	1 center in Belgium
GDX-44-004	NCT02633501	Randomized, double-blind, crossover	0.025 to 0.2 mmol/kg i.v.	Contrast to noise ratio in CNS lesions	312	Patients with known or highly suspected enhancing lesions of the CNS	28 centers in United States of America, Mexico, Belgium, Italy, Czech Republic, Hungary, Poland, and South Korea

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Trial Identity	NCT No.	Study Design	Regimen/ Schedule/ Dose	Study Endpoints	No. of Patients Enrolled	Study Population	No. of Centers and Countries
GDX-44-005	NCT03657784	Non-randomized, open-label, prospective	0.1 mmol/kg i.v.	Pharmacokinetic parameters	40	Healthy volunteers with stable normal renal function, and patients with stable mild, moderate, or severe renal impairment, or end-stage renal failure.	2 centers in Moldova and Romania
GDX-44-006	NCT03657264	Randomized, crossover, double-blind, placebo controlled and open-label, positive controlled	0.1 and 0.3 mmol/kg i.v.	Cardiac safety (QT and QTc intervals)	48	Adult healthy volunteers	1 center in Belgium

Source: FDA clinical reviewer
Abbreviations: CNS, central nervous system; i.v., intravenous; MRI, magnetic resonance imaging

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7.2. Review Strategy

Primary evidence of effectiveness and safety of gadopiclenol as a contrast agent for MRI was provided in two prospective trials, GDX-44-010 (PICTURE) and GDX-44-011 (PROMISE). GDX-44-010 was conducted in adult patients with lesions in the CNS and GDX-44-11 was conducted in adult patients with lesions in the chest, abdomen, pelvis, head and neck, or musculoskeletal system.

GDX-44-007 assessed population pharmacokinetics in pediatric patients aged 2 years to 17 years. Safety data were collected, but only limited effectiveness data were obtained, so this study is not reviewed in detail. A brief overview is provided in Section 8.1.5.

GDX-44-008 was an exploratory study of the ability of gadopiclenol to characterize liver lesions as hepatocellular carcinoma in patients at risk for the disease. The study was not designed to serve as an adequate and well-controlled investigation to support a marketing claim. Results from the study are briefly discussed in Section 8.1.6.

Studies GDX-44-005 (pharmacokinetics in patients with renal impairment) and GDX-44-006 (cardiac safety) did not collect efficacy data but are included in the safety review.

Analyses performed by the clinical reviewer used JMP version 16.2.0 and JMP Clinical 8.0.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. GDX-44-010: Efficacy and Safety of Gadopiclenol for Central Nervous System Magnetic Resonance Imaging

Trial Design

GDX-44-010 was a prospective, multi-center, randomized, double-blind, crossover phase 3 study of gadopiclenol for MRI of the CNS. This study was performed in 33 centers in Belgium, Taiwan, France, Germany, Hungary, Italy, South Korea, Poland, Spain, United States of America, and Mexico. The results from outside the U.S. are considered applicable to the U.S. population.

The study included adult patients with at least one known or highly suspected brain or spine lesion with focal areas of blood-brain barrier disruption who were scheduled to undergo a clinically indicated contrasted MRI of the CNS. The presence or suspicion of a CNS lesion was established through a previous imaging procedure within 12 months prior to enrollment. The enrolled patients underwent two MRIs, one with gadopiclenol at 0.05 mmol/kg and the other with gadobutrol at 0.1 mmol/kg. Gadobutrol is an approved product for CNS MRI and was used at the labeled dose. The higher relaxivity of gadopiclenol relative to currently marketed GBCAs

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was part of the rationale for use of a lower dose. This rationale and early phase dose finding study data are further discussed in the Clinical Pharmacology Section.

Patients presenting with extra-cranial lesions or extra-dural lesions were excluded from this study. However, it is noted that patients with such lesions would potentially be eligible for enrollment in GDX-44-011. Patients with acute relapse of multiple sclerosis as their qualifying CNS lesion were also excluded. Their exclusion was justified by the potential for rapid change in lesions between scans in the same patient. Additional key exclusion criteria were: expected/scheduled to have any treatment or medical procedure that may impact the imaged lesions between the two MRI examinations, eGFR less than 30 cc/min/1.73 m^2, and known sensitivity to other GBCAs.

The enrolled patients were randomly assigned in a 1:1 ratio to one of two series of contrast-enhanced MRI examinations: gadopiclenol for the first MRI and then gadobutrol for the second MRI or vice-versa. A follow-up safety visit was performed 1 day after each of the two MRI visits.

Each patient received pre-contrast and post-contrast MRI with gadopiclenol, and pre-contrast and post-contrast MRI with gadobutrol. For brain imaging, the minimum pre-contrast pulse sequences were axial T1-weighted SE/TSE, 3D T1-weighted gradient echo, 2D T2-FLAIR, and T2-weighted TSE. Post-contrast brain minimum pulse sequences were axial 2D T1-weighted SE/TSE, and 3D T1-weighted gradient echo. For spine, the minimum pre-contrast pulse sequences were sagittal T2-weighted TSE and T1-weighted SE/TSE. Post-contrast spine pulse sequences were axial and sagittal T1-weighted SE/TSE. For brain MRI, it was required to send diffusion weighted images for off-site reading if they were obtained, but diffusion weighted imaging did not need to be performed. This is essentially a standard of care sequence, and its absence may negatively affect some of the secondary endpoints, however, this is not expected to have a major impact on the primary endpoints.

The investigator and the patient remained blinded to investigational medical product (IMP) allocation (identity of the IMP and the order of the IMP injection).

Off-site image reading was performed by multiple independent readers. Readers were neuroradiologists or radiologists with expertise in interpretation of brain and spine MRI. For most analyses, including the primary endpoint analyses, three readers who were blinded to all clinical information, the identity and dose of the contrast agent, and any other imaging examination beyond the images to be evaluated were used. Only protocol-specified sequences were made available to the readers, except for diffusion weighted imaging for brain scans. Readers were presented with batches of approximately 20 to 40 MRIs containing either pre-contrast or paired pre- and post-contrast images in random order. Both gadopiclenol and gadobutrol contrasted images could be present in a batch, but not for the same patient. At least two weeks was required between presentation of pre-contrast and paired images for the same patient to a reader and between presentation of paired images for gadopiclenol and gadobutrol for the same patient. A fourth independent, unblinded reader evaluated all images concurrently to track lesions between image sets and between readers. Reader preference assessment between paired pre- and post-contrast images from MRI with gadopiclenol and MRI

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with gadobutrol was performed by three additional independent blinded radiologists. The study design schema is provided in Figure 12 and the schedule of assessments in Table 44.

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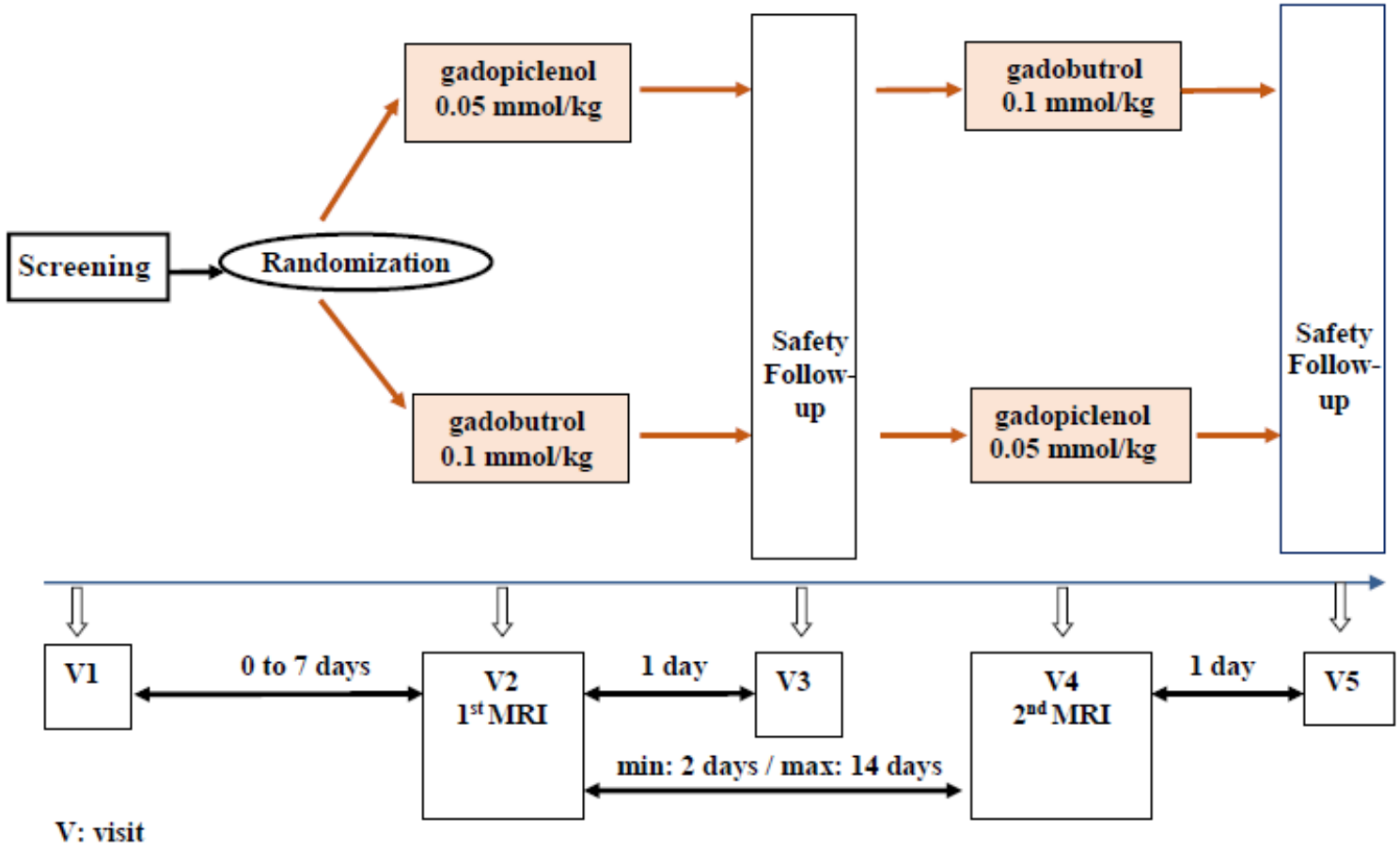
Figure 12. GDX-44-010 Study Design



Source: GDX-44-010 Clinical Study Report Figure 9-1
Abbreviations: MRI, magnetic resonance imaging; V, visit

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Table 44. GDX-44-010 Schedule of Assessments

Visit	V1	V2			V3	V4			V5
Evaluation/Procedure	Screening	Randomization 1st Contrast Agent Injection Baseline			Safety Follow-Up	2nd Contrast Agent Injection (2 to 14 Days Post V2)			Safety Follow-Up
Time Point	≤7 days	Prior to MRI	MRI	60± 15min	1 day after V2	Prior to MRI	MRI	60± 15min	1 day after V4
Informed consent signature	X								
Eligibility criteria	X	X							
Demographic data and height	X					X			
Medical history including CNS disease	X								
Contrastagents intolerance history	X								
Physical examination	X								
Body weight		X				X			
Concomitant treatments	←	———	———	———	———	———	———	———	→
Pregnancy test	X	X				X			
Local creatinine and eGFR evaluation		X			X	X			X
Clinical laboratory parameters		X			X	X			X
Vital signs		X		X	X	X		X	X
IMP injection			X				X		
Images acquisition			X				X		
IWRS	X	X			X	X			X
Injection-site tolerance			X	X	X		X	X	X
Adverse events		←	———	———	———	———	———	→	
Procedures/Therapeutic measures	←	———	———	———	———	→			

Source: Modified from GDX-44-010 Clinical Study Report Table 9-1
Abbreviations: CNS, central nervous system; eGFR, estimated glomerular filtration rate; IMP, investigational medical product; IWRS, Interactive Web Response System; MRI, magnetic resonance imaging; V, visit

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Study Endpoints

Three co-primary endpoints related to lesion visualization were selected for GDX-44-010: border delineation, internal morphology, and degree of contrast enhancement. Each endpoint was assessed on a 4-point scale, as detailed below. FDA agreed to use of these endpoints in a Special Protocol Assessment, with an agreement letter sent November 30, 2018. Of note, very similar endpoints have been used to support effectiveness for visualization claims for other GBCAs as well as iodinated contrast media.

Border delineation was defined as the distinction of the lesion from surrounding tissues, structures, or edema and the detection of the extent of the lesion. The scale for border delineation was:

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 of the lesion was defined as identification of lesion architecture and intra-lesion features such as necrosis, hemorrhage, and vascularity. The scale for internal morphology was:

1 = Poor: poorly seen
2 = Moderate: majority of lesion is poorly seen but with minor parts of lesion visible
3 = Good: majority of lesion is clearly seen but with minor parts of lesion invisible
4 = Excellent: lesion is well seen and can see “through” lesion to observe any complex areas of necrosis or hemorrhage or cyst formation

The degree of contrast enhancement was a qualitative assessment (not based on signal intensity measurement) according to the following scale:

1 = No: no enhancement
2 = Moderate: weakly enhanced
3 = Good: clearly enhanced
4 = Excellent: clearly and brightly enhanced

Readers scored each of the three co-primary criteria for up to three of the most representative lesions. For pre-contrast images, the three largest potentially enhancing lesions were selected. For paired pre- and post-contrast images, the three largest enhancing lesions were prioritized.

Patient-level scores for each criterion were used for the primary analysis. These were defined as the arithmetic mean of the available lesion-level scores for a patient, considering only lesions that were scored both on the pre-contrast and paired pre- and post-contrast images by the same reader. If the MR images were not assessable or if no matching lesion was identified, then the patient was not included in the primary analysis.

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Secondary endpoints of particular interest for this review included:

- Difference in lesion visualization scores between gadopiclenol and gadobutrol
- Improvement in lesion visualization scores at patient-level (expressed as number/percentage of patients) and lesion-level
- Number, size, and location of lesions
- Reader preference between gadopiclenol and gadobutrol
- Predicted change in management based on MRI results
- Intra-reader and inter-reader variability

Statistical Analysis Plan

Applicant-defined populations of interest to this review included:

- Safety Set: All patients who received at least one injection of IMP (gadopiclenol or gadobutrol)
- Extended Full Analysis Sets (FAS):
  - Extended FAS 1: All patients who have both pre-contrast and paired pre- and post-gadopiclenol contrast images assessable
  - Extended FAS 2: All patients who have both gadopiclenol and gadobutrol paired images assessable
- Full Analysis Sets:
  - FAS 1: All patients who have both pre-contrast and paired pre- and post- gadopiclenol contrast images assessable and at least one matching lesion for at least one central reader
  - FAS 2: All patients who have both gadopiclenol and gadobutrol paired images assessable and at least one matching lesion for at least one central reader
- Per-Protocol Sets (PPS):
  - PPS 1: all patients from FAS 1 who have no major protocol deviations
  - PPS 2: all patients from FAS 2 who have no major protocol deviations

The primary objective of GDX-44-010 was to determine whether paired pre- and post-contrast imaging with gadopiclenol is superior to pre-contrast imaging in terms of the three patient-level co-primary endpoints described above. Analyses for this objective included patients in FAS 1. The null hypothesis was that the difference in mean scores between paired and pre-contrast images for each co-primary endpoint was 0, and the alternate hypothesis was that this difference was greater than 0. Significance was tested at α=0.025. The null hypothesis had to be rejected for all three co-primary endpoints for a reader to be successful, and at least two of the three readers had to be successful for study win.

An additional objective, determination of whether paired pre- and post-contrast imaging with gadopiclenol is non-inferior to paired imaging with gadobutrol was considered secondary for FDA but primary for the European Medicines Agency. This analysis used the same three patient-level co-primary visualization endpoints as the primary objective but included patients in PPS 2. The noninferiority margin was based on the assumption that a 10% difference in visualization

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score was clinically unimportant and the expectation that the mean score for each endpoint would be 3.5 (from the results of phase 2 study GDX-44-004). We note that the co-primary endpoints are subjective and discontinuous, and they are not validated against a reference standard. There also may not be a linear relationship between "image quality" and lesion score. Furthermore, no data were presented to validate the clinical non-significance of a 0.35 decrement in a patient-level visualization score. Therefore, it was not clear that a 10% difference in visualization score would be clinically unimportant, and potential demonstration of noninferiority in this study was not considered sufficient to establish an efficacy claim. However, the comparison between the two GBCAs was expected to provide valuable supportive information.

Protocol Amendments

The protocol was amended once, dated May 21, 2019, upon the request of French Competent Authorities. This amendment was applied only to French sites and included the following changes:

- "Addition of a safety follow-up contact between 7 and 14 days after the last IMP injection"
- "Addition of a non-inclusion criterion for patients with known liver failure or liver transplantation"

8.1.2. Study Results

Compliance With Good Clinical Practices

The Applicant stated that the study was conducted in compliance with GCP, U.S. and local regulatory requirements, and standard operating procedures concerning the preparation, monitoring, and follow-up of clinical trials.

Financial Disclosure

The Applicant stated that none of the investigators had disclosable financial interests for this study.

Patient Disposition

Of 256 patients randomized, 247 (96%) received a dose of gadopiclenol. The stated reasons for exiting the study in the nine patients who did not receive gadopiclenol were withdrawal of consent (n=4), adverse event (n=2), COVID-19 pandemic preventing the patient from following protocol schedule (n=1), planned surgery (n=1), and failure to meet enrollment criteria (n=1). Note that gadobutrol also was not administered to these patients as part of the study except for one of the patients who withdrew consent, the patient affected by the COVID-19 pandemic, and the patient who had planned surgery.

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The primary efficacy analysis was performed using FAS 1, which contained 239 patients (93% of randomized patients). The eight patients who received gadopiclenol but were excluded from FAS 1 were all found to have no matching lesion between pre-contrast and paired images for any reader. Most of these patients had one or two lesions identified on both pre-contrast and paired images, though one patient had a relatively large number of lesions on paired images. The number of lesions in these patients is shown in Table 45.

Table 45. Lesion Number Reported on Gadopiclenol Imaging Among Patients Who Received Gadopiclenol but Were Excluded From FAS 1

	Reader 1		Reader 2		Reader 3	
Subject Identifier	**Pre**	**Paired**	**Pre**	**Paired**	**Pre**	**Paired**
GDX-44-010-(b) (6)	1	1	1	1	1	1
GDX-44-010-	1	0	1	1	1	0
GDX-44-010-	10	10	2	27	2	18
GDX-44-010-	1	1	1	1	1	1
GDX-44-010-	1	1	1	1	1	0
GDX-44-010-	1	1	1	1	0	1
GDX-44-010-	NR	NR	0	NR	NR	NR
GDX-44-010-	1	1	4	3	0	1

Source: FDA clinical review team analysis
Subject GDX-44-010-(b) (6) had a suspected technical problem for the gadopiclenol scan.
Abbreviations: FAS 1, full analysis set 1; NR, not reported

Protocol Violations/Deviations

The applicant reported 36 major protocol deviations in 27 of 256 randomized patients (11%), however, some of these deviations did not affect the gadopiclenol MRI or the primary efficacy analysis. The protocol deviations that were related to gadopiclenol included no matching lesion on pre-contrast and paired imaging for any reader (eight patients), MRI examination with gadopiclenol not performed (eight patients), gadopiclenol volume administered differed from intended by more than 20% (two patients), MRI examination performed but gadopiclenol not administered (one patient), and suspicion of lack of efficacy for gadopiclenol (one patient). Note that the protocol deviations for lack of matching lesion and for MRI with gadopiclenol not performed resulted in the affected patients being excluded from the primary endpoint analysis. These patients are discussed in the prior section.

These protocol deviations are not expected to have a substantial impact on the primary efficacy analysis.

Demographic Characteristics

Demographics for patients in the primary efficacy analysis and for patients in the safety set are presented in Table 46. Because relatively few patients in the safety set were excluded from the primary analysis, these sets are very similar in demographics. Representation of patients at least 65 years old is greater than the general United States population (36% versus 17%;

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https://www.census.gov/quickfacts/fact/table/US/PST045221, accessed 8/7/2022), but we expect that the population who will use the drug will trend older than the national average due to the increased prevalence with age of medical conditions for which MRI is indicated. Nearly equal numbers of patients of each sex were enrolled. The fractions of patients in FAS 1 who were black or African American or Hispanic or Latino were lower than the general U.S. population (2% versus 14% and 7% versus 19%, respectively). These differences likely reflect the large number of patients enrolled outside the U.S., particularly in Europe. Based on the drug mechanism of action and the anticipated uses of gadopiclenol, we do not expect drug efficacy or safety to differ in non-white patients.

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Table 46. Patient Demographics in GDX-44-010

Parameter	Full Analysis Set 1 (n=239) n (%)	Safety Set (n=250) n (%)
Age		
Mean years (SD)	57.2 (13.8)	57.2 (13.8)
Median (years)	59.0	59.0
Min, max (years)	18, 84	18, 84
Age Group		
<65 years	153 (64%)	160 (64%)
≥65 years	86 (36%)	90 (36%)
≥75 years	18 (8%)	18 (7%)
Sex		
Female	124 (52%)	134 (54%)
Male	115 (48%)	116 (46%)
Race		
White	199 (83%)	208 (83%)
Black or African American	4 (2%)	5 (2%)
Asian	18 (8%)	19 (8%)
American Indian or Alaska Native	16 (7%)	16 (6%)
Native Hawaiian or Other Pacific Islander	1 (<1%)	1 (<1%)
Other	1 (<1%)	1 (<1%)
Ethnicity		
Hispanic or Latino	17 (7%)	17 (7%)
Not Hispanic or Latino	222 (93%)	233 (93%)
Region		
United States	41 (17%)	45 (18%)
Outside United States	198 (83%)	205 (82%)
Region		
North America	57 (24%)	61 (24%)
Europe	166 (69%)	172 (69%)
Asia	16 (7%)	17 (7%)

Source: Adapted from GDX-44-010 Clinical Study Report, Table 10-6 (Full Analysis Set 1) and 14.1.4.3 (Safety Set)
Abbreviations: n, number of patients; SD, standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

As shown in Table 47, the most common disease diagnoses that led to MRI in the trial were meningioma, metastasis, and glioblastoma, representing benign primary neoplasm, malignant secondary neoplasm, and malignant primary neoplasm, respectively. While several diagnoses lacked specificity, it can be stated that the large majority of patients, more than 91% of FAS 1, were enrolled due to a CNS neoplasm. Two patients were enrolled for a clearly non-neoplastic diagnosis, neurocysticercosis in both cases. Therefore, the study is not powered to assess

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effectiveness of gadopiclenol for non-neoplastic lesions. However, we note that the mechanism of localization of gadopiclenol, accumulation in areas with increased blood flow and permeability of the blood-brain barrier, is expected to apply to inflammatory and other non-neoplastic lesions, and there is no reason to expect that lesion visualization scores will generally differ in non-neoplastic lesions.

Table 47. Baseline Characteristics for Patients in GDX-44-010

Parameter	Full Analysis Set 1 (n=239) n (%)
Disease Diagnosis	
Meningioma	71 (30%)
Metastasis to central nervous system	43 (18%)
Glioblastoma	26 (11%)
Acoustic neuroma	20 (8%)
Glioma	7 (3%)
Schwannoma	6 (3%)
Oligodendroglioma	5 (2%)
Central nervous system lesion	11 (5%)
Other (including all diagnoses with less than 5 patients)	50 (20%)
MRI Examination	
Brain	234 (98%)
Spine	5 (2%)
MRI Magnetic Field Strength	
1.5 Tesla	109 (46%)
3 Tesla	130 (54%)
eGFR at Gadopiclenol Administration	
≥90 mL/min/1.73 m^2	123 (51%)
60-89 mL/min/1.73 m^2	98 (41%)
30-59 mL/min/1.73 m^2	18 (8%)
<30 mL/min/1.73 m^2	0

Source: Adapted from GDX-44-010 Clinical Study Report, Tables 10-7 and 10-11, FDA clinical review team analysis (eGFR at Gadopiclenol Administration)
Abbreviations: eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; n = number of patients

Most patients enrolled in the trial had brain lesions. Among the 239 patients included in FAS 1, only 5 patients (2%) had lesions in the spine. However, based on the mechanism of action of this drug and performance of other drugs in the class, we believe the results to be applicable for use in the spine.

Patients with severe chronic renal insufficiency were excluded from enrollment due to increased risk of nephrogenic systemic fibrosis, and no protocol deviation for this was found. Nearly half of the patients enrolled had mild or moderately decreased eGFR. This is an

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important group to include as it is expected to be a common comorbidity in the population of intended use.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug was administered at the clinical sites; therefore, drug compliance is not applicable.

Efficacy Results – Primary Endpoint

The primary analysis results for GDX-44-010 are shown in Table 48. The 95% confidence intervals for all three visualization co-primary endpoints were greater than 0 at their lower bound for all three readers. The p-values in the Applicant's mixed model were <0.0001 for all differences. Therefore, the Applicant met their predefined study success criteria. The improvement in lesion visualization is expected to be clinically relevant, and this study provides substantial evidence of effectiveness for gadopiclenol. Note that the number of patients with lesion visualization scores for each reader is less than the number of patients in FAS 1 because a patient was only required to have a matching lesion for a single reader to be included in the set. Multiple sensitivity analyses evaluating the impact of excluding these patients without matching lesions from analysis were conducted by the Applicant and reviewed by the Statistics team, as discussed in Section 8.3.1.

Table 48. Average Patient-Level Lesion Visualization Scores in Pre-Contrast and Paired MRI for Gadopiclenol Among Patients in FAS 1 (n=239) for GDX-44-010

		LS Mean (SE)			95% CI	p-
Parameter	**n**	**Paired**	**Pre**	**Difference**	**Difference**	**value**
Border delineation						
Reader 1	227	3.90 (0.02)	2.08 (0.02)	1.82 (0.03)	(1.76, 1.88)	<.0001
Reader 2	229	3.64 (0.04)	1.74 (0.04)	1.90 (0.05)	(1.81, 2.00)	<.0001
Reader 3	202	3.97 (0.03)	2.61 (0.03)	1.36 (0.04)	(1.29, 1.44)	<.0001
Internal morphology						
Reader 1	227	3.92 (0.03)	1.66 (0.03)	2.26 (0.03)	(2.20, 2.33)	<.0001
Reader 2	229	3.65 (0.03)	1.88 (0.03)	1.77 (0.04)	(1.69, 1.85)	<.0001
Reader 3	202	3.97 (0.04)	2.01 (0.04)	1.96 (0.05)	(1.85, 2.06)	<.0001
Degree of contrast enhancement						
Reader 1	227	3.77 (0.03)	1.00 (0.03)	2.77 (0.04)	(2.69, 2.85)	<.0001
Reader 2	229	3.58 (0.03)	1.00 (0.03)	2.58 (0.05)	(2.49, 2.67)	<.0001
Reader 3	202	3.90 (0.02)	1.00 (0.02)	2.90 (0.03)	(2.84, 2.95)	<.0001

Source: GDX-44-010 Clinical Study Report, Table 11-1
Notes: Only matching lesions are considered. The models include lesion visualization factor as a dependent variable, MRI modality (pre-contrast and paired MRI) as fixed factors, and patient as a random factor.
Abbreviations: CI, confidence interval; FAS, full analysis set; LS, least squares; MRI, magnetic resonance imaging; SE, standard error

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Roughly one-third of the patients in FAS 1 were over 65 years of age. Little difference was seen for lesion visualization scores in patients older and younger than 65 years (Table 49), and the direction of the differences tended to differ between readers, except for degree of contrast enhancement, where all readers scored the difference as greater in older patients. This finding is of doubtful significance.

Table 49. Difference in Average Patient-Level Lesion Visualization Scores Between Paired and Pre-Contrast MRI for Gadopiclenol in FAS 1 (n=239) for GDX-44-010 by Patient Age

	Age <65			Age ≥65		
Parameter	**n**	**Difference**	**95% CI**	**n**	**Difference**	**95% CI**
Border delineation						
Reader 1	143	1.85	(1.77, 1.93)	84	1.77	(1.66, 1.87)
Reader 2	146	1.88	(1.76, 2.00)	83	1.94	(1.78, 2.10)
Reader 3	126	1.40	(1.30, 1.49)	76	1.31	(1.18, 1.43)
Internal morphology						
Reader 1	143	2.27	(2.18, 2.35)	84	2.25	(2.14, 2.36)
Reader 2	146	1.71	(1.61, 1.81)	83	1.87	(1.74, 2.00)
Reader 3	126	1.98	(1.85, 2.11)	76	1.91	(1.74, 2.08)
Degree of contrast enhancement						
Reader 1	143	2.75	(2.65, 2.85)	84	2.81	(2.68, 2.94)
Reader 2	146	2.54	(2.42, 2.65)	83	2.66	(2.50, 2.81)
Reader 3	126	2.87	(2.80, 2.94)	76	2.94	(2.86, 3.03)

Source: GDX-44-010 Clinical Study Report, Figure 11-1
Abbreviations: CI, confidence interval; FAS, full analysis set; MRI, magnetic resonance imaging

Roughly equal numbers of males and females were included in FAS 1. As for age, little difference was seen in lesion visualization scores between the sexes (Table 50).

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Table 50. Difference in Average Patient-Level Lesion Visualization Scores Between Paired and Pre-Contrast MRI for Gadopiclenol in FAS 1 (n=239) for GDX-44-010 by Patient Sex

	Female			Male		
Parameter	**n**	**Difference**	**95% CI**	**n**	**Difference**	**95% CI**
Border delineation						
Reader 1	119	1.79	(1.70, 1.88)	108	1.86	(1.77, 1.95)
Reader 2	116	1.85	(1.71, 1.98)	113	1.96	(1.82, 2.09)
Reader 3	99	1.34	(1.23, 1.45)	103	1.39	(1.28, 1.49)
Internal morphology						
Reader 1	119	2.22	(2.13, 2.31)	108	2.30	(2.21, 2.40)
Reader 2	116	1.78	(1.67, 1.89)	113	1.76	(1.64, 1.87)
Reader 3	99	1.94	(1.79, 2.09)	103	1.97	(1.83, 2.12)
Degree of contrast enhancement						
Reader 1	119	2.74	(2.63, 2.85)	108	2.81	(2.69, 2.93)
Reader 2	116	2.56	(2.43, 2.69)	113	2.60	(2.47, 2.73)
Reader 3	99	2.90	(2.83, 2.98)	103	2.89	(2.82, 2.96)

Source: GDX-44-010 Clinical Study Report, Figure 11-1
Abbreviations: CI, confidence interval; MRI, magnetic resonance imaging

There was not sufficient enrollment of non-white patients to support a meaningful subgroup analysis by race. The Applicant attempted this analysis, and it did not show obvious differences, but the confidence intervals were very wide. Since most patients (69%) were enrolled in Europe, this subgroup was compared to the U.S. patients. The scores were similar between the subgroups (Table 51).

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Table 51. Difference in Average Patient-Level Lesion Visualization Scores Between Paired and Pre-Contrast MRI for Gadopiclenol in FAS 1 (n=239) for GDX-44-010 by Site Location

	United States			Europe		
Parameter	**n**	**Difference**	**95% CI**	**n**	**Difference**	**95% CI**
Border delineation						
Reader 1	36	1.78	(1.62, 1.94)	160	1.85	(1.77, 1.92)
Reader 2	38	1.79	(1.56, 2.02)	160	1.92	(1.80, 2.03)
Reader 3	27	1.28	(1.08, 1.49)	148	1.38	(1.29, 1.47)
Internal morphology						
Reader 1	36	2.26	(2.10, 2.43)	160	2.27	(2.19, 2.35)
Reader 2	38	1.74	(1.54, 1.94)	160	1.77	(1.67, 1.87)
Reader 3	27	1.74	(1.47, 2.02)	148	2.03	(1.91, 2.14)
Degree of contrast enhancement						
Reader 1	36	2.77	(2.57, 2.97)	160	2.76	(2.66, 2.85)
Reader 2	38	2.53	(2.30, 2.75)	160	2.56	(2.45, 2.67)
Reader 3	27	2.96	(2.82, 3.11)	148	2.88	(2.82, 2.94)

Source: GDX-44-010 Clinical Study Report, Figure 11-1
Abbreviations: CI, confidence interval; FAS, full analysis set; MRI, magnetic resonance imaging

In general, increased magnetic field strength leads to lower relaxivity with GBCAs. However, increased field strength also tends to increase tissue T1 values, so often the net effect on apparent contrast enhancement is minimal. A subgroup analysis comparing patients scanned at 1.5 T to patients scanned at 3 T showed similar lesion visualization scores.

Data Quality and Integrity

FDA Office of Scientific Investigations audits of the contract research organization that performed the MRI reads and two representative clinical study sites revealed no significant GCP deviations.

Efficacy Results – Secondary and Other Relevant Endpoints

More than 95% of patients with matching lesions had an increase in each of the three lesion visualization scores from pre-contrast to paired gadopiclenol MRI for all three readers (Table 52). This supports the primary analysis by demonstrating that few patients were assessed as having unchanged or worsened lesion visualization.

Table 52. Change in Patient-Level Lesion Visualization Scores Between Pre-Contrast and Paired MRI With Gadopiclenol Among Patients in FAS 1 (n=239) for GDX-44-010

Parameter	**Number of Patients**	**Number (%) of Patients With Decreased or Unchanged Score**	**Number (%) of Patients With Increased Score**
Border delineation			
Reader 1	227	1 (0.4%)	226 (99.6%)
Reader 2	229	7 (3.1%)	222 (96.9%)

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Parameter	Number of Patients	Number (%) of Patients With Decreased or Unchanged Score	Number (%) of Patients With Increased Score
Reader 3	202	5 (2.5%)	197 (97.5%)
Internal morphology			
Reader 1	227	0	227 (100%)
Reader 2	229	10 (4.4%)	219 (95.6%)
Reader 3	202	1 (0.5%)	201 (99.5%)
Degree of contrast enhancement			
Reader 1	227	6 (2.6%)	221 (97.4%)
Reader 2	229	6 (2.6%)	223 (97.4%)
Reader 3	202	1 (0.5%)	201 (99.5%)

Source: GDX-44-010 Clinical Study Report, Table 11-13
Abbreviations: FAS, full analysis set; MRI, magnetic resonance imaging

The clinical review team also examined the lesion scores without averaging by patient. Among lesions that were scored on both pre-contrast and paired images for gadopiclenol, no reader scored any lesion worse on pre-contrast than on paired for any of the visualization criteria.

Table 53 compares the lesion visualization scores among matched lesions for gadopiclenol MRI (0.05 mmol/kg) and gadobutrol MRI (0.1 mmol/kg). The results obtained for the two GBCAs were very similar, and the 95% confidence interval (CI) for the difference contained 0 in most cases. Since gadobutrol carries an indication for CNS lesion visualization, these results provide supportive evidence of effectiveness of gadopiclenol.

Table 53. Average Patient-Level Lesion Visualization Scores in Paired Gadopiclenol MRI and Paired Gadobutrol MRI Among Patients in PPS 2 (n=236) for GDX-44-010

		LS Mean (SE)			95% CI
Parameter	n	Gadopiclenol	Gadobutrol	Difference	Difference
Border delineation					
Reader 1	227	3.91 (0.02)	3.93 (0.02)	-0.02 (0.02)	(-0.06, 0.02)
Reader 2	231	3.64 (0.04)	3.60 (0.04)	0.03 (0.04)	(-0.04, 0.11)
Reader 3	220	3.97 (0.01)	3.95 (0.01)	0.02 (0.02)	(-0.01, 0.05)
Internal morphology					
Reader 1	227	3.93 (0.02)	3.93 (0.02)	-0.01 (0.02)	(-0.04, 0.03)
Reader 2	231	3.64 (0.04)	3.62 (0.04)	0.02 (0.03)	(-0.05, 0.09)
Reader 3	220	3.97 (0.02)	3.92 (0.02)	0.05 (0.02)	(0.01, 0.08)
Degree of contrast enhancement					
Reader 1	227	3.78 (0.04)	3.77 (0.04)	0.01 (0.03)	(-0.04, 0.07)
Reader 2	231	3.57 (0.04)	3.52 (0.04)	0.05 (0.04)	(-0.03, 0.12)
Reader 3	220	3.89 (0.03)	3.81 (0.03)	0.09 (0.03)	(0.03, 0.15)

Source: GDX-44-010 Clinical Study Report, Table 11-2
Note: Only matching lesions are considered.
Abbreviations: CI, confidence interval; LS, least squares; MRI, magnetic resonance imaging; PPS, per protocol set; SE, standard error

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While the visualization parameters were only scored for up to three lesions per patient, which was necessary for feasibility of the image evaluations, the readers did count the total number of lesions per patient for pre-contrast and paired imaging with both gadopiclenol and gadobutrol. This endpoint is important to consider because contrast may increase or in some cases decrease lesion detection. Since the primary endpoint considered only matching lesions that were detected on both pre-contrast and paired images, changes in detectability will not be directly reflected. On average, the number of lesions detected was larger for paired imaging than pre-contrast imaging with gadopiclenol (Table 54), though it is noted that there was appreciable inter-reader difference in lesion number assessment. The Applicant performed similar analyses for paired imaging with gadopiclenol and gadobutrol, not shown here, which did not demonstrate substantial differences between the drugs.

Table 54. Number of Lesions Per Patient in Pre-Contrast and Paired MRI With Gadopiclenol Among Patients in Extended FAS 1 for GDX-44-010

	Reader 1		Reader 2		Reader 3	
Parameter	**Pre**	**Paired**	**Pre**	**Paired**	**Pre**	**Paired**
Number of patients	246	246	246	246	245	244
Mean lesion number (SD)	1.6 (1.5)	2.1 (2.3)	2.1 (6.5)	2.9 (7.8)	1.7 (3.1)	2.1 (3.9)
Median lesion number	1	1	1	1	1	1
Range (min, max)	0, 10	0, 10	1, 99	1, 99	0, 40	0, 35

Source: GDX-44-010 Clinical Study Report, Table 11-18
Abbreviations: FAS, full analysis set; max, maximum; min, minimum; MRI, magnetic resonance imaging; SD, standard deviation

To further explore the lesion number endpoint, patients were categorized as having the same number of lesions on pre-contrast and paired MRI or more lesions with one or the other, as shown in Table 55. The majority of patients had the same number of lesions reported on pre-contrast and paired images with gadopiclenol. More patients saw an increase in lesion number on the paired images than a decrease, but there were non-trivial numbers of patients who had fewer lesions seen on paired MRI. The findings were similar between gadopiclenol and gadobutrol.

Table 55. Change in Lesion Numbers Between Pre-Contrast and Paired MRI for Gadopiclenol and Gadobutrol Among Patients in the Safety Set (n=250) for GDX-44-010

	Number (%) of Patients With More Lesions on Pre		Number (%) of Patients With Same Number of Lesions		Number (%) of Patients With More Lesions on Paired	
Reader	**Gadopiclenol**	**Gadobutrol**	**Gadopiclenol**	**Gadobutrol**	**Gadopiclenol**	**Gadobutrol**
Reader 1	12 (5%)	17 (7%)	183 (74%)	172 (70%)	51 (21%)	55 (23%)
Reader 2	23 (9%)	19 (8%)	167 (68%)	166 (68%)	56 (23%)	60 (24%)
Reader 3	30 (12%)	28 (12%)	161 (66%)	162 (66%)	52 (22%)	54 (22%)

Source: FDA clinical review team analysis
Notes: Patients with missing data for pre-contrast or paired lesion number are excluded. Number of excluded patients

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ranges from 4 to 7 per reader and GBCA.
Abbreviations: GBCA, gadolinium-based contrast agent; MRI, magnetic resonance imaging

Detection of additional lesions after administration of contrast is usually regarded as beneficial, and detection of fewer lesions might raise concerns for masking of lesions on the contrasted images. However, it is important to note that lesions are not validated against a reference standard in this study. Therefore, not all additional lesions seen on the paired images represent additional pathology. Moreover, some lesions seen on pre-contrast imaging may be more accurately characterized as non-lesions on post-contrast imaging. This issue might also be accentuated by the training given to the readers, who were encouraged to identify all suspected lesions on pre-contrast images in order to prevent missing any potential lesion, which could lead to overcalling.

The potential for identifying different numbers of lesions on pre-contrast and paired MRI will also be influenced by the spectrum of pathology in the study. For example, meningiomas are most often solitary and can be large, therefore a patient would be more likely to have the same number of lesions on pre-contrast and paired MRI than a patient presenting with metastatic malignancy. An additional consideration is the reliability of lesion counting. In the analysis for gadopiclenol in Table 55, the pairwise reader discordance rates between categories (more lesions on pre-contrast, same number of lesions, and more lesions on paired) were 26%, 30%, and 31% for reader 1 vs. reader 2, reader 1 vs. reader 3, and reader 2 vs. reader 3, respectively. Finally, the similarities of the results for gadopiclenol and gadobutrol are reassuring given the long-standing use of gadobutrol for CNS lesion visualization.

Thus, we do not consider every finding of fewer lesions on paired MRI than pre-contrast MRI to necessarily represent lower effectiveness or an adverse outcome from administration of gadopiclenol. Because routine clinical MRI generally includes pre-contrast sequences and practicing radiologists are well aware of the potential for GBCAs to occasionally obscure lesions, we believe that a warning in the prescribing information is sufficient to mitigate any related risk.

Three independent readers who were blinded to GBCA and who did not provide assessments for the primary analyses were asked for their overall diagnostic preference between paired images obtained with gadopiclenol and paired images obtained with gadobutrol presented side-by-side. Images with gadopiclenol were preferred to images with gadobutrol in 45% to 57% of the cases. Gadobutrol was preferred in 15% to 24% of cases. No preference was observed in the remainder of the cases.

The local investigators were asked to report the number of patients who could have a change in management from the pre-contrast MRI after obtaining contrasted images. For 56/240 patients (23%), the local investigator stated that the treatment plan could have been changed after gadopiclenol MRI. Similar results (57/241; 24%) were obtained with gadobutrol. Note that the investigators were not required to state a treatment plan based on the pre-contrast images prior to seeing the contrasted images. Also, data regarding the actual administered treatment or its outcome were not collected.

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Intra-reader variability was assessed based on rereads of a random selection of 10% of images. For the pre-contrast and paired images with gadopiclenol, the intra-class correlation (ICC) ranged from 0.89 to 0.99 across the three lesion visualization parameters and three readers. Pairwise ICCs for inter-reader variability ranged from 0.89 to 0.98 for the three lesion visualization parameters and the three readers.

Dose/Dose Response

Gadopiclenol was administered at a concentration of 0.5 M and a nominal dose of 0.05 mmol/kg body weight, however the volume to be injected was rounded to the nearest whole number of mL. One (<1%) patient in FAS 1 received less than the intended volume and 4 (2%) patients more than the intended volume. The mean dose was 0.051 mmol/kg, with a range of 0.044 mmol/kg to 0.10 mmol/kg. One patient was excluded from this calculation as their weight was not recorded.

The recommended injection rate in the protocol was 2 mL/sec. Four (2%) patients in FAS 1 were injected with gadopiclenol at 2.5 mL/sec; the remainder were injected at the recommended rate.

8.1.3. GDX-44-011: Efficacy and Safety of Gadopiclenol for Body Magnetic Resonance Imaging

Trial Design

GDX-44-011 was a prospective, multi-center, randomized, double-blind, crossover phase 3 study of gadopiclenol MRI for non-CNS anatomic regions, including head and neck, thorax, abdomen, pelvis, and the musculoskeletal system. This study was performed in 33 centers in Bulgaria, Germany, Spain, France, Hungary, Ukraine, Italy, Republic of Korea, Poland, United States of America, and Mexico. The results from outside the U.S. are considered applicable to U.S. population.

At a high level, the design of GDX-44-011 was identical to the design of GDX-44-010, and reference is made to Section 8.1.1 for description of the design. Important differences included:

- Instead of CNS lesions, patients were required to have a known or suspected enhancing abnormality or lesion in at least one non-CNS anatomic region as listed in the prior paragraph. The clinically indicated contrasted MRI was to be of the body part that had the lesion rather than the CNS. Note that patients enrolled in the U.S. were required to have a clinically indicated breast MRI to comply with the U.S. labeling of the comparator agent, gadobutrol.
- Patients with extracranial or extradural head, neck, or spine lesions were allowed to enroll in this study. However, patients referred for CNS MRI, cardiac MRI, or MRI angiography were excluded.
- The required minimum MRI sequences were different (Table 56). Note these protocols are considered acceptable for the purposes of the study.

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- Three separate sets of image readers were used depending on the imaged body part: head and neck, musculoskeletal system, or thorax/abdomen/pelvis. This applied to the lesion visualization parameter scoring as well as the reader preference assessment. These readers were "MR radiologist with expertise in the interpretation of targeted organs/regions." A single lesion tracker was used. Therefore, there were a total of 19 readers for this study.

Table 56. Minimum MRI Protocols Used in GDX-44-011

Imaged Body Part	Pre-Contrast Sequences	Post-Contrast Sequences
Head and neck	T2 SE/FSE T1 SE T1 GRE	T1 SE T1 GRE
Breast	axial T2 axial T1 3D axial T1 FS	3D axial dynamic T1 FS (minimum 3 phases)
Liver	axial T2 FS axial T1 GRE in and out of phase 3D T1 FS	3D dynamic T1 FS (minimum 3 phases)
Pancreas	T2 FS DWI T1 GRE in and out of phase T1 GRE FS	dynamic T1 GRE FS (minimum 3 phases)
Kidney	T2 FS DWI T1 GRE in and out of phase T1 GRE FS	dynamic T1 GRE FS (minimum 2 phases)
Abdomen (other than liver, pancreas, kidney)	T2 FS DWI T1 GRE in and out of phase T1 GRE FS	T1 GRE FS
Female pelvis	T2 SE/TSE DWI axial T1 SE/FSE axial T1 GRE	axial T1 SE/FSE axial T1 GRE
Prostate	T2 SE/FSE T1 SE/FSE T1 GRE	dynamic T1 GRE (minimum 20 phases) T1 SE/FSE
Musculoskeletal	STIR T2 FS axial T1 SE/FSE	axial T1 SE/FSE

Source: GDX-44-011 Blinded Image Evaluation Charter
Abbreviations: 3D, 3 dimensional; DWI, diffusion weighted imaging; FS, fat saturated; FSE, fast spin-echo; GRE, gradient echo; MRI, magnetic resonance imaging; SE, spin-echo; TSE, turbo spin echo

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Study Endpoints

The primary and most secondary endpoints for GDX-44-011 were the same as for GDX-44-010. Because there were three groups of readers, three meta-readers were created by pooling one reader for each area of expertise (head and neck, musculoskeletal system, and thorax/abdomen/pelvis). These pools were based on the reader number assigned by the imaging CRO prior to initiation of image evaluations. Sensitivity analyses of other reader combinations were performed by the Applicant and reviewed by the Statistics team (Section 8.3.2). Note that in the remaining parts of this section and in the results section, unless otherwise specified, the term reader will refer to the Applicant's predefined meta-readers.

Statistical Analysis Plan

Refer to the discussion of the statistical analysis plan for GDX-44-010.

Protocol Amendments

The global protocol was amended twice. The first amendment was prepared in early June 2020 but never submitted to FDA. The purpose of this amendment was not described. A total of 37 patients signed an informed consent for the study between June 1, 2020, and June 29, 2020.

The second amendment, implemented June 30, 2020, increased the sample size from 250 to 300 patients due to a higher than anticipated rate of non-evaluable patients.

In addition, the separate French version of the protocol was amended twice. The first amendment on May 17, 2019, added additional safety follow-up and an exclusion criterion for liver failure, as also added to GDX-44-010. The second amendment on June 30, 2020, increased the sample size from 250 to 300 patients.

8.1.4. Study Results

Compliance With Good Clinical Practices

The Applicant stated that the study was conducted in compliance with GCP, U.S. and local regulatory requirements, and standard operating procedures concerning the preparation, monitoring, and follow-up of clinical trials.

Financial Disclosure

The Applicant stated that none of the investigators for this study had disclosable financial interests.

Patient Disposition

Of 304 patients randomized, 288 (95%) patients received a dose of gadopiclenol. The reasons for discontinuing the study listed for the 16 patients who did not receive gadopiclenol included withdrawal of consent (n=4), missed visit window due to MR machine technical issue (n=3),

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claustrophobia (n=2), COVID-19 pandemic preventing patient from following protocol schedule (n=2), transport strike (n=1), severe artifact caused by breast prosthesis (n=1), no possibility of contrast MRI (n=1), adverse event (n=1), and discovery of an unexpected risk to patients enrolled in the trial (n=1). The patients who were affected by the MRI scanner technical issue were all from the same site and all had been scanned using gadobutrol on the same day. The patient who discontinued for adverse event experienced injection site pain and cystatin C increase 2 days following gadobutrol administration. The patient affected by the unexpected risk did not receive gadopiclenol or gadobutrol, and the unexpected risk was not further defined. However, the ADPR dataset lists this patient as unable to have MRI due to being overweight. Twelve of these 16 patients did receive an MRI with gadobutrol as part of the study.

The primary efficacy analysis was performed using FAS 1, which contained 278 patients (91% of randomized patients). The 10 patients who received gadopiclenol but were excluded from FAS 1 all had protocol deviations for no matching lesions between pre-contrast and paired images for any reader. The lesion numbers for these patients are shown in Table 57. Note that the local investigator assessed the images for patient GDX-44-011-(b) (6) as non-diagnostic and unassessable due to artifact.

Table 57. Lesion Number Reported on Gadopiclenol Imaging Among Patients Who Received Gadopiclenol but Were Excluded From FAS 1 in GDX-44-011

	Reader 1		Reader 2		Reader 3	
Subject Identifier	**Pre**	**Paired**	**Pre**	**Paired**	**Pre**	**Paired**
GDX-44-011-(b) (6)	1	10	1	8	NR	7
GDX-44-011-	0	1	1	1	NR	1
GDX-44-011-	3	2	1	0	3	1
GDX-44-011-	NR	NR	NR	NR	NR	NR
GDX-44-011-	NR	NR	NR	NR	NR	NR
GDX-44-011-	1	1	1	1	1	3
GDX-44-011-	2	1	2	1	3	1
GDX-44-011-	1	0	0	1	1	1
GDX-44-011-	3	3	1	1	3	1
GDX-44-011-	3	20	20	1	3	1

Source: FDA clinical review team analysis
Abbreviations: FAS 1, full analysis set 1; NR, not reported

Protocol Violations/Deviations

The Applicant reported 65 major protocol deviations in 50 of 304 randomized patients (16%), however, some of these deviations did not affect the gadopiclenol MRI or the primary efficacy analysis. The protocol deviations that were related to gadopiclenol included MRI with gadopiclenol not performed (17 patients), no matching lesion on pre-contrast and paired MRI for any reader (10 patients), gadopiclenol volume administered differed from intended by >20% (five patients), met exclusion criterion for patients with lesions of the CNS or heart or patients

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referred for MRI angiography (5 patients), and patient did not receive IMP allocated by randomization (one patient; received gadopiclenol at visit 2 instead of the intended gadobutrol). As in study GDX-44-010, some of these deviations resulted in exclusion of patients from the full analysis set, not just the per protocol set.

These protocol deviations are not expected to have a substantial impact on the primary efficacy analysis.

Demographic Characteristics

Demographic characteristics for patients in the primary efficacy analysis and for patients in the safety set are presented in Table 58. Representation of patients at least 65 years old is greater than the general United States population (34% versus 17%; https://www.census.gov/quickfacts/fact/table/US/PST045221, accessed 8/7/2022), but we expect that the population who will use the drug will trend older than the national average due to the increased prevalence with age of medical conditions that are imaged by MRI. More women than men were enrolled, likely due to the inclusion of patients receiving breast MRI examinations. The fraction of patients in FAS 1 who were black or African American was lower than the general U.S. population (2% versus 14%). This difference likely reflects the large number of patients enrolled outside the U.S., particularly in Europe. Based on the drug mechanism of action and the anticipated uses of gadopiclenol, we do not expect drug efficacy or safety to differ in non-white patients.

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Table 58. Patient Demographics in GDX-44-011

Parameter	Full Analysis Set 1 (n=278) n (%)	Safety Set (n=301) n (%)
Age		
Mean years (SD)	57.2 (13.0)	57.1 (12.9)
Median (years)	58.0	58.0
Min, max (years)	21, 86	21, 86
Age group		
<65 years	184 (66%)	202 (67%)
≥65 years	94 (34%)	99 (33%)
≥75 years	29 (10%)	31 (10%)
Sex		
Female	164 (59%)	179 (69%)
Male	114 (41%)	122 (41%)
Race		
White	196 (71%)	215 (71%)
Black or African American	6 (2%)	6 (2%)
Asian	44 (16%)	46 (15%)
American Indian or Alaska Native	30 (11%)	31 (10%)
Multiple	0	1 (<1%)
Other	2 (<1%)	2 (<1%)
Ethnicity		
Hispanic or Latino	51 (18%)	52 (17%)
Not Hispanic or Latino	227 (82%)	249 (83%)
Region		
United States	45 (16%)	50 (17%)
Outside United States	233 (84%)	251 (83%)
Region		
North America	75 (27%)	81 (27%)
Europe	159 (57%)	174 (58%)
Asia	44 (16%)	46 (15%)

Source: Adapted from GDX-44-011 Clinical Study Report, Table 10-7 (Full Analysis Set 1) and 14.1.4.5 (Safety Set)
Abbreviations: max, maximum; min, minimum; n, number of patients; SD, standard deviation

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

For a majority of patients enrolling in GDX-44-011, the reason for imaging was neoplasm (Table 59). In a similar manner as for the CNS neoplasms in GDX-44-010, we expect that the performance for non-neoplastic lesions may be generally similar to that for neoplastic lesions given the nonspecific mechanism of gadopiclenol localization in the extracellular fluid.

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Table 59. Baseline Characteristics for Patients in GDX-44-011

Parameter	Full Analysis Set 1 (n=278) n (%)
Disease Diagnosis Primary System Organ Class	
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	183 (66%)
Reproductive system and breast disorders	42 (15%)
Hepatobiliary disorders	19 (7%)
Musculoskeletal and connective tissue disorders	9 (3%)
Gastrointestinal disorders	6 (2%)
Other (including all with less than 5 patients)	19 (7%)
MRI Examination	
Head and neck	21 (8%)
Thorax	73 (26%)
Abdomen	101 (36%)
Pelvis	61 (22%)
Musculoskeletal	22 (8%)
MRI Magnetic Field Strength	
1.5 Tesla	206 (74%)
3 Tesla	72 (26%)
eGFR at Gadopiclenol Administration	
≥90 mL/min/1.73 m^2	143 (51%)
60-89 mL/min/1.73 m^2	110 (40%)
30-59 mL/min/1.73 m^2	25 (9%)
<30 mL/min/1.73 m^2	0

Source: GDX-44-011 Clinical Study Report, Tables 10-12 and 14.1.4.6, FDA clinical review team analysis (eGFR at Gadopiclenol Administration)
Abbreviations: eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging

More than half of the patients received an MRI of the abdomen or pelvis. Based on the disease diagnosis that prompted imaging, the most common organ of interest in this anatomic region was the liver (63 patients, 23% of FAS 1), but there was broad representation of other organs, including pancreas, gallbladder, adrenal glands, kidneys, spleen, colon, prostate, uterus, and ovaries. A total of 69 of the patients with thoracic imaging had breast as the organ of interest, representing 95% of the thorax scans and 25% of FAS 1. The head and neck imaging patients had diagnoses associated with the oral cavity, pharynx, larynx, salivary glands, and thyroid. Note that three of these patients had diagnoses of CNS lesions (brain metastasis, meningioma, and multiple sclerosis). The numbers of patients in the head and neck and musculoskeletal groups were smaller than the other body regions, however based on the mechanism of action of this drug and performance of other drugs in the class, we do not expect performance to meaningfully differ in these regions. Subgroup analyses by region will be discussed in subsequent sections.

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Patients with severe chronic renal insufficiency were excluded from enrollment due to increased risk of NSF, and no protocol deviation for this exclusion was found. Nearly half of the patients enrolled had mild or moderately decreased eGFR. This is an important group to include as it is expected to be a common comorbidity in the population of intended use.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Study drug was administered at the clinical sites. Therefore, drug compliance is not applicable.

Efficacy Results – Primary Endpoint

The primary analysis results for GDX-44-011 are shown in Table 60. The 95% confidence intervals for all three visualization co-primary endpoints were greater than 0 at their lower bound for all three meta-readers. The p-values in the Applicant's mixed model were <0.0001 for all differences. Therefore, the Applicant met their predefined study success criteria. The improvement in lesion visualization is expected to be clinically relevant, and this study provides substantial evidence of effectiveness for gadopiclenol. Note that the number of patients with lesion visualization scores for each meta-reader is lower than the number of patients in FAS 1 because a patient was only required to have a matching lesion for a single meta-reader to be included in the set. Multiple sensitivity analyses evaluating the impact of excluding patients without matching lesions from analysis and evaluating different combinations of readers to form meta-readers were conducted by the Applicant and reviewed by the Statistics team, as discussed in Section 8.3.2.

Table 60. Average Patient-Level Lesion Visualization Scores in Pre-Contrast and Paired MRI for Gadopiclenol Among Patients in FAS 1 (n=278) for GDX-44-011

		LS Mean (SE)			95% CI	
Parameter	**n**	**Paired**	**Pre**	**Difference**	**Difference**	**p-value**
Border delineation						
Reader 1	251	3.79 (0.03)	2.26 (0.03)	1.53 (0.04)	(1.46, 1.60)	<.0001
Reader 2	230	3.48 (0.06)	3.01 (0.06)	0.47 (0.06)	(0.36, 0.58)	<.0001
Reader 3	262	3.49 (0.03)	1.78 (0.03)	1.71 (0.04)	(1.65, 1.78)	<.0001
Internal morphology						
Reader 1	251	3.80 (0.02)	1.99 (0.02)	1.81 (0.03)	(1.76, 1.87)	<.0001
Reader 2	230	3.75 (0.05)	3.22 (0.05)	0.53 (0.06)	(0.42, 0.64)	<.0001
Reader 3	262	3.72 (0.03)	1.69 (0.03)	2.03 (0.04)	(1.95, 2.11)	<.0001
Degree of contrast enhancement						
Reader 1	251	3.64 (0.03)	1.00 (0.03)	2.64 (0.04)	(2.56, 2.72)	<.0001
Reader 2	230	2.82 (0.05)	1.00 (0.05)	1.82 (0.07)	(1.68, 1.96)	<.0001
Reader 3	262	3.33 (0.03)	1.00 (0.03)	2.33 (0.04)	(2.26, 2.41)	<.0001

Source: GDX-44-011 Clinical Study Report, Table 11-1
Notes: Readers in this table refer to meta-reader pools containing 1 head and neck, 1 musculoskeletal, and 1 thorax/abdomen/pelvis image evaluator. Only matching lesions are considered. The models include lesion visualization factor as a dependent variable, MRI modality (pre-contrast and paired MRI) as fixed factors, and

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patient as a random factor.
Abbreviations: CI, confidence interval; FAS, full analysis set; LS, least squares; MRI, magnetic resonance imaging; SE, standard error

Roughly one-third of the patients in FAS 1 were over 65 years of age. Little change was seen in the difference between paired and pre-contrast lesion visualization scores in patients older and younger than 65 years (Table 61). There was a general trend to smaller differences in the older patients for all parameters and meta-readers, but because of the small size of the change this observation is of doubtful significance.

Table 61. Difference in Average Patient-Level Lesion Visualization Scores Between Paired and Pre-Contrast MRI for Gadopiclenol in FAS 1 (n=278) for GDX-44-011 by Patient Age

	Age <65			Age ≥65		
Parameter	**n**	**Difference**	**95% CI**	**n**	**Difference**	**95% CI**
Border delineation						
Reader 1	164	1.56	(1.48, 1.65)	87	1.46	(1.34, 1.58)
Reader 2	147	0.56	(0.42, 0.69)	83	0.32	(0.14, 0.50)
Reader 3	176	1.73	(1.65, 1.81)	86	1.68	(1.56, 1.81)
Internal morphology						
Reader 1	164	1.85	(1.79, 1.92)	87	1.74	(1.65, 1.83)
Reader 2	147	0.59	(0.46, 0.73)	83	0.42	(0.24, 0.60)
Reader 3	176	2.04	(1.95, 2.14)	86	2.00	(1.87, 2.14)
Degree of contrast enhancement						
Reader 1	164	2.67	(2.57, 2.77)	87	2.59	(2.46, 2.73)
Reader 2	147	1.93	(1.75, 2.10)	83	1.63	(1.40, 1.86)
Reader 3	176	2.39	(2.30, 2.47)	86	2.23	(2.10, 2.35)

Source: GDX-44-011 Clinical Study Report, Figure 11-5
Notes: Readers in this table refer to meta-reader pools containing 1 head and neck, 1 musculoskeletal, and 1 thorax/abdomen/pelvis image evaluator.
Abbreviations: CI, confidence interval; FAS, full analysis set; MRI, magnetic resonance imaging

Approximately 1.4 times as many females were included in FAS 1 as males. A general trend was seen to slightly smaller differences between paired and pre-contrast lesion visualization scores in males (Table 62). The small size of this trend makes its clinical significance doubtful.

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Table 62. Difference in Average Patient-Level Lesion Visualization Scores Between Paired and Pre-Contrast MRI for Gadopiclenol in FAS 1 (n=278) for GDX-44-011 by Patient Sex

	Female			Male		
Parameter	**n**	**Difference**	**95% CI**	**n**	**Difference**	**95% CI**
Border delineation						
Reader 1	148	1.56	(1.47, 1.65)	103	1.49	(1.38, 1.60)
Reader 2	130	0.55	(0.40, 0.69)	100	0.37	(0.21, 0.54)
Reader 3	159	1.79	(1.70, 1.88)	103	1.60	(1.49, 1.70)
Internal morphology						
Reader 1	148	1.86	(1.79, 1.93)	103	1.75	(1.66, 1.83)
Reader 2	130	0.54	(0.39, 0.69)	100	0.52	(0.35, 0.69)
Reader 3	159	2.08	(1.98, 2.18)	103	1.95	(1.83, 2.08)
Degree of contrast enhancement						
Reader 1	148	2.69	(2.58, 2.79)	103	2.57	(2.45, 2.70)
Reader 2	130	1.88	(1.70, 2.07)	100	1.74	(1.53, 1.95)
Reader 3	159	2.36	(2.27, 2.45)	103	2.30	(2.18, 2.41)

Source: GDX-44-011 Clinical Study Report, Figure 11-5
Notes: Readers in this table refer to meta-reader pools containing 1 head and neck, 1 musculoskeletal, and 1 thorax/abdomen/pelvis image evaluator.
Abbreviations: CI, confidence interval; FAS, full analysis set; MRI, magnetic resonance imaging

There was not sufficient enrollment of non-white patients to support a meaningful subgroup analysis by race. The Applicant attempted this analysis and did not identify obvious differences, but the confidence intervals around these estimates were wide. Since the majority of patients (57%) were enrolled in Europe, this subgroup was compared to the U.S. patients (Table 63). A general trend to larger differences in visualization score was seen for all three parameters and all meta-readers in the U.S., particularly reader 2. One possible reason for this was that all patients enrolled in the U.S. were required by the Applicant to have breast MRI due to the use of gadobutrol as a comparator in the study.

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Table 63. Difference in Average Patient-Level Lesion Visualization Scores Between Paired and Pre-Contrast MRI for Gadopiclenol in FAS 1 (n=278) for GDX-44-011 by Site Location

	United States			Europe		
Parameter	**n**	**Difference**	**95% CI**	**n**	**Difference**	**95% CI**
Border delineation						
Reader 1	44	1.56	(1.39, 1.73)	143	1.52	(1.43, 1.61)
Reader 2	36	0.81	(0.54, 1.08)	134	0.28	(0.14, 0.42)
Reader 3	45	1.91	(1.75, 2.08)	149	1.62	(1.53, 1.71)
Internal morphology						
Reader 1	44	1.98	(1.85, 2.10)	143	1.77	(1.70, 1.84)
Reader 2	36	0.57	(0.30, 0.84)	134	0.41	(0.27, 0.56)
Reader 3	45	2.33	(2.14, 2.51)	149	1.89	(1.79, 2.00)
Degree of contrast enhancement						
Reader 1	44	2.90	(2.71, 3.09)	143	2.58	(2.47, 2.69)
Reader 2	36	2.35	(2.01, 2.70)	134	1.72	(1.54, 1.90)
Reader 3	45	2.60	(2.43, 2.77)	149	2.26	(2.16, 2.35)

Source: GDX-44-011 Clinical Study Report, Figure 11-5
Note: Readers in this table refer to meta-reader pools containing 1 head and neck, 1 musculoskeletal, and 1 thorax/abdomen/pelvis image evaluator.
Abbreviations: CI, confidence interval; FAS, full analysis set; MRI, magnetic resonance imaging

Table 64 shows the results of a subgroup analysis by body region for the co-primary endpoints. These values are true per-reader results, as the head and neck and musculoskeletal readers are presented separately from the thorax/abdomen/pelvis reader. We note that despite the smaller sample sizes, the lower bounds of the 95% confidence intervals for the difference in visualization score between paired and pre-contrast images exceeds 0 for at least two of three readers in each body region, suggesting effectiveness for lesion visualization of gadopiclenol MRI in each region.

These results highlight some inter-reader variability, with the thorax/abdomen/pelvis reader 2 reporting smaller differences between paired and pre-contrast images than the others. There is also a trend to larger differences for thorax compared to abdomen and pelvis, best seen for reader 2 for all parameters and for all readers for degree of contrast enhancement. Because nearly all of the thoracic MRIs were for breast lesions, it is possible that under the conditions of the trial, gadopiclenol may improve visualization of breast lesions more than lesions in the abdomen or pelvis. We also note generally lower scores for musculoskeletal lesions than those in other body regions. Because of the nature of these visualization endpoints and the lack of a reference standard, it is not clear whether these findings are clinically meaningful. They do, however, likely explain the trend to larger difference scores in the US compared to Europe described above.

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Table 64. Difference in Average Patient-Level Lesion Visualization Scores Between Paired and Pre-Contrast MRI for Gadopiclenol in FAS 1 (n=278) for GDX-44-011 by Body Region

	Reader 1		Reader 2		Reader 3	
Parameter	**Difference**	**95% CI**	**Difference**	**95% CI**	**Difference**	**95% CI**
Border delineation						
Head and neck (n=13-19)	1.58	(1.30, 1.86)	1.42	(1.07, 1.77)	1.08	(0.82, 1.33)
Thorax (n=55-73)	1.58	(1.44, 1.71)	0.75	(0.54, 0.96)	1.91	(1.80, 2.02)
Abdomen (n=89-97)	1.58	(1.47, 1.70)	0.26	(0.10, 0.42)	1.85	(1.76, 1.95)
Pelvis (n=50-58)	1.55	(1.40, 1.69)	0.26	(0.04, 0.48)	1.72	(1.60, 1.84)
Musculoskeletal (n=17-21)	0.94	(0.68, 1.21)	0.24	(-0.14, 0.61)	0.76	(0.56, 0.96)
Internal morphology						
Head and neck (n=13-19)	1.93	(1.75, 2.12)	1.68	(1.37, 2.00)	1.38	(1.11, 1.66)
Thorax (n=55-73)	1.97	(1.88, 2.06)	0.56	(0.38, 0.75)	2.28	(2.17, 2.40)
Abdomen (n=89-97)	1.86	(1.78, 1.93)	0.25	(0.11, 0.40)	2.25	(2.15, 2.35)
Pelvis (n=50-58)	1.77	(1.67, 1.86)	0.20	(0.00, 0.39)	1.91	(1.78, 2.04)
Musculoskeletal (n=17-21)	1.00	(0.82, 1.18)	1.59	(1.26, 1.92)	0.86	(0.64, 1.07)
Degree of contrast enhancement						
Head and neck (n=13-19)	2.60	(2.29, 2.91)	2.68	(2.25, 3.12)	2.92	(2.62, 3.22)
Thorax (n=55-73)	2.92	(2.77, 3.07)	2.28	(2.02, 2.53)	2.58	(2.46, 2.71)
Abdomen (n=89-97)	2.62	(2.50, 2.74)	1.42	(1.22, 1.62)	2.25	(2.14, 2.36)
Pelvis (n=50-58)	2.60	(2.45, 2.76)	1.52	(1.25, 1.79)	2.12	(1.98, 2.27)
Musculoskeletal (n=17-21)	1.82	(1.53, 2.11)	2.33	(1.87, 2.80)	2.06	(1.83, 2.30)

Source: GDX-44-011 Clinical Study Report, Figure 11-1
Abbreviations: CI, confidence interval; FAS, full analysis set; MRI, magnetic resonance imaging

In general, increased magnetic field strength leads to lower relaxivity with GBCAs. However, increased field strength also tends to increase tissue T1 values, so often the net effect on

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apparent contrast enhancement is minimal. A subgroup analysis comparing patients scanned at 1.5 T to patients scanned at 3 T showed similar lesion visualization scores.

Data Quality and Integrity

FDA Office of Scientific Investigations audits of the CRO that performed the MRI reads and one representative clinical study site revealed no significant GCP deviations.

Efficacy Results – Secondary and Other Relevant Endpoints

More than 95% of patients with matching lesions had an increase in each of the three lesion visualization scores from pre-contrast to paired gadopiclenol MRI for two of the three meta-readers (Table 65). However, meta-reader 2 was more likely to find the border delineation and internal morphology to be unchanged or decreased at a patient level.

Table 65. Change in Patient-Level Lesion Visualization Scores Between Pre-Contrast and Paired MRI With Gadopiclenol Among Patients in FAS 1 (n=278) for GDX-44-011

Parameter	Number of Patients	Number (%) of Patients With Decreased or Unchanged Score	Number (%) of Patients With Increased Score
Border delineation			
Reader 1	251	7 (3%)	244 (97%)
Reader 2	230	133 (58%)	97 (42%)
Reader 3	262	5 (2%)	257 (98%)
Internal morphology			
Reader 1	251	3 (1%)	248 (99%)
Reader 2	230	130 (57%)	100 (43%)
Reader 3	262	4 (2%)	258 (98%)
Degree of contrast enhancement			
Reader 1	251	4 (2%)	247 (98%)
Reader 2	230	30 (13%)	200 (87%)
Reader 3	262	1 (<1%)	261 (100%)

Source: GDX-44-011 Clinical Study Report, Table 11-15
Abbreviations: FAS, full analysis set; MRI, magnetic resonance imaging

The clinical review team also examined the lesion scores without averaging by patient. Among lesions that were scored on both pre-contrast and paired images for gadopiclenol, only one lesion was scored lower on paired than pre-contrast images by meta-readers 1 or 3 (meta-reader 1, border delineation decreased from 3 to 2). Meta-reader 2 scored 315 matched lesions. For border delineation, 27 (9%) were scored lower on paired than pre-contrast images, 172 (54%) the same, and 116 (37%) higher. For internal morphology, the counts were 33 (10%), 197 (62%), and 88 (28%), and for degree of contrast enhancement they were 0, 49 (16%), and 266 (84%), respectively.

Overall, these results support the primary analysis by demonstrating that for two of three readers, few patients were assessed as having unchanged or worsened lesion visualization.

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Table 66 compares the lesion visualization scores among matched lesions for gadopiclenol MRI (0.05 mmol/kg) and gadobutrol MRI (0.1 mmol/kg). The results obtained for the two GBCAs were very similar, and the 95% CIs for the difference contained 0 for all meta-readers and all lesion visualization parameters. We note that gadobutrol is not indicated for lesion visualization outside the CNS (though it does have a disease detection indication for malignant breast disease), so it is difficult to draw strong support for gadopiclenol effectiveness from these data from a regulatory perspective. However, gadobutrol has been used off label for non-CNS lesion visualization, and these results are considered to be favorable.

Table 66. Average Patient-Level Lesion Visualization Scores for Paired Gadopiclenol MRI and Paired Gadobutrol MRI Among Patients in PPS 2 (n=260) for GDX-44-011

		LS Mean (SE)			95% CI
Parameter	**n**	**Gadopiclenol**	**Gadobutrol**	**Difference**	**Difference**
Border delineation					
Reader 1	240	3.82 (0.02)	3.81 (0.02)	0.00 (0.03)	(-0.05, 0.05)
Reader 2	223	3.56 (0.05)	3.53 (0.05)	0.02 (0.04)	(-0.05, 0.10)
Reader 3	243	3.53 (0.03)	3.57 (0.03)	-0.04 (0.03)	(-0.10, 0.01)
Internal morphology					
Reader 1	240	3.83 (0.02)	3.83 (0.02)	0.00 (0.03)	(-0.06, 0.05)
Reader 2	223	3.75 (0.04)	3.75 (0.04)	0.00 (0.04)	(-0.07, 0.07)
Reader 3	243	3.74 (0.03)	3.77 (0.03)	-0.03 (0.02)	(-0.08, 0.02)
Degree of contrast enhancement					
Reader 1	240	3.69 (0.04)	3.68 (0.04)	0.01 (0.04)	(-0.06, 0.09)
Reader 2	223	2.88 (0.07)	2.86 (0.07)	0.03 (0.05)	(-0.07, 0.12)
Reader 3	243	3.35 (0.04)	3.37 (0.04)	-0.02 (0.03)	(-0.08, 0.04)

Source: GDX-44-011 Clinical Study Report, Table 11-2
Note: Only matching lesions are considered.
Abbreviations: CI, confidence interval; LS, least squares; MRI, magnetic resonance imaging; PPS, per protocol set; SE, standard error

For study feasibility reasons, visualization parameters were only scored for up to three lesions per patient. However, the readers did count the total number of lesions per patient for pre-contrast and paired imaging with both gadopiclenol and gadobutrol. This endpoint is important to consider because contrast may increase or in some cases decrease lesion detection. Since the primary endpoint considered only matching lesions that were detected on both pre-contrast and paired images, changes in detectability will not be directly reflected. For two of the three meta-readers, the average number of lesions counted per patient decreased after administration of gadopiclenol (Table 67). The Applicant performed similar analyses for paired imaging with gadopiclenol and gadobutrol (Table 68), which did not demonstrate substantial differences between the two drugs.

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Table 67. Number of Lesions Per Patient in Pre-Contrast and Paired MRI With Gadopiclenol Among Patients in Extended FAS 1 (n=286) for GDX-44-011

	Reader 1		Reader 2		Reader 3	
Parameter	**Pre**	**Paired**	**Pre**	**Paired**	**Pre**	**Paired**
Number of patients	286	286	286	284	284	285
Mean lesion number (SD)	2.5 (2.5)	3.0 (3.9)	2.8 (7.9)	2.4 (6.5)	2.7 (3.1)	2.5 (3.2)
Median lesion number	2.0	2.0	1.0	1.0	2.0	2.0
Range (min, max)	0, 30	0, 30	0, 99	0, 99	0, 30	0, 30

Source: GDX-44-011 Clinical Study Report, Table 11-21
Abbreviations: FAS, full analysis set, max, maximum; min, minimum; MRI, magnetic resonance imaging; SD, standard deviation

Table 68. Number of Lesions Per Patient in Paired MRI With Gadopiclenol and With Gadobutrol Among Patients in Extended FAS 2 (n=276) for GDX-44-011

	Reader 1		Reader 2		Reader 3	
Parameter	**Gadopiclenol**	**Gadobutrol**	**Gadopiclenol**	**Gadobutrol**	**Gadopiclenol**	**Gadobutrol**
Number of patients	276	274	274	276	275	275
Mean lesion number (SD)	3.0 (3.9)	2.7 (2.9)	2.4 (6.6)	2.5 (6.6)	2.5 (3.1)	2.5 (3.6)
Median lesion number	2.0	2.0	1.0	1.0	2.0	2.0
Range (min, max)	0, 30	0, 20	0, 99	0, 99	0, 30	0, 35

Source: GDX-44-011 Clinical Study Report, Table 11-22
Abbreviations: FAS, full analysis set; max, maximum; min, minimum; MRI, magnetic resonance imaging; SD, standard deviation

To further explore the lesion number endpoint, patients were categorized as having the same number of lesions on pre-contrast and paired MRI or more lesions with one or the other, as shown in Table 69. The majority of patients had the same number of lesions reported on pre-contrast and paired images with gadopiclenol. In contrast to the results from GDX-44-010, more patients saw a decrease in lesion number on the paired images than an increase. The findings were similar between gadopiclenol and gadobutrol.

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Table 69. Change in Lesion Numbers Between Pre-Contrast and Paired MRI for Gadopiclenol and Gadobutrol in the Safety Set (n=301) for GDX-44-011

	Number (%) of Patients with More Lesions on Pre		Number (%) of Patients with Same Number of Lesions		Number (%) of Patients with More Lesions on Paired	
Reader	**Gadopiclenol**	**Gadobutrol**	**Gadopiclenol**	**Gadobutrol**	**Gadopiclenol**	**Gadobutrol**
Reader 1	71 (25%)	82 (29%)	149 (52%)	146 (51%)	66 (23%)	58 (20%)
Reader 2	66 (23%)	62 (21%)	180 (64%)	179 (62%)	38 (13%)	48 (17%)
Reader 3	77 (27%)	89 (31%)	175 (62%)	153 (54%)	31 (11%)	44 (15%)

Source: FDA clinical review team analysis
Notes: Patients with missing data for pre-contrast or paired lesion number are excluded. Number of excluded patients ranges from 12 to 18 per reader and GBCA.
Abbreviations: MRI, magnetic resonance imaging

Detection of additional lesions after administration of contrast is usually regarded as beneficial, and detection of fewer lesions might raise concerns for masking of lesions on the contrasted images. However, it is important to note that lesions are not validated against a reference standard in this study. Therefore, not all additional lesions seen on the paired images represent additional pathology. Additionally, some lesions seen on pre-contrast imaging may be more accurately characterized as non-lesions on post-contrast imaging. This issue might also be accentuated by the training given to the readers, who were encouraged to identify all suspected lesions on pre-contrast images in order to prevent missing any potential lesion, which could lead to overcalling.

The potential for identifying different numbers of lesions on pre-contrast and paired MRI will also be influenced by the spectrum of pathology in the study. An additional consideration is the reliability of the lesion counting. In the analysis for gadopiclenol in Table 69, the pairwise reader discordance rates between categories (more lesions on pre-contrast, same number of lesions, and more lesions on paired) were 48%, 48%, and 49% for reader 1 vs. reader 2, reader 1 vs. reader 3, and reader 2 vs. reader 3 respectively. Finally, the similarities of the results for gadopiclenol and gadobutrol are reassuring.

Thus, we do not consider every finding of fewer lesions on paired MRI than pre-contrast MRI to represent lower effectiveness or an adverse outcome from administration of gadopiclenol. Because MRI standard of care generally includes pre-contrast sequences and practicing radiologists are well aware of the potential for GBCAs to occasionally obscure lesions, we believe any potential risk for decreased lesion detection can be mitigated by a warning in the prescribing information, as exists for other GBCAs indicated for visualization of lesions outside the CNS.

Three additional sets of three independent readers who were blinded to the administered GBCA and who did not provide assessments for the primary analyses were asked their overall diagnostic preference between paired images obtained with gadopiclenol and paired images obtained gadobutrol presented side-by-side. Images with gadopiclenol were preferred to images with gadobutrol in 12% to 15% of the cases. Gadobutrol was preferred in 5% to 11% of cases. No preference was observed in the remainder of the cases.

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Local investigators were asked to report the number of patients who could have a change in management from the pre-contrast MRI after obtaining contrasted images. For 83 of 276 patients (30%), the local investigator stated that the treatment plan could have been changed after gadopiclenol MRI. Similar results (81/276; 29%) were obtained with gadobutrol. Note that the investigators were not required to state a treatment plan based on the pre-contrast images prior to seeing the contrasted images. Also, data regarding the actual administered treatment and its outcome were not collected.

Intra-reader variability was assessed based on rereads of a random selection of 10% of images. For the pre-contrast and paired images with gadopiclenol, the ICC ranged from 0.42 to 0.98 across the three lesion visualization parameters and three meta-readers. It was noted that meta-reader 2 had much lower ICCs (0.42 to 0.86) than meta-readers 1 and 3 (0.91 to 0.98). Pairwise ICCs for inter-reader variability ranged from 0.61 to 0.95 for the three lesion visualization parameters and the three meta-readers.

Dose/Dose Response

Gadopiclenol was administered at a concentration of 0.5 M and a nominal dose of 0.05 mmol/kg body weight, however the volume to be injected was rounded to the nearest whole number of mL. Two (<1%) patients in FAS 1 received less than the intended volume and 5 (2%) patients more than the intended volume. The mean dose was 0.051 mmol/kg, with a range of 0.041 mmol/kg to 0.10 mmol/kg.

The recommended injection rate in the protocol was 2 mL/sec. The mean injection rate was reported as 2.1 mL/sec, with a standard deviation of 0.5 mL/sec.

8.1.5. GDX-44-007: PK, Safety, and Efficacy of Gadopiclenol in Pediatric Patients 2-17 Years

This study was primarily designed to investigate the pharmacokinetics of gadopiclenol at 0.05 mmol/kg in pediatric patients with known or suspected lesions scheduled to undergo routine contrasted MRI of the CNS or other body organs. Secondary endpoints related to efficacy included technical adequacy for diagnosis, assessment of contrast quality (percentage of lesion enhancement, lesion to background ratio), lesion visualization variables, and change in diagnostic confidence. These endpoints were assessed by the local investigators.

The CNS cohort included 60 patients, distributed in three age groups (20 patients per group): 2 to 6 years, 7 to 11 years, and 12 to 17 years. The body cohort included 20 patients (6 aged 2 to 6 years, 3 aged 7 to 11 years, and 11 aged 12 to 17 years).

In the CNS cohort, lesions were identified in 32 patients (53%) with pre-contrast images and 34 patients (57%) with paired images. For two patients, lesions were visible on post-contrast images only. In the body cohort, 12 lesions were detected in 11 patients (55%) on both pre-contrast images and paired images.

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Up to three lesions per patient were evaluated on 4-point scales by the onsite radiologist for lesion visualization criteria.

Overall, the mean (SD) sum of lesions scores for pre-contrast and paired images were 2.9 (0.8) and 3.0 (0.8) for lesion border delineation, 2.9 (1.0) and 3.0 (0.9) for internal morphology, and 1.0 (0.0) and 1.9 (1.2) for the degree of contrast enhancement, respectively.

Important limitations of this study from a regulatory point of view with respect to efficacy include:

- No hypothesis-tested primary endpoints for effectiveness.
- No central image evaluation.
- Readers were not blinded to clinical information.
- Relatively small sample size.

While the results of this study do not provide substantial evidence of effectiveness, they support extrapolation of efficacy established in adults to pediatric patients of ages 2 to 17 years.

8.1.6. GDX-44-008: Proof of Concept Study Concerning Efficacy of Gadopiclenol-Enhanced MR Imaging in HCC Diagnosis

This was an exploratory, non-randomized, open-label phase 2 study including two cohorts of patients:

- 30 patients who were administered gadopiclenol at 0.1 mmol/kg
- 10 patients who were administered gadopiclenol at 0.05 mmol/kg.

All patients were required to have chronic liver disease or cirrhosis and one to three untreated hepatic nodules that were previously characterized by CT or MRI as hepatocellular carcinoma (HCC) or lesion other than HCC. Imaging results could be supplemented by histopathology obtained before or after imaging with gadopiclenol.

The diagnostic performance of MRI with gadopiclenol for HCC was assessed using a reference standard based on previous imaging and/or histology. Two radiologists (one from each clinical site) with expertise in the interpretation of MR images of liver diseases and HCC evaluated the images. In case of diagnostic discordance between readers regarding the primary criterion, results were determined by consensus.

The sensitivity and specificity for gadopiclenol-enhanced MRI at the dose of 0.1 mmol/kg were 62% (95% CI: 38%, 82%) and 86% (95% CI: 65%, 97%), respectively.

The results of this study were not reviewed in detail due to its exploratory nature. The study design and results are not sufficient to support a characterization claim, but they provide some indirect support for the body lesion visualization claim. Important limitations of this study include:

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- The study did not investigate the population of intended use as disease status was known at enrollment.
- No predefined study success criteria.
- Two readers, both from participating study sites, reported in consensus.
- Lack of reader blinding.
- Small sample size.

8.1.7. Integrated Assessment of Effectiveness

The Applicant's data provide substantial evidence for the effectiveness of gadopiclenol for MRI of the CNS and body. The two efficacy trials used a paradigm very similar to trials for the approval of lesion visualization claims for other GBCAs, where multiple blinded, independent readers scored the border delineation, internal morphology, and contrast enhancement of lesions in the absence of the drug and on image sets obtained before and after administration of the drug. While both trials met their primary objectives, there were several issues related to effectiveness that arose during review.

Both main trials employed crossover designs using gadobutrol at the labeled dose as a comparator. The two drugs were compared as secondary endpoints in a noninferiority design. The lesion visualization scores and number of visualized lesions were very similar between the two drugs, and this is considered important supportive information. However, we note that the noninferiority margin for the comparison of lesion visualization scores was determined based on an assumption that a 10% difference would be clinically unimportant and that the mean score would be 3.5 (on a 4-point scale). We believe that it is difficult to apply a 10% noninferiority margin or perhaps any noninferiority margin to this subjective 4-point scale. In addition, we note that while gadobutrol is labeled for CNS visualization with an indication similar to that desired for gadopiclenol, it does not carry an indication for visualization of body lesions. Together, these points argue against placement of detailed comparative results in the prescribing information for gadopiclenol.

The body lesion visualization indication essentially encompasses all organ systems except the CNS, as it includes the musculoskeletal system, unlike most other GBCAs with similar claims. Accordingly, patient enrollment in the main trials was allowed to be broad. However, some body regions, including spine, head and neck, and musculoskeletal, were represented by relatively small numbers of patients. For a nontargeted, extracellular GBCA, it is expected that body region will not have a major impact on drug performance. This is supported by exploratory analyses of the data in these three body regions. Therefore, we believe that the submitted data are acceptably supportive of the body regions to be indicated.

In both confirmatory efficacy studies, but especially in GDX-44-011, there were patients who were reported to have fewer lesions in the paired images compared to the pre-contrast images. Note that the paired images contain the pre-contrast images in their entirety. In the absence of a reference standard, it is not possible to tell whether lesions that were identified on pre-contrast but not paired image evaluations were obscured by the contrast or were assessed as not representing a lesion based on the additional contrasted images. Because of this issue, and

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in keeping with labeling of other GBCAs that have received body lesion visualization indications, the addition of a warning to the prescribing information regarding the potential for interference with visualization of lesions seen on non-contrast MRI is a reasonable risk mitigation step.

(b) (4)

As noted above, it is anticipated that anatomic region will have relatively little impact on the performance of a nontargeted GBCA. In addition, the results were generally similar between GDX-44-010 and GDX-44-011. Therefore, we consider these trials to be mutually supportive.

After considering the above-mentioned issues and limitations, we find that the Applicant has submitted substantial evidence of effectiveness, in the form of two adequate and well-controlled clinical trials and additional supportive evidence, to meet the regulatory standards for approval.

8.2. Review of Safety

8.2.1. Safety Review Approach

The clinical safety data for gadopiclenol were collected from eight clinical studies, and all of these data sources were evaluated. The bulk of the data were obtained from the two major effectiveness studies GDX-44-010 and GDX-44-011. Other notable data sources include a study in patients with impaired renal function (GDX-44-005), a study in patients with chronic liver disease or cirrhosis (GDX-44-008), a cardiac safety study (GDX-44-006), and a study in pediatric patients (GDX-44-007).

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant pooled safety data from patients and healthy volunteers from the eight studies that comprised their clinical development program. This pooling approach was not discussed in the pre-NDA meeting package or FDA preliminary comments. While this is a reasonable strategy and this group will be considered throughout the safety review, we chose to focus our analyses of the pooled data on the patients who were intended to receive gadopiclenol at the recommended dose of 0.05 mmol/kg due to the possibility that higher or lower doses may alter the adverse event (AE) profile. Note that this subgroup excludes all patients and healthy volunteers in the GDX-44-005 renal impairment study and the GDX-44-006 thorough QT study.

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The pooled safety set (n=1047) is defined as all patients (n=955) and healthy volunteers (n=92) enrolled in one of the eight clinical studies who received at least one dose of gadopiclenol. The pooled 0.05 mmol/kg safety set (n=708) is defined as all patients (n=699) and healthy volunteers (n=9) in the pooled safety set who received at least one dose of gadopiclenol at the intended dose.

A total of 80 (11%) of the patients in the pooled 0.05 mmol/kg safety set were pediatric patients, with ages ranging from 2 years to 17 years (Table 70). Patients 65 years or older made up 29% of the set, and patients 75 years or older 8%. The age distribution appears to be reasonably representative of the population of intended use.

Table 70. Demographic and Baseline Characteristics of the Pooled Safety Sets

Parameter	Pooled 0.05 mmol/kg Safety Set (n=708) n (%)	Pooled Safety Set (n=1047) n (%)
Age		
Mean years (SD)	51.2 (19.9)	50.8 (18.4)
Median (years)	55.0	55.0
Min, max (years)	2, 88	2, 88
Age Group		
≤17 years	80 (11%)	80 (8%)
<65 years	504 (71%)	777 (74%)
≥65 years	204 (29%)	270 (26%)
≥75 years	55 (8%)	62 (6%)
Sex		
Female	393 (56%)	565 (54%)
Male	315 (44%)	482 (46%)
Race		
White	563 (80%)	828 (79%)
Black or African American	15 (2%)	25 (2%)
Asian	71 (10%)	95 (9%)
American Indian or Alaska Native	47 (7%)	48 (5%)
Native Hawaiian or other Pacific Islander	3 (<1%)	3 (<1%)
Other	3 (<1%)	3 (<1%)
Not collected	9 (1%)	48 (5%)
Ethnicity		
Hispanic or Latino	91 (13%)	144 (14%)
Not Hispanic or Latino	608 (86%)	855 (82%)
Not collected	9 (1%)	48 (4%)
Region		
United States	104 (15%)	134 (13%)
Outside United States	604 (85%)	913 (87%)

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Parameter	Pooled 0.05 mmol/kg Safety Set (n=708) n (%)	Pooled Safety Set (n=1047) n (%)
Region		
North America	173 (25%)	255 (25%)
Europe	469 (66%)	705 (67%)
Asia	66 (9%)	87 (8%)
Dose		
Mean (mmol/kg) (SD)	0.051 (0.005)	0.078 (0.064)
Min, max (mmol/kg)	0.025, 0.104	0.023, 0.307
Renal Impairment at Baseline		
Moderate (eGFR <60 mL/min/1.73 m^2 and ≥30 mL/min/1.73 m^2)	46 (6%)	57 (5%)
Severe (eGFR <30 mL/min/1.73 m^2 or on dialysis)	0	16 (2%)
Other Characteristics at Baseline		
Hepatic insufficiency	40 (6%)	67 (6%)
Cardiac disease	72 (10%)	100 (10%)
History of allergic diseases	96 (14%)	120 (12%)

Source: Summary of Clinical Safety, Tables 2.7.4-6 and 2.7.4-7 (Pooled Safety Set), Pooled Safety Data from gadopiclenol clinical studies, Tables 9 and 15 (Pooled 0.05 mmol/kg Safety Set), FDA clinical review team analysis (Ethnicity, Dose)
Notes: For patients who received more than one dose of gadopiclenol, only the highest dose per patient was used for calculating the average in the Pooled Safety Set. A single dose of gadopiclenol was administered to patients in the Pooled 0.05 mmol/kg Safety Set.
Abbreviations: eGFR, estimated glomerular filtration rate; max, maximum; min, minimum; SD, standard deviation

Most of the patients in the safety sets were white. A large majority were enrolled outside the U.S., mainly from European countries. However, we are not aware of a mechanistic rationale or data to suggest that race or geographic region will influence likelihood or severity of AEs.

The mean dose administered to patients in the pooled 0.05 mmol/kg safety set was 101% of the intended dose. The dose range was approximately 50% to 200% of intended, but more than 98% of patients in the set had doses between 0.46 and 0.56 mmol/kg. The pooled safety set had more variability, as the intended doses ranged from 0.025 to 0.3 mmol/kg.

Patients with renal impairment are of particular interest due to reports of NSF and of acute kidney injury for other drugs in the class. The pooled 0.05 mmol/kg safety set contains most of the patients from the pooled safety set who had moderate chronic renal insufficiency. Patients with severe chronic renal insufficiency were only included in GDX-44-005, where gadopiclenol was dosed at 0.1 mmol/kg. The pooled safety set will therefore be used for the analysis of issues thought to be linked to renal insufficiency.

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Adequacy of the Safety Database:

The size and demographic distribution of the safety database are acceptable.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Categorization of Adverse Events

For all studies that provided safety data, AE collection began from signing of the informed consent document. Formal collection of AE data varied between studies, but was at least one day after administration of gadopiclenol in all cases. Severity of AEs was categorized as mild, moderate, or severe in all studies. All but GDX-44-003 classified relatedness of AEs as related or not related. GDX-44-003, which enrolled 66 patients in total, including 48 patients who received gadopiclenol, classified relatedness as possibly related, doubtfully related, or not related.

Treatment emergent adverse events (TEAEs) were defined as AEs whose onset was during or after the injection of the contrast agent, unknown, or missing. AEs that were present at baseline, but whose severity increased after injection, and events having no start date were also considered TEAEs.

For the pooled safety analysis, the Applicant coded AEs using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. The coding of verbatim terms to lowest level terms was audited by the clinical reviewer and no significant issues were identified.

Patients in all studies were specifically asked about injection site tolerance, including injection site pain, with the assessment to be performed over the first day after injection.

In GDX-44-005 (renal impairment study; 40 patients) and GDX-44-007, (pediatric study; 80 patients), patients were also asked about signs or symptoms of NSF at follow-up durations of up to 6 months (GDX-44-005) or 3 months (GDX-44-007) post-administration of gadopiclenol. Note that GDX-44-007 also incorporated physical examination for signs of NSF at the 3 month follow-up visit.

Routine Clinical Tests

Vital sign measurements were collected in all studies. The least intensive measurements were in GDX-44-010 and GDX-44-011, where heart rate and blood pressure were assessed at 60 minutes and 1 day after injection of gadopiclenol. Data for temperature and respiratory rate were found only for GDX-44-003.

Biochemistry and hematology laboratory results were obtained in all studies, most often at baseline and 1 day after gadopiclenol administration. Urinalysis was evaluated in GDX-44-003, GDX-44-004, and GDX-44-005.

ECGs were obtained in all studies except GDX-44-008, GDX-44-010, and GDX-44-011. ECG timing was relatively late in most studies, beginning 30 min to 60 min post-injection, compared

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to the expected peak gadopiclenol concentration. However, GDX-44-006, the thorough QT study, performed extensive ECG collection, including at early time points.

8.2.4. Safety Results

Deaths

Among all clinical studies, two deaths were reported after injection of a contrast agent.

A 59-year-old man enrolled in the severe renal impairment cohort of GDX-44-005 died 22 days after administration of 0.102 mmol/kg gadopiclenol. Other medical history included hypertension, ischemic heart disease, congestive heart failure, ischemic stroke, antiphospholipid syndrome, dyslipidemia, hypertensive nephropathy, hyperuricemia, secondary hyperparathyroidism, renal osteodystrophy, hepatosteatosis, and retinal angiopathy. His family history was notable for sudden death in his father. One day prior to gadopiclenol administration, his eGFR was 19 mL/min/1.73 m^2, and there was no substantial change at follow-up visits (20 and 18 mL/min/1.73 m^2 2 days and 7 days post-injection, respectively). He reported no adverse events, including at a study visit scheduling contact on the morning of death. Death was sudden and according to the patient's wife was without prodromal sign or symptom. Cause of death was stated as cardio-respiratory insufficiency. Autopsy was not performed. This death was considered unrelated to gadopiclenol by the investigator and the Applicant. This reviewer evaluated the complete narrative for this death and concurs with the assessment of non-relatedness. The death occurred after gadopiclenol would be expected to have been excreted (even in the presence of severe renal impairment), was not preceded by signs or symptoms of drug toxicity, and is more likely explained by the patient's comorbid medical conditions.

A 67-year-old female patient with a history of widely metastatic breast cancer experienced worsening of general condition 5 days after administration of 0.095 mmol/kg gadobutrol in GDX-44-010, and she ultimately died on day 9 post-injection. Cause of death was stated as respiratory failure due to tumor progression. The events were assessed as not related to gadobutrol by the investigator and Applicant. This death was not related to gadopiclenol as gadopiclenol had not yet been administered.

Serious Adverse Events

A total of 17 serious adverse events (SAE) were reported in 12 patients (1.1%) after administration of gadopiclenol, including the fatal event of cardiopulmonary failure discussed in the prior section (Table 71). Among patients who received the to-be-marketed dose of 0.05 mmol/kg, 12 non-fatal SAEs were observed in 7 patients (1%). All of the SAEs in the pooled safety set that were not included in the pooled 0.05 mmol/kg safety set occurred at doses of gadopiclenol higher than 0.05 mmol/kg.

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Table 71. Gadopiclenol-Treatment Emergent Serious Adverse Events

	Pooled 0.05 mmol/kg Safety Set (n=708)		Pooled Safety Set (n=1047)	
MedDRA SOC or PT	**n (%) patients**	**n SAEs**	**n (%) patients**	**n SAEs**
At least one SAE	7 (1.0%)	12	12 (1.1%)	17
General disorders and administration site conditions	3 (0.4%)	3	3 (0.3%)	3
Condition aggravated	3 (0.4%)	3	3 (0.3%)	3
Injury, poisoning and procedural complications	2 (0.3%)	2	3 (0.3%)	3
Femoral neck fracture	0	0	1 (0.1%)	1
Head injury	1 (0.1%)	1	1 (0.1%)	1
Procedural complication	1 (0.1%)	1	1 (0.1%)	1
Cardiac disorders	0	0	2 (0.2%)	2
Cardiac failure congestive	0	0	1 (0.1%)	1
Cardiopulmonary failure	0	0	1 (0.1%)	1
Infections and infestations	2 (0.3%)	2	2 (0.2%)	2
COVID-19	1 (0.1%)	1	1 (0.1%)	1
Tonsillitis	1 (0.1%)	1	1 (0.1%)	1
Nervous system disorders	2 (0.3%)	3	2 (0.2%)	3
Coma	1 (0.1%)	1	1 (0.1%)	1
Depressed level of consciousness	1 (0.1%)	1	1 (0.1%)	1
Epilepsy	1 (0.1%)	1	1 (0.1%)	1
Gastrointestinal disorders	1 (0.1%)	1	1 (0.1%)	1
Gastric perforation	1 (0.1%)	1	1 (0.1%)	1
Investigations	0	0	1 (0.1%)	1
Blood creatinine increased	0	0	1 (0.1%)*	1*
Renal and urinary disorders	1 (0.1%)	1	1 (0.1%)	1
Hydronephrosis	1 (0.1%)	1	1 (0.1%)	1
Surgical and medical procedures	0	0	1 (0.1%)	1
Abortion induced	0	0	1 (0.1%)	1

Source: Summary of Clinical Safety, Table 2.7.4-15 (Pooled Safety Set), Pooled Safety Data from gadopiclenol clinical studies, Table 29 (Pooled 0.05 mmol/kg Safety Set)
Note: * indicates an event that was assessed as related to gadopiclenol administration by the investigator.
Abbreviations: MedDR, Medical Dictionary for Regulatory Activities; PT, preferred term; SAE, serious adverse event; SOC, system organ class

One SAE, blood creatinine increased, in one patient who received gadopiclenol at a nominal dose of 0.1 mmol/kg in GDX-44-004 was considered related to the drug by the investigator and Applicant. The patient was a 40-year-old female who had a past medical history that included oligodendroglioma, epilepsy, and hypothyroidism. At enrollment, she had serum creatinine of 0.83 mg/dL, on the day of (prior to) gadopiclenol injection 0.71 mg/dL, and 1 day after administration 0.90 mg/dL. This last value represented a 27% increase from pre-injection. eGFR was 91 mL/min/1.73 m^2 and 69 mL/min/1.73 m^2 on the day of and day after gadopiclenol

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administration, respectively. No associated symptoms were reported, and no treatment was administered. Serum creatinine decreased to 0.81 mg/dL by 20 days post-injection. The event was considered serious due to investigator assessment of medical importance. It also met a protocol-defined subject stopping rule of increase in serum creatinine of more than 25% or 0.5 mg/dL and led to the patient's discontinuation from the study. Due to temporal association and the lack of competing explanation for the finding, we concur with the assessment that the event was related, though we note that the absolute change in creatinine was small. As will be discussed in subsequent sections, blood creatinine increase that was not assessed as serious occurred after dosing of gadopiclenol at 0.05 mmol/kg, and this adverse reaction will be included in labeling.

The remaining SAEs were considered unrelated to gadopiclenol by the investigators and the Applicant. Based on review of the narratives, the clinical reviewer agrees with the assessment of non-relatedness. Brief summaries of the narratives are as follows:

- Abortion induced: A 25-year-old female was exposed to gadopiclenol 14 days prior to a positive pregnancy test (pregnancy tests were negative on the day of administration and 1 day after). Genetic testing was performed due to maternal history of congenital cavernous hemangioma, with positive result. Abortion was elected based on the result of genetic testing.
- Femoral neck fracture: A 59-year-old female with history of right hemiparesis suffered a fall after stubbing her foot on carpet 11 days after administration of gadopiclenol.
- Congestive heart failure: A 71-year-old male with complex medical history including severe renal impairment, hypertension, type 2 diabetes with associated neuropathy and retinopathy, and ischemic cardiomyopathy (but not congestive heart failure) was hospitalized for congestive heart failure 20 days after receiving gadopiclenol. This patient also experienced an increase in creatinine from 2.68 mg/dL on the day prior to injection and 2.78 mg/dL 2 days after to 3.21 mg/dL 7 days after gadopiclenol. This was an AE of special interest in the study, considered as unrelated to the drug or the congestive heart failure by the investigator. We note that the associated change in eGFR (23, 22, and 19 mL/min/1.73 m^2, respectively) was minimal.
- Tonsillitis: A 14-year-old female with past medical history of hemiparesis and suspected Lyme disease was hospitalized for suspected viral infection due to headache, nausea, and sore throat beginning 2 days after receiving gadopiclenol. She was discharged after 1 week but returned 22 days after gadopiclenol dosing with headache and sore throat, was diagnosed with acute tonsillitis, and was again hospitalized. Tonsillitis was reported as resolved 9 days after the second admission.
- Hydronephrosis and condition aggravated: A 17-year-old female diagnosed with urinary tract infection and right hydronephrosis approximately 2 years prior to enrollment presented with right sided abdominal pain and urinary tract infection 2 days after administration of gadopiclenol. Three days later, an ultrasound showed dilation of the right renal collecting system and the patient was hospitalized for worsening of hydronephrosis. Note the investigational MRI showed dilation of the right renal collecting system, but measurements were not stated.

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- Epilepsy, head injury, coma, condition aggravated: A 6-year-old male with history of leukodystrophy, psychomotor developmental delay, and spastic paresis, but no prior seizures, experienced convulsions, loss of consciousness, fall, and head injury 65 days after gadopiclenol administration. In the emergency room, he received diazepam and thiopental and was admitted to the hospital in a coma. Head CT was without evidence of intracranial injury. Coma was considered resolved 2 weeks after admission. After a prolonged hospital stay, the diagnoses of epilepsy and worsening of neurodegenerative disease were made.
- Procedural complication, gastric perforation: A 67-year-old female with history of hepatitis C, nonalcoholic steatohepatitis, and cirrhosis underwent percutaneous biopsy of a lesion in the left hepatic lobe 14 days after gadopiclenol administration and suffered a complication of gastric perforation.
- Condition aggravated: A 40-year-old male with history of hepatitis B and a large lesion in the right lobe of the liver presented to the emergency department 3 days after administration of gadopiclenol with about 1 month of fever and new onset abdominal pain and weakness. He was discharged the same day with a diagnosis of worsening liver tumor.
- Depressed level of consciousness: A 68-year-old male with a complex medical history notable for hepatic cirrhosis, esophageal varices, splenomegaly, thrombocytopenia, aortic stenosis, and alcohol abuse was noted to have anemia 1 day after injection of gadopiclenol (hemoglobin 12.5 g/dL on day of injection and 11.7 g/dL on day after) which was assessed by the investigator as unrelated. Four days after gadopiclenol, he was hospitalized due to deterioration of consciousness, weakness, and fainting. The investigator assessed the most likely cause as worsening of liver function. Note there is little detail available in the narrative regarding the event or its treatment.
- COVID-19 infection: A 64-year-old male with a liver lesion found on CT was diagnosed with COVID-19 infection 8 days after administration of gadopiclenol. He required hospitalization 3 days after diagnosis.

Dropouts and/or Discontinuations Due to Adverse Effects

A total of seven patients experienced non-fatal AEs after administration of gadopiclenol that led to study dropout or discontinuation. Four of these events, blood creatinine increased, COVID-19 infection, depressed level of consciousness, and femoral neck fracture, were considered serious and are described in the prior section. The remaining three events were claustrophobia, upper respiratory tract infection, and electrocardiogram QT interval abnormality. The Applicant also notes an additional five patients who were discontinued from GDX-44-004 due to subject stopping rules but were not reported as having AEs, two for blood creatinine increase of >25%, two for QTc >500 msec, and one for increase in QTC >60 msec over baseline.

The reported discontinuations due to AEs do not suggest a significant safety issue. The potential for gadopiclenol to affect renal function or the cardiac conduction system will be discussed in subsequent sections.

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Significant Adverse Events

A total of seven severe AEs were reported in five patients (0.7%) in the pooled 0.05 mmol/kg safety set. Three of these, namely depressed level of consciousness, gastric perforation, and procedural complication, were also considered serious and are discussed above. The remaining events were upper abdominal pain, headache, and long QT syndrome (two reports in the same patient).

An additional seven severe AEs occurred in six patients who received more than 0.05 mmol/kg gadopiclenol. These include the three SAEs of cardiopulmonary failure (fatal), femoral neck fracture, and abortion induced. Non-serious, but severe AEs in this population were injection site pain (in two patients), upper abdominal pain, and low back pain.

Adverse Events of Special Interest (AESI) were defined by the Applicant as:

- Suspected NSF or symptoms suspected to be related to NSF in GDX-44-004, GDX-44-005, GDX-44-006, GDX-44-007, GDX-44-008, GDX-44-010, and GDX-44-011.
- Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation and flutter, syncope (excluding vasovagal reaction due to blood sampling), and seizures in GDX-44-006.
- Decrease in kidney function characterized by an increase in serum creatinine by more than 25% or 0.5 mg/dL compared to the value measured at inclusion, occurring between inclusion and discharge in GDX-44-005.

There is no report of suspected NSF or symptoms related to NSF. While NSF has been detected as soon as 1 day after administration of GBCAs, the median onset has been reported as 42 days with an interquartile range of 19 to 90 days (Rudnick et al. 2022). As noted above, only GDX-44-005 and GDX-44-007 incorporated delayed assessment for NSF into the protocol, and the majority of the pooled safety set does not have a sufficient protocol-defined follow-up period to reliably detect symptoms of NSF. However, this is offset by the fact that GDX-44-005 contains all of the patients at highest risk for NSF (i.e., patients with severe renal impairment and end stage renal disease) and by the likelihood that due to the well-known strong association with GBCAs and severity of the condition, any case of NSF identified after participation in the trial would likely be reported to the Applicant. While no cases of suspected or confirmed NSF were reported in the gadopiclenol clinical development program, the class-wide boxed warning for NSF is considered necessary for gadopiclenol to be used in a safe manner.

No Torsade de pointes, sudden death, ventricular tachycardia, ventricular fibrillation or flutter, syncope, or seizure was reported in the thorough QT study GDX-44-006.

One AESI of decrease in kidney function was reported in a 71-year-old patient with severe renal impairment in GDX-44-005. This patient also developed an SAE, congestive heart failure, and a brief narrative is provided in the Serious Adverse Events section.

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Treatment Emergent Adverse Events and Adverse Reactions

Adverse events considered to be gadopiclenol-treatment emergent (as opposed to treatment emergent to one of the other drugs included in the clinical studies) are listed by MedDRA system organ class in Table 72. A total of 390 AEs were reported in 247 patients in the pooled safety set, and 188 AEs were reported in 119 patients in the pooled 0.05 mmol/kg safety set. Of the 390 AEs reported in the pooled safety set, 325 (83.3%) were mild, 50 (12.8%) were moderate, and 14 (3.6%) were severe. Severity information of one AE was missing.

Table 72. Gadopiclenol-Treatment Emergent Adverse Events by System Organ Class

	Pooled 0.05 mmol/kg Safety Set (n=708)		Pooled Safety Set (n=1047)	
MedDRA SOC	**n (%) patients**	**n AEs**	**n (%) patients**	**n AEs**
At least one AE	119 (16.8%)	188	247 (23.6%)	390
General disorders and administration site conditions	40 (5.6%)	48	92 (8.8%)	120
Nervous system disorders	33 (4.7%)	36	59 (5.6%)	66
Gastrointestinal disorders	21 (3.0%)	24	38 (3.6%)	46
Investigations	12 (1.7%)	13	24 (2.3%)	25
Infections and infestations	12 (1.7%)	13	16 (1.5%)	17
Injury, poisoning, and procedural complications	9 (1.3%)	9	10 (1.0%)	10
Skin and subcutaneous tissue disorders	8 (1.1%)	8	22 (2.1%)	26
Renal and urinary disorders	8 (1.1%)	9	15 (1.4%)	16
Musculoskeletal and connective tissue disorders	6 (0.8%)	7	14 (1.3%)	16
Respiratory, thoracic, and mediastinal disorders	5 (0.7%)	5	10 (1.0%)	11
Metabolism and nutrition disorders	3 (0.4%)	3	7 (0.7%)	8
Blood and lymphatic system disorders	3 (0.4%)	3	3 (0.3%)	3
Cardiac disorders	2 (0.3%)	3	5 (0.5%)	8
Psychiatric disorders	2 (0.3%)	2	3 (0.3%)	3
Vascular disorders	1 (0.1%)	1	4 (0.4%)	5
Eye disorders	1 (0.1%)	1	3 (0.3%)	3
Ear and labyrinth disorders	1 (0.1%)	1	2 (0.2%)	2
Surgical and medical procedures	1 (0.1%)	1	2 (0.2%)	2
Immune system disorders	1 (0.1%)	1	1 (0.1%)	1
Pregnancy, puerperium, and perinatal conditions	0	0	1 (0.1%)	1
Reproductive system and breast disorders	0	0	1 (0.1%)	1

Source: Summary of Clinical Safety, Table 2.7.4-18 (Pooled Safety Set), Pooled Safety Data from gadopiclenol clinical studies, Table 27 (Pooled 0.05 mmol/kg Safety Set)
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class

The AE incidence was lower in patients who received the to-be-marketed dose, 16.8% versus 23.6%. As shown in Figure 13, there is a trend to higher AE rates with higher dose of

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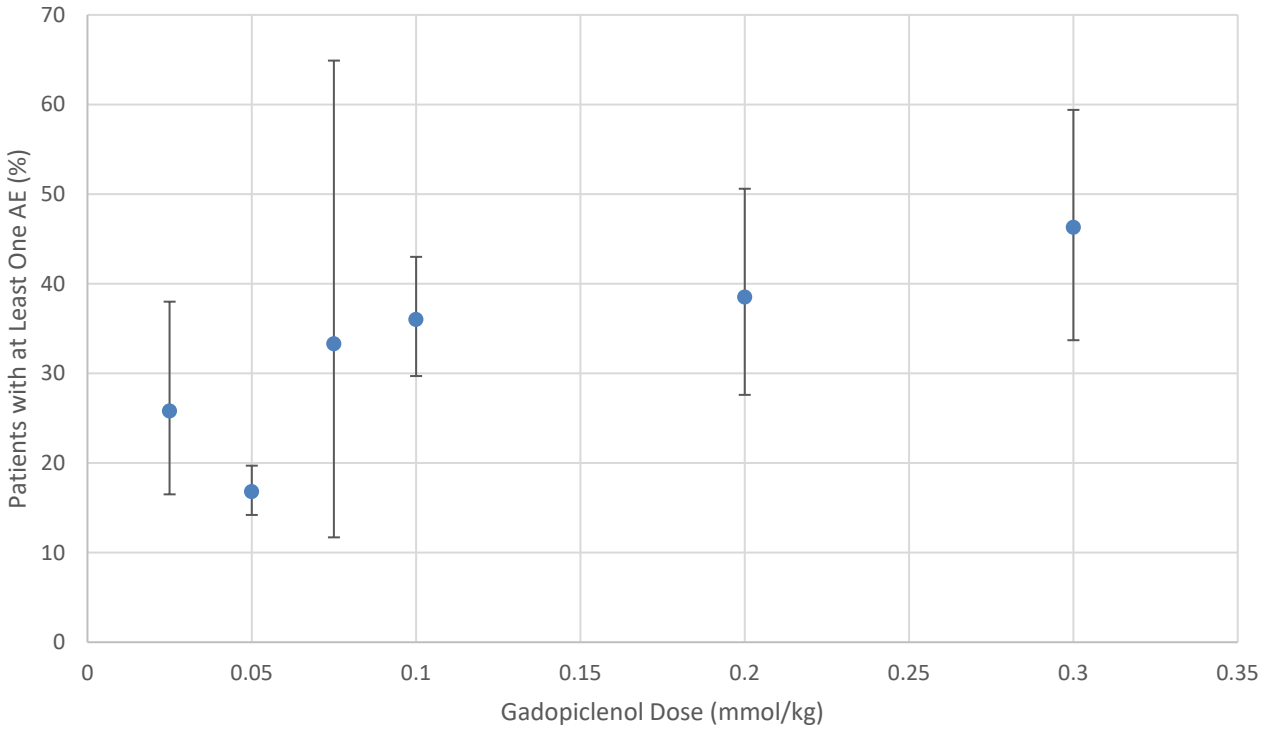
gadopiclenol. The rank order of AEs by system organ class was very similar for 0.05 mmol/kg and all doses combined. The most notable difference was a lower ranking of skin and subcutaneous tissue disorders at 0.05 mmol/kg, due mainly to lower incidence of contact dermatitis than was reported for 0.1 mmol/kg and 0.3 mmol/kg. Among the most commonly reported preferred terms, trends to higher incidence of headache (i.e., 22/708 [3.1%] at 0.05 mmol/kg versus 7/54 [13.0%] at 0.3 mmol/kg) and injection site pain (i.e., 12/708 [1.7%] at 0.05 mmol/kg versus 9/65 [13.8%] at 0.2 mmol/kg) were noted at higher doses.

Figure 13. Incidence of Gadopiclenol-Treatment Emergent Adverse Events by Dose in the Pooled Safety Set (n=1047)



Source: Pooled Safety Data from gadopiclenol clinical studies, Table 27
Note: Error bars are 95% confidence intervals.
Abbreviation: AE, adverse event

The gadopiclenol clinical development program included three studies that used a crossover design with other GBCAs, GDX-44-004 (gadobenate dimeglumine), GDX-44-010 (gadobutrol), and GDX-44-011 (gadobutrol). Both gadobenate dimeglumine and gadobutrol are approved for visualization claims for CNS lesions (among other indications) and were used in the studies at the recommended dose of 0.1 mmol/kg. As shown in Table 73, the fraction of patients who reported AEs after each of the three drugs is relatively similar. There was also little difference among them in rank order of AE incidence by system organ class. These findings suggest that the AE profile of gadopiclenol is similar to other GBCAs, at least for common AEs.

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Table 73. Frequency of Treatment Emergent Adverse Events by Administered Contrast Agent and by System Organ Class

MedDRA SOC	Gadopiclenol 0.05 mmol/kg (n=708)	Gadobenate dimeglumine 0.1 mmol/kg (n=256)	Gadobutrol 0.1 mmol/kg (n=535)
At least one AE	119 (16.8%)	59 (23.0%)	101 (18.9%)
General disorders and administration site conditions	40 (5.6%)	20 (7.8%)	41 (7.7%)
Nervous system disorders	33 (4.7%)	11 (4.3%)	16 (3.0%)
Gastrointestinal disorders	21 (3.0%)	11 (4.3%)	13 (2.4%)
Investigations	12 (1.7%)	6 (2.3%)	12 (2.2%)
Infections and infestations	12 (1.7%)	1 (0.4%)	0
Injury, poisoning, and procedural complications	9 (1.3%)	0	5 (0.9%)
Skin and subcutaneous tissue disorders	8 (1.1%)	4 (1.6%)	7 (1.3%)
Renal and urinary disorders	8 (1.1%)	11 (4.3%)	4 (0.7%)
Musculoskeletal and connective tissue disorders	6 (0.8%)	1 (0.4%)	6 (1.1%)
Respiratory, thoracic, and mediastinal disorders	5 (0.7%)	0	4 (0.7%)
Metabolism and nutrition disorders	3 (0.4%)	2 (0.8%)	1 (0.2%)
Blood and lymphatic system disorders	3 (0.4%)	1 (0.4%)	8 (1.5%)
Cardiac disorders	2 (0.3%)	3 (1.2%)	1 (0.2%)
Psychiatric disorders	2 (0.3%)	1 (0.4%)	1 (0.2%)
Vascular disorders	1 (0.1%)	3 (1.2%)	0
Eye disorders	1 (0.1%)	0	1 (0.2%)
Ear and labyrinth disorders	1 (0.1%)	2 (0.8%)	1 (0.2%)
Surgical and medical procedures	1 (0.1%)	1 (0.4%)	0
Immune system disorders	1 (0.1%)	0	1 (0.2%)
Product issues	0	0	2 (0.4%)

Source: Summary of Clinical Safety, Table 2.7.4-18 (gadobenate dimeglumine, gadobutrol), Pooled Safety Data from gadopiclenol clinical studies, Table 27 (gadopiclenol)
Note: Results are expressed as the number of patients with at least one AE (%).
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SOC, system organ class

The most common AEs reported after gadopiclenol administration are shown by preferred term in Table 74.

Table 74. Gadopiclenol-Treatment Emergent Adverse Events Occurring in Five or More Patients in the Pooled Safety Set by Preferred Term

	Pooled 0.05 mmol/kg Safety Set (n=708)		Pooled Safety Set (n=1047)	
MedDRA PT	n (%) Patients	n AEs	n (%) Patients	n AEs
Headache	22 (3.1%)	23	41 (3.9%)	46

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	Pooled 0.05 mmol/kg Safety Set (n=708)		Pooled Safety Set (n=1047)	
MedDRA PT	**n (%) Patients**	**n AEs**	**n (%) Patients**	**n AEs**
Injection site pain	12 (1.7%)	12	31 (3.0%)	34
Nausea	10 (1.4%)	10	15 (1.4%)	15
Dizziness	7 (1.0%)	7	10 (1.0%)	10
Injection site bruising	6 (0.8%)	6	7 (0.7%)	7
Incorrect dose administered	6 (0.8%)	6	6 (0.6%)	6
Blood pressure increased	4 (0.6%)	4	8 (0.8%)	8
Diarrhea	3 (0.4%)	3	7 (0.7%)	7
Dermatitis contact	2 (0.3%)	2	13 (1.2%)	17
Injection site hematoma	2 (0.3%)	2	11 (1.1%)	11
Fatigue	2 (0.3%)	2	7 (0.7%)	7
Injection site coldness	2 (0.3%)	2	6 (0.6%)	6
Abdominal pain	2 (0.3%)	2	6 (0.6%)	6
Vomiting	2 (0.3%)	2	5 (0.5%)	5
Leukocyturia	2 (0.3%)	2	5 (0.5%)	5
Catheter site pain	1 (0.1%)	1	5 (0.5%)	5
Injection site erythema	1 (0.1%)	1	5 (0.5%)	5
Injection site edema	1 (0.1%)	1	5 (0.5%)	5
Back pain	0	0	5 (0.5%)	5

Source: Summary of Clinical Safety, Table 2.7.4-14 (Pooled Safety Set), Pooled Safety Data from gadopiclenol clinical studies, Table 27 (Pooled 0.05 mmol/kg Safety Set)
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term

AEs that were reported in at least two patients and were assessed as related to gadopiclenol by the investigators are shown in Table 75. As previously stated, the pooled 0.05 mmol/kg safety set was used as the primary analysis population for the adverse reactions section of the prescribing information.

Table 75. Adverse Events Occurring in Two or More Patients in the Pooled Safety Set (n=1047) Reported as Related to Gadopiclenol

	Pooled 0.05 mmol/kg Safety Set (n=708)		Pooled Safety Set (n=1047)	
MedDRA SOC or PT	**n (%) Patients**	**n AEs**	**n (%) Patients**	**n AEs**
General disorders and administration site conditions	14 (2.0%)	15	42 (4.0%)	49
Injection site pain	5 (0.7%)	5	20 (1.9%)	21
Injection site warmth	3 (0.4%)	3	3 (0.3%)	3
Injection site coldness	2 (0.3%)	2	6 (0.6%)	6
Feeling hot	1 (0.1%)	1	3 (0.3%)	3
Fatigue	0	0	4 (0.4%)	4
Injection site edema	0	0	3 (0.3%)	3

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	Pooled 0.05 mmol/kg Safety Set (n=708)		Pooled Safety Set (n=1047)	
MedDRA SOC or PT	**n (%) Patients**	**n AEs**	**n (%) Patients**	**n AEs**
Nervous system disorders	7 (1.0%)	8	19 (1.8%)	21
Headache	5 (0.7%)	5	14 (1.3%)	15
Dizziness	2 (0.3%)	2	3 (0.3%)	3
Dysgeusia	1 (0.1%)	1	2 (0.2%)	2
Gastrointestinal disorders	5 (0.7%)	6	15 (1.4%)	18
Nausea	3 (0.4%)	3	7 (0.7%)	7
Diarrhea	1 (0.1%)	1	4 (0.4%)	4
Vomiting	1 (0.1%)	1	2 (0.2%)	2
Abdominal pain	0	0	2 (0.2%)	2
Investigations	4 (0.6%)	4	9 (0.9%)	9
Blood creatinine increased	1 (0.1%)	1	3 (0.3%)	3
Electrocardiogram QT prolonged	1 (0.1%)	1	2 (0.2%)	2
Skin and subcutaneous tissue disorders	4 (0.6%)	4	5 (0.5%)	5
Pruritis	1 (0.1%)	1	2 (0.2%)	2
Musculoskeletal and connective tissue disorders	0	0	2 (0.2%)	2
Back pain	0	0	2 (0.2%)	2

Source: Pooled Safety Data from gadopiclenol clinical studies, Tables 26 and 27
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class

Additional AEs reported as related in the pooled 0.05 mmol/kg safety set but not included in Table 75 were body temperature increased, pyrexia, swelling of eyelid, oral paresthesia, maculopapular rash, allergic dermatitis, erythema, swelling, injection site paresthesia, Cystatin C increased, renal failure, and decreased appetite.

Headache, nausea, dizziness, and various injection site reactions are all listed as adverse reactions in the labeling for multiple GBCAs, and the reported incidence of these events is of a similar magnitude. Therefore, these were considered adverse reactions. The AE of electrocardiogram QT prolonged was considered not related to gadopiclenol based on the presence of a more likely cause (anxiety-induced tachycardia), the level of exposure to the drug, and the results of the thorough QT study. We also assessed the events of body temperature increase and decreased appetite as not related to gadopiclenol based on narrative information provided by the Applicant. For the other events, there was insufficient evidence available to exclude relatedness to gadopiclenol, and the investigator assessment was accepted. Swelling (corresponding to a verbatim term of temporary chin swelling) and swelling of eyelid were combined as localized swelling due to their similarity. The event of renal failure was reworded as worsening renal failure based on the narrative summary.

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(b) (4)

We note that in the pooled safety set there were four seizure-related AEs reported as treatment emergent to gadopiclenol in four patients (epilepsy (n=2), partial seizure, and seizure) and that none were considered related to gadopiclenol by the investigator or the Applicant. Further, the association of GBCAs with seizure is most closely linked with intrathecal administration, which is not a labeled route for gadopiclenol. Among the currently marketed GBCAs, none carry a warning specific to seizures, and only gadodiamide (Omniscan) has a warning that mentions seizure risk, under the heading "Not for Intrathecal Use." (b) (4)

As a class, GBCAs generally cause irritation of the perivascular soft tissues if extravasated, and gadopiclenol does not appear to be an exception. Signs and symptoms related to the injection site were specifically evaluated in all clinical studies and adverse events at the injection site are included in labeling. We concur with the Applicant's warning regarding extravasation and injection site reactions in Section 5 of the prescribing information.

Another class-wide concern with GBCAs is hypersensitivity. No gadopiclenol-treatment emergent AEs were explicitly reported as hypersensitivity. As expected, there were multiple AEs that were nonspecific but could have been related to hypersensitivity. To address this, the events of all patients in the pooled safety set who had at least one AE contained within the standardized MedDRA queries of anaphylactic reaction, angioedema, drug reaction with eosinophilia and systemic symptoms syndrome, or hypersensitivity were reviewed. We identified five patients in this analysis who might have been more likely to have had hypersensitivity reactions based on clustering of AEs or on investigator assessment:

- A 23-year-old reported dyspnea and flushing of the face and neck two minutes after injection of 0.1 mmol/kg gadopiclenol. These events were assessed by the investigator as moderate in severity and possibly related to the drug.
- A 48-year-old was recorded as having allergic hyperemia on the right side of the neck 41 minutes after administration of 0.05 mmol/kg gadopiclenol. It was considered mild in intensity and related to the drug.
- A 54-year-old had face itching and temporary chin swelling, both beginning 6 hours after injection of 0.05 mmol/kg gadopiclenol and of mild intensity. These events were considered drug-related by the investigator.
- A 60-year-old was recorded as having mild, related allergic skin reaction of the upper limbs and head beginning 20 minutes after administration of 0.05 mmol/kg gadopiclenol.
- A 9-year-old had higher level of eosinophils approximately 23 hours after administration of 0.05 mmol/kg gadopiclenol, considered mild in intensity and not related to the drug. Approximately 5 days after injection the patient developed a diffuse maculopapular rash of moderate intensity, assessed as related to gadopiclenol.

The number, type, and severity of these events among these patients or among the pooled safety set as a whole do not appear to be greater than reported for the drug class. The

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Applicant has included a contraindication for patients with a history of hypersensitivity to the product and a warning regarding hypersensitivity reactions. These risk mitigation strategies are considered reasonable.

Laboratory Findings

Hematology, chemistry, and urinalysis data were analyzed by descriptive statistics, shift tables, and examining results in patients considered to have clinically significant abnormalities. In most cases, the determination of whether a laboratory abnormality or change was clinically significant was left to the investigators, though as noted in prior sections, GDX-44-005 considered an increase in serum creatinine by more than 25% or 0.5 mg/dL compared to the value measured at inclusion to be an AESI, and GDX-44-004 included a patient stopping rule related to renal function.

A total of 33 laboratory findings were reported as clinically significant gadopiclenol-treatment emergent AEs in the pooled safety set. Of these AEs, 16 were from chemistry, 3 from hematology, and 14 from urinalysis results. Events that were reported more than once were blood creatinine increased (n=4), hypertriglyceridemia (n=2), leukocyturia (n=5), proteinuria (n=3), and bilirubinuria (n=2). A total of six of these AEs were considered related to gadopiclenol, including blood creatinine increased (n=3), Cystatin C increased, renal failure, and hyperkalemia (n=1 each).

The average change from baseline was close to 0 for all analyzed hematology and chemistry parameters. There were slight shift imbalances towards higher creatinine and Cystatin C after administration of gadopiclenol (Table 76), but this was most notable when comparing the 0 to +15% and -15% to 0 ranges, i.e., smaller changes in the measured parameter, and are of uncertain clinical significance.

Table 76. Relative Change in Creatinine and Cystatin C in the Pooled Safety Set (n=1047)

Relative Change From Baseline	Creatinine n Patients (%)	Cystatin C n Patients (%)
≤-50%	0	0
>-50% to ≤-25%	9 (0.8%)	8 (0.7%)
>-25% to ≤-15%	33 (3.0%)	17 (1.6%)
>-15 to <0%	446 (40.7%)	317 (28.9%)
≥0% to <15%	513 (46.8%)	360 (32.9%)
≥15% to <25%	58 (5.3%)	33 (3.0%)
≥25% to <50%	25 (2.3%)	7 (0.6%)
≥50%	3 (0.3%)	4 (0.4%)
Not determined or missing	15 (1.4%)	349 (31.9%)

Source: Pooled Safety Data from gadopiclenol clinical studies, Table 74

The potential risk of renal impairment is adequately addressed in the prescribing information through inclusion of laboratory finding-related AEs in Section 6 and through the class wide acute kidney injury warning in Section 5.

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JMP Clinical version 8.0 was used to screen for potential Hy's Law cases. No patients with findings suggestive of drug induced liver injury were identified.

Vital Signs

Vital signs were analyzed by descriptive statistics and examining results in patients considered to have clinically significant abnormalities. The decision of whether a vital sign or change in vital sign was clinically significant was made by the investigator.

There were 12 vital sign abnormalities reported as gadopiclenol-treatment emergent AEs in the pooled safety set, 10 from increases in blood pressure, 1 from increase in heart rate, and 1 from increase in temperature. One event of blood pressure increased was considered related by the investigator (142/95 mmHg at 1 hour from 108/79 mmHg at baseline). The mean changes from baseline in systolic blood pressure, diastolic blood pressure, and heart rate were close to zero and similar to the mean changes observed in patients after administration of gadobutrol or gadobenate dimeglumine.

No significant safety signal is identified from the available vital sign data.

Electrocardiograms

Other than in GDX-44-006, ECG findings were limited to investigator assessed clinically significant abnormalities. There were six gadopiclenol-treatment emergent AEs in five patients reported based on ECG data. These included electrocardiogram QT prolonged (two events in two patients), long QT syndrome (two events in one patient), electrocardiogram QT interval abnormal, and sinus arrhythmia. The events of electrocardiogram QT prolonged and electrocardiogram QT interval abnormal were considered by the investigator to be related, while long QT syndrome and sinus arrhythmia were not.

Considering these results in addition to the results of the thorough QT study described below, no significant safety signal is identified from the available ECG data.

QT

The Interdisciplinary Review Team for Cardiac Safety Studies was consulted to evaluate the results of the thorough QT study GDX-44-006. Their assessment was summarized as no significant QTc prolongation effect of gadopiclenol detected in this study.

Immunogenicity

Clinical immunogenicity studies were not conducted. Based on the findings of the animal immediate hypersensitivity study (see Section 5.5.7) and the AE profile observed in clinical trials, a clinical immunogenicity study is not needed for this small molecule drug.

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8.2.5. Analysis of Submission-Specific Safety Issues

Gadolinium Retention

Free gadolinium is considered toxic at doses necessary for MRI. Therefore GBCAs, including gadopiclenol, are complexes of a chelator and the gadolinium ion. In addition to preventing toxicity from free gadolinium, the chelator moiety largely determines the biodistribution and elimination of the complex.

In recent years it has become clear that there is potential for gadolinium to be retained for prolonged periods in multiple human tissues after administration of a GBCA. In patients with severely impaired renal function, this can result in NSF, however in patients with normal or mildly impaired renal function the clinical consequences of gadolinium retention have not been established. The retention of gadolinium is thought to be greater for GBCAs with less stable interaction between the gadolinium ion and the chelator. For the GBCAs in current use, a distinction is usually made between linear chelators and macrocyclic chelators, with macrocyclic chelators considered more stable. Gadopiclenol has a macrocyclic chelating moiety.

Studies of gadolinium retention in humans can be challenging to conduct due to the relatively low levels of gadolinium being investigated and the need for tissue sampling. Accordingly, no clinical data on tissue gadolinium retention in clinically relevant organs such as brain or bone after administration of gadopiclenol are presented by the Applicant. The presence of gadolinium in the blood or urine after multiple drug elimination half-lives has been used as a marker of gadolinium retention, and such data were collected in the renal impairment and pediatric clinical studies. In GDX-44-005, 40 patients with renal function varying from normal to end stage renal disease were all reported to have plasma levels of gadopiclenol below the limit of quantification (5 µg/mL) at 1, 3, and 6 months after administration of a single 0.1 mmol/kg dose of gadopiclenol. In the 32 patients who were not on dialysis, the spot urine gadopiclenol levels were also below the limit of quantification at these time points. In GDX-44-007, urine gadopiclenol levels were quantifiable but <10 µg/mL in 10 of 80 children at 8 days post-injection. The other 70 patients had levels below the limit of quantification. By 3 months, all but one tested patient had urine gadopiclenol below the limit of quantification. The patient with measurable urine gadopiclenol at 3 months had been undetectable at 8 days, raising the possibility of a measurement error.

As discussed in Section 5.5.7, the tissue retention of gadolinium was examined in a non-GLP rat study after administration of gadopiclenol, gadobutrol (macrocyclic), or gadodiamide (linear) at equimolar doses. Compared to gadodiamide, gadopiclenol had lower retention in all tested organs, including brain, bone, kidney, liver, and muscle. In brain, gadopiclenol and gadobutrol had similar levels of gadolinium retention, while in the other tested organs, gadolinium retention was 2-fold to 3-fold higher for gadopiclenol than gadobutrol. It is not possible to extrapolate the results of the rat study to humans. Beyond the obvious issue of species difference, the recommended clinical dose of gadopiclenol is half that of the comparator agents on a molar basis and the overall exposure to the drugs was much higher in the animal study than is expected clinically.

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Based on these results, the clinical team makes the following assessments and recommendations:

- There are insufficient data to ascertain whether gadopiclenol will result in more, less, or the same amount of gadolinium retention as other macrocyclic GBCAs when administered to patients at the intended clinical doses. This should be conveyed in the prescribing information.
- We expect gadolinium retention after gadopiclenol administration to be lower than for linear GBCAs.
- The gadopiclenol prescribing information should contain a boxed warning for NSF and a warning gadolinium retention, as for other drugs in the GBCA class.
- It is reasonable to group gadopiclenol with other macrocyclic GBCAs when discussing NSF and gadolinium retention in labeling. Gadopiclenol should use NSF warning language similar to that used for currently marketed macrocyclic GBCAs.
- No additional human data for tissue gadolinium retention are needed to make a determination of whether or not this NDA should be approved.
- Because of the uncertainty regarding the clinical effects of retained gadolinium, particularly in the CNS, the Applicant should be required to obtain post-marketing data on neurobehavioral outcomes in patients who receive repeated doses of gadopiclenol, as for other drugs in the GBCA class.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

COA data were not collected and were not needed.

8.2.7. Safety Analyses by Demographic Subgroups

As shown in Table 77, the fractions of pediatric patients and of older adult patients who experienced at least one AE were similar to or mildly lower than the fractions of those age groups enrolled in the clinical studies. Subgroup analyses of AE incidence by race were not performed due to the relatively small numbers of non-white patients.

Table 77. Adverse Events by Patient Age in the Pooled 0.05 mmol/kg Safety Set (n=708)

Age Group	Patients n (% of total)	Patients with AE n (% of total)	AE n (% of total)
2-17	80 (11%)	14 (12%)	31 (17%)
18-64	424 (60%)	82 (69%)	121 (64%)
≥65	204 (29%)	23 (19%)	36 (19%)
≥75	55 (8%)	4 (3%)	4 (2%)

Source: Pooled Safety Data from gadopiclenol clinical studies, Table 35
Abbreviations: AE, adverse event

There was a mildly higher incidence of AEs in females than would be expected based on enrollment (Table 78). Notable differences between sexes at the system organ class level

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included general disorders and administration site conditions (7.1% of females versus 3.8% of males) and nervous system disorders (6.1% of females versus 2.9% of males, largely driven by increased headache in females). The clinical relevance of these observations is doubtful.

Table 78. Adverse Events by Patient Sex in the Pooled 0.05 mmol/kg Safety Set (n=708)

Sex	Patients n (% of total)	Patients With AE n (% of total)	AE n (% of total)
Female	393 (56%)	75 (63%)	130 (69%)
Male	315 (44%)	44 (37%)	58 (31%)

Source: Pooled Safety Data from gadopiclenol clinical studies, Table 41
Abbreviations: AE, adverse event

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No studies of carcinogenicity were performed, and none were needed.

Human Reproduction and Pregnancy

One patient was exposed to gadopiclenol shortly before she became aware she was pregnant. This pregnancy was terminated for reasons unrelated to study participation. No clinical data are available to determine the risks from administration of gadopiclenol during pregnancy.

Pediatrics and Assessment of Effects on Growth

The gadopiclenol safety database included 80 pediatric patients aged 2 years to 17 years. One adverse reaction, maculopapular rash, occurred in one pediatric patient. No evidence of increased rate or severity of adverse events in children was identified.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The highest dose of gadopiclenol administered in the clinical development program was 0.307 mmol/kg, approximately 6-fold the recommended dose. No abuse potential is expected for gadopiclenol.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

At the time of NDA submission, gadopiclenol had not been marketed in any country. As discussed above, post-market experience with related drugs has influenced our recommendations for safety labeling.

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Expectations on Safety in the Postmarket Setting

The safety profile of gadopiclenol appears to be similar to other GBCAs. Notable safety issues are likely to include hypersensitivity reactions, the possibility of NSF, and gadolinium retention, all of which are addressed in the prescribing information as for other members of the GBCA class.

8.2.10. Integrated Assessment of Safety

The key safety issues for gadopiclenol are the potential for hypersensitivity reactions, NSF, and gadolinium retention. These issues are shared among the GBCAs, and gadopiclenol does not appear to represent a greater risk than related drugs. The most common adverse reactions were headache, nausea, and injection site reactions. The overall safety profile is acceptable.

8.3. Statistical Issues

The NDA submission includes data from two phase 3 studies in adult subjects intended to provide confirmatory evidence of effectiveness for gadopiclenol for intravenous use. The studies are designed to show that contrasted MRI with gadopiclenol improves visualization of lesions. Study GDX-44-010 investigated the effect of gadopiclenol in the CNS (brain, spine, and surrounding tissues), and Study GDX-44-011 investigated the effect of gadopiclenol in the body (head and neck, thorax including breast, abdomen including liver and kidneys, pelvis including prostate, and the musculoskeletal system).

8.3.1. Study GDX-44-010 [CNS]

GDX-44-010 was a prospective phase 3, multi-center, multi-reader, randomized, double-blind, controlled, cross-over clinical study in adult subjects with known or highly suspected CNS lesions with focal areas of disrupted blood brain barrier (e.g., primary and secondary tumors) based on results of a previous imaging procedure.

The selected dose for gadopiclenol was 0.05 mmol/kg. The dose for the active comparator gadobutrol was 0.1 mmol/kg, which is the approved dose for MRI of the CNS. After screening, subjects were randomized in a 1:1 ratio to receive either sequence 1 (gadopiclenol 0.05 mmol/kg followed by gadobutrol 0.1 mmol/kg) or sequence 2 (gadobutrol 0.1 mmol/kg followed by gadopiclenol 0.05 mmol/kg). The investigators and the subjects remained blinded to the IMP allocation. There was a wash-out period of minimum 2 days and maximum 14 days between the administrations of the two drugs. Two MRI examinations were performed for each subject, one with each drug. All images were sent to a core laboratory and blinded centralized image evaluations were performed by three independent blinded radiologists. To allow for lesion matching between imaging modalities (pre-contrast and paired pre- and post-contrast) and between the two MRI examinations with gadopiclenol and gadobutrol, an additional independent radiologist performed lesion tracking.

For the FDA, the primary objective was to demonstrate the superiority of paired pre- and post-gadopiclenol MRI at 0.05 mmol/kg compared to pre-gadopiclenol MRI alone in terms of three

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lesion visualization co-primary efficacy endpoints (border delineation, internal morphology, and degree of contrast enhancement) using each subject as their own control. The three lesion visualization co-primary efficacy endpoints were assessed by three independent off-site blinded readers on paired (pre- and post-contrast) images and pre-contrast images using the 4-point scales described in Section 8.1.1. The evaluation was performed for up to the three most representative lesions (defined according to lesion size and contrast enhancement). The three co-primary efficacy endpoints were assessed using the means of the scores for each patient and each efficacy endpoint, which were calculated as follows:

> Mean of scores = score of lesion 1 + score of lesion 2 (if any) + score of lesion 3 (if any) divided by the number of lesions (up to 3 most representative lesions).

For each reader, only matching lesions between paired images and pre-contrast images were considered for evaluation. If the MR images were not assessable or if no matching lesion between paired images and pre-contrast images was identified, the subject was not included in the primary analysis. The differences between “paired” - “pre” images were analyzed using paired t-tests on matching lesions for each of the three co-primary efficacy endpoints. To demonstrate gadopiclenol effectiveness, two out of three blinded readers needed to show a statistically significant (one-sided $p \geq 0.025$) positive difference in mean scores for the three co-primary efficacy endpoints simultaneously.

Subject-Level Analyses

A total of 256 subjects were randomized. Among them, 239 subjects had both pre-contrast and paired images with gadopiclenol assessable for at least one matching lesion, at least one off-site reader, and at least one valid primary efficacy endpoint (FAS 1). The number of subjects for primary efficacy analysis varied between 202 and 229 among the three blinded readers. The differences in mean of scores for border delineation, internal morphology, and degree of contrast enhancement were significantly different from zero with a type 1 error set at a one-sided 0.025 level in favor of paired images compared to pre-contrast images for all three readers ($p<0.0001$ in all cases). Therefore, the null hypothesis was rejected and the primary objective was achieved. Table 79 shows the primary efficacy results, which were confirmed by the FDA statistical reviewer.

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Table 79. [CNS, Subject-Level] Co-Primary Efficacy Endpoints: Off-Site Reading – MRI With Gadopiclenol – Paired vs. Pre – Mixed Model - FAS 1

FAS 1 (N=239)	n	LS Mean (SE) Paired	Pre	Difference	95% CI Difference	p-value
Border delineation						
Reader 1	227	3.90 (0.02)	2.08 (0.02)	1.82 (0.03)	(1.76, 1.88)	<.0001
Reader 2	229	3.64 (0.04)	1.74 (0.04)	1.90 (0.05)	(1.81, 2.00)	<.0001
Reader 3	202	3.97 (0.03)	2.61 (0.03)	1.36 (0.04)	(1.29, 1.44)	<.0001
Internal morphology						
Reader 1	227	3.92 (0.03)	1.66 (0.03)	2.26 (0.03)	(2.20, 2.33)	<.0001
Reader 2	229	3.65 (0.03)	1.88 (0.03)	1.77 (0.04)	(1.69, 1.85)	<.0001
Reader 3	202	3.97 (0.04)	1.96 (0.05)	1.96 (0.05)	(1.85, 2.06)	<.0001
Degree of contrast enhancement						
Reader 1	227	3.77 (0.03)	1.00 (0.03)	2.77 (0.04)	(2.69, 2.85)	<.0001
Reader 2	229	3.58 (0.03)	1.00 (0.03)	2.58 (0.05)	(2.49, 2.67)	<.0001
Reader 3	202	3.90 (0.02)	1.00 (0.02)	2.90 (0.03)	(2.84, 2.95)	<.0001

Source: Table 11-1 on page 83/150 of GDX-44-010 Study Report: report-body-4-21-00161.pdf, confirmed by the FDA statistical reviewer analysis.
Notes: Only matching lesions are considered. The models include lesion visualization factor as dependent variable, MRI modality (pre-contrast and paired MRI) as fixed factors, subject as random factor.
Abbreviations: CI, Confidence Interval; CNS, central nervous system; FAS, full analysis set; LS, Least Squares; MRI, magnetic resonance imaging; SE, Standard Error

The primary analyses of off-site blinded reading (MRI with gadopiclenol, paired vs. pre) using mixed models were repeated including non-matching lesions using the extended FAS 1 (N=246). For readers 1, 2, and 3, 245, 246, and 244 subjects were analyzed, respectively, i.e., an additional 18, 17, and 42 subjects were included in the analysis. Results were confirmed by the FDA statistical reviewer. These results, presented in Table 80 below, are similar to those obtained for the primary analyses.

Table 80. [CNS, Subject-Level, Non-Matching Lesion Included] Lesion Visualization Efficacy Endpoints - Off-Site Readings – MRI With Gadopiclenol – Paired vs. Pre – Mixed Model Including Matching and Non-Matching Lesions – Extended FAS 1

Extended FAS 1 (N=246)	n	LS Mean (SE) Paired	Pre	Difference	95% CI Difference	p-value
Border delineation						
Reader 1	245	3.90 (0.02)	2.08 (0.02)	1.82 (0.03)	(1.75, 1.88)	<.0001
Reader 2	246	3.64 (0.04)	1.72 (0.04)	1.91 (0.05)	(1.82, 2.01)	<.0001
Reader 3	244	3.97 (0.03)	2.53 (0.03)	1.44 (0.04)	(1.37, 1.51)	<.0001
Internal morphology						
Reader 1	245	3.91 (0.03)	1.64 (0.03)	2.27 (0.03)	(2.21, 2.33)	<.0001
Reader 2	246	3.64 (0.03)	1.87 (0.03)	1.77 (0.04)	(1.69, 1.84)	<.0001
Reader 3	244	3.97 (0.04)	1.93 (0.03)	2.04 (0.05)	(1.94, 2.13)	<.0001

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Extended FAS 1 (N=246)	n	LS Mean (SE) Paired	Pre	Difference	95% CI Difference	p-value
Degree of contrast enhancement						
Reader 1	245	3.77 (0.03)	1.00 (0.03)	2.77 (0.04)	(2.69, 2.84)	<.0001
Reader 2	246	3.57 (0.03)	1.00 (0.03)	2.57 (0.04)	(2.48, 2.65)	<.0001
Reader 3	244	3.89 (0.02)	1.00 (0.02)	2.89 (0.02)	(2.85, 2.94)	<.0001

Source: Table 14.2.1.20 on page 342/617 of 'csr-section-14-4-21-00162.pdf', confirmed by the FDA statistical reviewer.
Notes: Matching and not matching lesions are considered. The models include lesion visualization factor as dependent variable, MRI modality (pre-contrast and paired MRI) as fixed factors, subject as random factor.
Abbreviations: CI, Confidence Interval; CNS, central nervous system; FAS, full analysis set; LS, Least Squares; MRI, magnetic resonance imaging; SE, Standard Error

In response to an FDA information request (IR) dated April 21, 2022, requesting sensitivity analyses (including imputations) for the primary efficacy endpoints to evaluate the potential impact or bias due to excluding subjects with non-matching lesions between paired and pre-contrast images, the Applicant performed four additional sensitivity analyses based on the following assignments:

- Assigning the subject mean of scores of the pre-contrast read to the paired read when the paired read score is missing and the reverse so that there is no difference between paired read and pre-contrast read.
- Assigning the global mean of scores (over pre-contrast and paired values) when either paired or pre-contrast lesions are not seen.
- Assigning the subject mean of scores (over pre-contrast and paired values) when either paired or pre-contrast lesions are not seen.
- Assigning the worst score (1) to a lesion not seen in either the paired or pre-contrast reading when seen with the other.

The results of the four additional sensitivity analyses were all statistically significant and were similar to those obtained by the primary analysis. As an illustration, Table 81 below presents the results using the worst score imputation. The corresponding statistical analysis SAS programs for these additional sensitivity analyses were verified by the FDA statistical reviewer.

Table 81. [CNS, Subject-Level Sensitivity Analysis] Lesion Visualization Efficacy Endpoints - Off-Site Readings – MRI With Gadopiclenol – Paired vs Pre – Mixed Model Including Matching and Non-Matching Lesions – With Imputation (#4: Worst Score Assignment) for Non-Matching Lesion - Extended FAS 1

Extended FAS 1 (N=246)	n	LS Mean (SE) Paired	Pre	Difference	95% CI Difference	p-value
Border delineation						
Reader 1	245	3.69 (0.03)	1.95 (0.03)	1.74 (0.04)	(1.66, 1.82)	<.0001
Reader 2	246	3.39 (0.04)	1.64 (0.04)	1.75 (0.05)	(1.65, 1.85)	<.0001
Reader 3	244	3.56 (0.05)	2.31 (0.05)	1.25 (0.06)	(1.14, 1.36)	<.0001

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Extended FAS 1 (N=246)	n	LS Mean (SE) Paired	Pre	Difference	95% CI Difference	p-value
Internal morphology						
Reader 1	245	3.70 (0.03)	1.58 (0.03)	2.12 (0.04)	(2.04, 2.20)	<.0001
Reader 2	246	3.38 (0.04)	1.75 (0.04)	1.64 (0.05)	(1.54, 1.73)	<.0001
Reader 3	244	3.56 (0.05)	1.81 (0.05)	1.74 (0.06)	(1.63, 1.86)	<.0001
Degree of contrast enhancement						
Reader 1	245	3.57 (0.03)	1.00 (0.03)	2.57 (0.05)	(2.47, 2.67)	<.0001
Reader 2	246	3.32 (0.04)	1.00 (0.04)	2.32 (0.05)	(2.22, 2.42)	<.0001
Reader 3	244	3.49 (0.04)	1.00 (0.04)	2.49 (0.05)	(2.39, 2.59)	<.0001

Source: Table 4 on page 7/15 of 'ir-response-clinical-4_22_00184.pdf', confirmed by the FDA statistical reviewer.
Notes: Non-matching lesions are imputed (#4) in such a way that they were equalized to the worst case (i.e., 1). The models include lesion visualization factor as dependent variable, MRI modality (pre-contrast and paired MRI) as fixed factors, subject as random factor.
Abbreviations: CI, Confidence Interval; CNS, central nervous system; FAS, full analysis set; LS, Least Squares; MRI, magnetic resonance imaging; SE, Standard Error

In response to the FDA IR dated June 17, 2022, the Applicant performed additional analyses regarding the percentage of subjects whose number of lesions detected on paired images with gadopiclenol exceeded that of pre-contrast images, and vice versa, by reader and across reader.

Table 82 below presents the results of these analyses. The percentage of subjects with more lesions detected with paired images was higher than that of subjects with more lesions detected with pre-contrast images for each reader and across readers.

Table 82. [CNS, Subject-Level, Comparison of Number/Percentage of Subjects With More Lesions on Paired Images Versus Pre-Contrast Images, by Reader and Across Reader] Comparison of Number of Lesions Detected With Pre and Paired Images- CNS - Extended FAS 1

Parameter	Considering the Number of Lesions Detected by Reader: Reader 1	Reader 2	Reader 3	Considering the Mean Number of Lesions Detected Across Readers
N subjects	246	246	246	246
n (%) subjects with more lesions detected with pre-contrast images	12 (4.88%)	23 (9.35%)	30 (12.20%)	43 (17.48%)
n (%) subjects with more lesions detected with paired images	51 (20.73%)	56 (22.76%)	52 (21.14%)	80 (32.52%)
n (%) subjects with the same number of lesions detected with pre and paired images	183 (74.39%)	167 (67.89%)	161 (65.45%)	123 (50.00%)

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Parameter	Considering the Number of Lesions Detected by Reader			Considering the Mean Number of Lesions Detected Across Readers
	Reader 1	Reader 2	Reader 3	
n (%) subjects with missing data	0	0	3 (1.22%)	*

Source: Table 4 on page 7/11 of 4_22_00242-response-to-fda-ir-statistics-17jun2022.pdf.
Notes: Missing indicates at least one evaluation (pre-contrast or paired) is either not diagnostic or not assessable.
Percentage is calculated by dividing the frequency of each cell by the total mean number of lesions across readers, which is defined as (n lesions seen by reader 1 + n lesions seen by reader 2 + n lesions seen by reader 3)/3.
*In case of missing data for one reader, the mean is calculated on the result from the other two readers.
Abbreviations: CNS, central nervous system; FAS, full analysis set; LS, Least Squares; SE, Standard Error

The Applicant pointed out that in routine clinical practice, some suspected lesions can be seen on pre-contrast images but not confirmed with paired pre- and post-contrast) images, depending on the pathology. Furthermore, the percentage of subjects with more lesions detected on pre-contrast images could also be explained by the rules given in the reading guidelines. The readers were encouraged to identify any suspected lesions/abnormalities on pre-contrast images, in order to not miss any potential true lesion. Reference is also made to the clinical review in Section 8.1.2.

Lesion-Level Analyses

The lesion visualization efficacy endpoints were analyzed at lesion-level using a mixed model in extended FAS 1 (N=246), and the results were similar to those obtained at subject-level as most subjects had only one lesion. Table 83 below shows the results at lesion-level.

Table 83. [CNS, Lesion-Level] Lesion Visualization Efficacy Endpoints at Lesion Level - Off-Site Readings – MRI With Gadopiclenol – Paired vs Pre – Mixed Model – Extended FAS 1

Extended FAS 1 (N=246)	n	LS Mean (SE)			95% CI
		Paired	Pre	Difference	Difference
Border delineation					
Reader 1	424	3.92 (0.02)	2.06 (0.02)	1.86 (0.03)	(1.81, 1.91)
Reader 2	453	3.60 (0.03)	1.69 (0.03)	1.92 (0.04)	(1.84, 2.00)
Reader 3	413	3.96 (0.02)	2.54 (0.02)	1.42 (0.03)	(1.36, 1.49)
Internal morphology					
Reader 1	424	3.93 (0.02)	1.64 (0.02)	2.28 (0.03)	(2.23, 2.34)
Reader 2	453	3.61 (0.03)	1.85 (0.03)	1.77 (0.03)	(1.70, 1.83)
Reader 3	413	3.96 (0.03)	1.92 (0.03)	2.04 (0.04)	(1.96, 2.12)
Degree of contrast enhancement					
Reader 1	424	3.77 (0.02)	1.00 (0.02)	2.77 (0.03)	(2.71, 2.83)
Reader 2	453	3.55 (0.03)	1.00 (0.03)	2.55 (0.04)	(2.47, 2.62)
Reader 3	413	3.89 (0.02)	1.00 (0.02)	2.89 (0.02)	(2.84, 2.93)

Source: Table 14.2.2.10 on page 365/617 of 'csr-section-14-4-21-00162.pdf', confirmed by the FDA statistical

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reviewer.
Notes: Matching and non-matching lesions are considered. The models include lesion visualization factor as dependent variable, MRI modality (pre-contrast and paired MRI) and contrast sequence as fixed factors, lesion as random factor.
Abbreviations: CI, Confidence Interval; CNS, central nervous system; FAS, full analysis set; LS, Least Squares; n, number of lesions; SE, Standard Error

Analyses like those presented in Table 83 but excluding contrast sequence as a fixed factor from the mixed model were also confirmed by the FDA statistical reviewer. The re-analyzed models include lesion visualization factor as a dependent variable, MRI modality (pre-contrast and paired MRI) as fixed factors, and subject as a random factor. The re-analyzed results were similar to those in Table 83.

In response to the FDA IR dated May 3, 2022, the Applicant performed additional exploratory lesion-level analyses which took into consideration lesion correlation within subject and provided the SAS program codes. As at subject-level, several analyses were performed:

- Non-matching lesions are not imputed. Missing data are handled by the SAS “mixed” procedure.
- Non-matching lesions are imputed (method #1) in such a way they are equal to the available assessment (no difference between paired read and pre-contrast read).
- Non-matching lesions are imputed (method #2) in such a way they are equal to the global average score of the available assessments for the designated parameter and reader.
- Non-matching lesions are imputed (method #3) in such a way they are equal to the subject average score of the available assessments for the designated parameter and reader.
- Non-matching lesions are imputed (method #4) in such a way they are equal to the worst case (i.e., assigned a score of 1).

The results of the requested exploratory lesion-level analyses taking into consideration the correlation within subject, with and without imputation, were all statistically significant and similar to those obtained by the lesion-level analysis (Table 83) that does not take into consideration the correlation within subject (source: Tables 1 - 5 on pages 6/15 - 10/15 of statistics-additional-ir-post-mid-cycle-review-9-may22.pdf). As an illustration, Table 84 below presents the results of lesion-level analyses taking into consideration lesion correlation within subject without imputation for non-matching lesions.

Table 84. [CNS, Lesion Level Analysis, Taking Into Consideration Correlation Within Subject] Lesion Visualization Efficacy Endpoints at Lesion Level - Off-Site Readings – MRI With

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Gadopiclenol – Paired vs Pre – Mixed Model – Without Imputation for Non-Matching Lesions - Extended FAS 1

Extended FAS 1 (N=246)	n	LS Mean (SE) Paired	Pre	Difference	95% CI Difference
Border delineation					
Reader 1	424	3.92 (0.02)	2.06 (0.02)	1.86 (0.03)	(1.81, 1.91)
Reader 2	453	3.63 (0.04)	1.71 (0.04)	1.92 (0.04)	(1.84, 2.00)
Reader 3	413	3.97 (0.02)	2.54 (0.02)	1.42 (0.03)	(1.37, 1.49)
Internal morphology					
Reader 1	424	3.92 (0.02)	1.64 (0.02)	2.28 (0.03)	(2.24, 2.33)
Reader 2	453	3.63 (0.03)	1.86 (0.03)	1.77 (0.03)	(1.71, 1.83)
Reader 3	413	3.97 (0.03)	1.92 (0.03)	2.04 (0.04)	(1.97, 2.12)
Degree of contrast enhancement					
Reader 1	424	3.77 (0.02)	1.00 (0.02)	2.77 (0.03)	(2.71, 2.82)
Reader 2	453	3.55 (0.03)	1.00 (0.03)	2.55 (0.03)	(2.48, 2.62)
Reader 3	413	3.89 (0.02)	1.00 (0.02)	2.89 (0.02)	(2.84, 2.93)

Source: Table 1 on page 6/15 of 'statistics-additional-ir-post-mid-cycle-review-9-may22.pdf', confirmed by the FDA statistical reviewer.
Notes: Matching and non-matching lesions are considered. The models include lesion visualization factor as dependent variable, MRI modality (pre-contrast and paired MRI) and center as fixed factors, lesion and subject as random factor.
Abbreviations: CI, Confidence Interval; CNS, central nervous system; FAS, full analysis set; LS, Least Squares; MRI, magnetic resonance imaging; n, number of lesions; SE, Standard Error

8.3.2. Study GDX-44-011 [Outside CNS]

Study GDX-44-011 was a prospective phase 3, multi-center, multi-reader, randomized, double-blind, controlled, cross-over clinical study in adult subjects with known or highly suspected enhancing abnormalities based on a previous imaging procedure in at least one anatomic region among the head and neck, thorax (including breast), abdomen (including liver, pancreas, and kidney), pelvis (including uterus, ovary, and prostate) and musculoskeletal system (including extremities).

The study design, blinded image evaluations, primary objective, and primary efficacy analyses were similar to Study GDX-44-010 except that the primary image evaluations were performed by nine independent blinded radiologists. This was because the imaged regions were very broad and specific expert readers were preferred by the Applicant. Therefore, three readers assessed images of the head and neck, three other readers assessed images of the musculoskeletal (MSK) system, and three other readers assessed images of the thorax, abdomen, and pelvis (body). As statistical analyses were performed on the whole set of subjects, readers from each expertise domain were combined into three meta-readers (one H&N reader + one body reader + one MSK reader per meta-reader). Thus, each "reader" presented in the clinical study report represented a combination of three actual readers which were put together based on numbering allocated randomly at the beginning of the trial.

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Sensitivity analyses of the co-primary efficacy analyses were performed by grouping readers from each expertise domain to yield a similar number of subjects with matching lesions for each meta-reader. That is, for the analyses pre versus paired in the gadopiclenol arm on one hand and for the analyses gadopiclenol versus gadobutrol on paired images on the other hand, readers were built by selecting the combination of readers from each expertise domain for which the differences of the sum of each reader compared with the sum of the average across readers was minimal, see Table 85.

In response to the FDA IR dated March 11, 2022, the Applicant confirmed that there are 36 possible combinations of readers from each of the three expertise domains to create three meta-readers. Per the FDA IR, the Applicant performed three additional sensitivity analyses using different numbering allocations, where the number allocation was selected at random from the 34 possible combinations that had not been used for the primary analysis or the pre-defined sensitivity analysis. Table 85 presents the combinations used for the primary analysis, the pre-specified sensitivity analysis, and the three additional post hoc sensitivity analyses.

Table 85. Combinations of Readers for the Primary Analysis and the Sensitivity Analyses

	Reader 1			Reader 2			Reader 3		
Combination	H&N Reader	Body Reader	MSK Reader	H&N Reader	Body Reader	MSK Reader	H&N Reader	Body Reader	MSK Reader
Primary	1	1	1	2	2	2	3	3	3
Sensitivity	1	2	3	2	1	2	3	3	1
Post hoc sensitivity 1	1	1	1	2	3	2	3	2	3
Post hoc sensitivity 2	1	2	2	2	1	3	3	3	1
Post hoc sensitivity 3	1	1	3	2	3	1	3	2	2

Source: Table 1 on page 4/7 of statistical-request-response-4-22-00154.pdf
Abbreviations: H&N, head and neck; MSK, musculoskeletal

Subject-Level Analyses

A total of 304 patients were randomized. Among them, 278 subjects had both pre-contrast and paired images with gadopiclenol assessable for at least one matching lesion, at least one off-site reader, and at least one valid primary efficacy endpoint (FAS 1). The number of subjects included in the primary efficacy analysis varied between 230 and 262 among the three blinded meta-readers. The differences in mean of scores for border delineation, internal morphology, and degree of contrast enhancement were significantly different from zero with a type 1 error set at a one-sided 0.025 in favor of paired images compared to pre-contrast images for all three meta-readers (p-value<0.0001 in all cases). Therefore, the null hypothesis was rejected and the primary objective was achieved. Table 86 shows the primary efficacy results, which were confirmed by the FDA statistical reviewer.

Reference ID: 5048631

Table 86. [Outside CNS, Subject-Level] Co-Primary Efficacy Endpoints: Off-Site Reading – MRI With Gadopiclenol – Paired vs Pre – Mixed Model – FAS 1

FAS 1 (N=278)	n	LS Mean (SE) Paired	Pre	Difference	95% CI Difference	p-value
Border delineation						
Reader 1	251	3.79 (0.03)	2.26 (0.03)	1.53 (0.04)	(1.46, 1.60)	<.0001
Reader 2	230	3.48 (0.06)	3.01 (0.06)	0.47 (0.06)	(0.36, 0.58)	<.0001
Reader 3	262	3.49 (0.03)	1.78 (0.03)	1.71 (0.04)	(1.65, 1.78)	<.0001
Internal morphology						
Reader 1	251	3.80 (0.02)	1.99 (0.02)	1.81 (0.03)	(1.76, 1.87)	<.0001
Reader 2	230	3.75 (0.05)	3.22 (0.05)	0.53 (0.06)	(0.42, 0.64)	<.0001
Reader 3	262	3.72 (0.03)	1.69 (0.03)	2.03 (0.04)	(1.95, 2.11)	<.0001
Degree of contrast enhancement						
Reader 1	251	3.64 (0.03)	1.00 (0.03)	2.64 (0.04)	(2.56, 2.72)	<.0001
Reader 2	230	3.82 (0.05)	1.00 (0.05)	1.82 (0.07)	(1.68, 1.96)	<.0001
Reader 3	262	3.33 (0.03)	1.00 (0.03)	2.33 (0.04)	(2.26, 2.41)	<.0001

Source: Table 11-1 on page 88/165 of the study report: report-body-4_21_00555.pdf, confirmed by the FDA statistical reviewer.
Notes: Only matching lesions are considered. The models include lesion visualization factor as dependent variable, MRI modality (pre and paired MRI) as fixed factors, subject as random factor.
Reader 1 is the combination of the following actual readers: H&N reader 1, body reader 1, and MSK reader 1.
Reader 2 is the combination of the following actual readers: H&N reader 2, body reader 2, and MSK reader 2.
Reader 3 is the combination of the following actual readers: H&N reader 3, body reader 3, and MSK reader 3.
Abbreviations: CI, Confidence Interval; CNS, central nervous system; FAS, full analysis set; H&N, head and neck; LS, Least Squares; MSK, musculoskeletal; SE. Standard Error

The primary analyses were repeated including non-matching lesions using the extended FAS 1 (N=286). For meta-readers 1, 2, and 3, 283, 279, and 286 subjects were analyzed, respectively. Therefore, an additional 32, 49, and 24 subjects were included in the analysis. The results are similar to those obtained in the primary analyses and are presented in Table 87 below.

Table 87. [Outside CNS, Subject-Level, Non-Matching Lesion Included] Lesion Visualization Efficacy Endpoints -Off-Site Readings – MRI With Gadopiclenol – Paired vs Pre – Mixed Model Including Matching and Non-Matching Lesions – Extended FAS 1

Extended FAS 1 (N=286)	n	LS Mean (SE) Paired	Pre	Difference	95% CI Difference	p-value
Border delineation						
Reader 1	283	3.77 (0.03)	2.23 (0.03)	1.53 (0.03)	(1.47, 1.60)	<.0001
Reader 2	279	3.45 (0.05)	2.90 (0.06)	0.55 (0.06)	(0.43, 0.66)	<.0001
Reader 3	286	3.48 (0.03)	1.77 (0.03)	1.71 (0.03)	(1.64, 1.77)	<.0001
Internal morphology						
Reader 1	283	3.79 (0.02)	1.98 (0.02)	1.81 (0.03)	(1.75, 1.86)	<.0001

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Extended FAS 1 (N=286)	n	LS Mean (SE) Paired	Pre	Difference	95% CI Difference	p-value
Reader 2	279	3.70 (0.05)	3.11 (0.05)	0.58 (0.06)	(0.47, 0.70)	<.0001
Reader 3	286	3.69 (0.03)	1.63 (0.03)	2.05 (0.04)	(1.98, 2.13)	<.0001
Degree of contrast enhancement						
Reader 1	283	3.65 (0.03)	1.00 (0.03)	2.65 (0.04)	(2.58, 2.72)	<.0001
Reader 2	279	3.88 (0.04)	1.00 (0.04)	1.88 (0.06)	(1.75, 2.00)	<.0001
Reader 3	286	3.34 (0.02)	1.00 (0.02)	2.34 (0.03)	(2.27, 2.41)	<.0001

Source: Table 11-11 on page 110/165 of the study report 'report-body-4_21_00555.pdf' and Table 14.2.1.28 on page 556/1645 of 'csr-section-14-4-21-00556.pdf', confirmed by the FDA statistical reviewer.
Notes: Matching and not matching lesions are considered. The models include lesion visualization factor as dependent variable, MRI modality (pre and paired MRI) as fixed factors, subject as random factor.
Reader 1 is the combination of the following actual readers: H&N reader 1, body reader 1, and MSK reader 1.
Reader 2 is the combination of the following actual readers: H&N reader 2, body reader 2, and MSK reader 2.
Reader 3 is the combination of the following actual readers: H&N reader 3, body reader 3, and MSK reader 3.
Abbreviations: CI, confidence interval; CNS, central nervous system; FAS, full analysis set; LS, Least Squares; MRI, magnetic resonance imaging; SE, Standard Error

In response to the FDA IR dated April 21, 2022, requesting sensitivity analyses (including imputations) for the primary efficacy endpoints to evaluate the potential impact or bias due to excluding subjects with non-matching lesions between paired and pre-contrast images, the Applicant performed four additional sensitivity analyses based on the following assignments (source: page 3/15 of ir-response-clinical-4_22_00184.pdf):

- Assigning the subject mean of scores of the pre-contrast read to the paired read when paired read score is missing and the reverse so that there is no difference between paired read and pre-contrast read.
- Assigning the global mean of scores (over pre-contrast and paired values) when either paired or pre-contrast lesions are not seen.
- Assigning the subject mean of scores (over pre-contrast and paired values) when either paired or pre-contrast lesions are not seen.
- Assigning the worst score (1) to a lesion not seen in either paired or pre-contrast reading when seen with the other.

The results of the four additional sensitivity analyses were all statistically significant and similar to those obtained for the primary analysis (source: Tables 5 - 8 on pages 8/15 - 11/15 of ir-response-clinical-4_22_00184.pdf). As an illustration, Table 88 below presents the results using the worst score imputation. The corresponding statistical analysis SAS programs for these additional sensitivity analyses were verified by the FDA statistical reviewer.

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Table 88. [Outside CNS, Subject-Level Sensitivity Analysis] Lesion Visualization Efficacy Endpoints - Off-Site Readings – MRI With Gadopiclenol – Paired vs Pre – Mixed Model Including Matching and Non-Matching Lesions – With Imputation (#4: Worst Score Assignment) for Non-Matching Lesion - Extended FAS 1

Extended FAS 1 (N=286)	n	LS Mean (SE) Paired	Pre	Difference	95% CI Difference	p-value
Border delineation						
Reader 1	283	3.19 (0.04)	2.05 (0.04)	1.14 (0.05)	(1.05, 1.24)	<.0001
Reader 2	279	3.02 (0.06)	2.68 (0.06)	0.34 (0.06)	(0.22, 0.46)	<.0001
Reader 3	286	3.03 (0.04)	1.68 (0.04)	1.35 (0.04)	(1.27, 1.44)	<.0001
Internal morphology						
Reader 1	283	3.20 (0.03)	1.83 (0.03)	1.38 (0.04)	(1.29, 1.46)	<.0001
Reader 2	279	3.23 (0.06)	2.85 (0.06)	0.38 (0.06)	(0.25, 0.51)	<.0001
Reader 3	286	3.20 (0.04)	1.57 (0.04)	1.63 (0.05)	(1.54, 1.72)	<.0001
Degree of contrast enhancement						
Reader 1	283	3.09 (0.03)	1.00 (0.03)	2.09 (0.05)	(1.99, 2.18)	<.0001
Reader 2	279	2.53 (0.04)	1.00 (0.04)	1.53 (0.06)	(1.41, 1.65)	<.0001
Reader 3	286	2.91 (0.03)	1.00 (0.03)	1.91 (0.05)	(1.82, 2.00)	<.0001

Source: Table 4 on page 11/15 of 'ir-response-clinical-4_22_00184.pdf', confirmed by the FDA statistical reviewer.
Notes: Non-matching lesions are imputed (#4) in such a way they were equalized to the worst case (i.e., 1).
The models include lesion visualization factor as dependent variable, MRI modality (pre and paired MRI) as fixed factors, subject as random factor.
Reader 1 is the combination of the following actual readers: H&N reader 1, body reader 1, and MSK reader 1.
Reader 2 is the combination of the following actual readers: H&N reader 2, body reader 2, and MSK reader 2.
Reader 3 is the combination of the following actual readers: H&N reader 3, body reader 3, and MSK reader 3.
Abbreviations: CI, confidence interval; CNS, central nervous system; FAS, full analysis set; LS, Least Squares; MRI, magnetic resonance imaging; SE, Standard Error

Lesion-Level Analyses

The lesion visualization efficacy endpoints were analyzed at lesion-level using a mixed model in extended FAS 1 (N=286). The results were similar to those obtained at subject-level and are presented in Table 89.

Reference ID: 5048631

Table 89. [Outside CNS, Lesion-Level] Lesion Visualization Efficacy Endpoints at Lesion Level - Off-Site Reading – MRI With Gadopiclenol – Paired vs Pre – Mixed Model – Extended FAS 1

Extended FAS 1 (N=286)	n	LS Mean (SE) Paired	Pre	Difference	95% CI Difference
Border delineation					
Reader 1	728	3.80 (0.03)	2.27 (0.03)	1.53 (0.02)	(1.48, 1.58)
Reader 2	555	3.45 (0.07)	3.00 (0.07)	0.46 (0.04)	(0.37, 0.55)
Reader 3	681	3.48 (0.04)	1.75 (0.04)	1.73 (0.03)	(1.68, 1.78)
Internal morphology					
Reader 1	728	3.83 (0.02)	2.00 (0.02)	1.83 (0.02)	(1.80, 1.87)
Reader 2	555	3.65 (0.06)	3.08 (0.05)	0.57 (0.05)	(0.49, 0.66)
Reader 3	681	3.68 (0.03)	1.58 (0.03)	2.09 (0.03)	(2.04, 2.15)
Degree of contrast enhancement					
Reader 1	728	3.71 (0.03)	1.03 (0.03)	2.68 (0.03)	(2.63, 2.73)
Reader 2	555	2.88 (0.05)	1.06 (0.05)	1.82 (0.05)	(1.72, 1.92)
Reader 3	681	3.37 (0.03)	1.05 (0.03)	2.32 (0.03)	(2.27, 2.37)

Source: Table 14.2.2.10 on page 599/1645 of 'csr-section-14-4-21-00556.pdf', confirmed by the FDA statistical reviewer.
Notes: Non-matching and matching lesions are considered. The models include lesion visualization factor as dependent variable, MRI modality (pre and paired MRI) and center as fixed factors, lesion as random factor.
Reader 1 is the combination of the following actual readers: H&N reader 1, body reader 1, and MSK reader 1.
Reader 2 is the combination of the following actual readers: H&N reader 2, body reader 2, and MSK reader 2.
Reader 3 is the combination of the following actual readers: H&N reader 3, body reader 3, and MSK reader 3.
Abbreviations: CI, confidence interval; CNS, central nervous system; FAS, full analysis set; LS, Least Squares; MRI, magnetic resonance imaging; SE, Standard Error

Analyses like those in Table 89 but excluding center as fixed factor from the mixed model were also confirmed by the FDA statistical reviewer. The re-analyzed models include lesion visualization factor as a dependent variable, MRI modality (pre-contrast and paired MRI) as fixed factors, subject as a random factor. The re-analyzed results were similar to those in Table 89.

In response to the FDA IR dated May 3, 2022, the Applicant performed additional exploratory lesion-level analyses which take into consideration lesion correlation within subject and provided the SAS program codes. As at subject-level, several analyses were performed:

- Non-matching lesions are not imputed. Missing data are handled by the SAS "mixed" procedure.
- Non-matching lesions are imputed (method #1) in such a way they are equal to the available assessment (no difference between paired read and pre-contrast read).
- Non-matching lesions are imputed (method #2) in such a way they are equal to the global average score of the available assessments for the designated parameter and reader.

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- Non-matching lesions are imputed (method #3) in such a way they are equal to the subject average score of the available assessments for the designated parameter and reader.
- Non-matching lesions are imputed (method #4) in such a way they are equal to the worst case (i.e., assigned a score of 1).

The results of the requested exploratory lesion-level analyses taking into consideration the correlation within subject, with and without imputation, were all statistically significant and similar to those obtained by the lesion-level analysis (Table 89) that does not take into consideration the correlation within subject (source: Tables 6 - 10 on pages 1/15 - 15/15 of statistics-additional-ir-post-mid-cycle-review-9-may22.pdf). As an illustration, Table 90 below presents the results of lesion-level analyses taking into consideration lesion correlation within subject without imputation for non-matching lesions.

Table 90. [Outside CNS, Lesion Level Analysis, Taking Into Consideration the Correlation Within Subject] Lesion Visualization Efficacy Endpoints at Lesion Level - Off-Site Readings – MRI With Gadopiclenol – Paired vs Pre – Mixed Model – Without Imputation for Non-Matching Lesions - Extended FAS 1

Extended FAS 1		LS Mean (SE)			95% CI
(N=286)	n	Paired	Pre	Difference	Difference
Border delineation					
Reader 1	728	3.79 (0.03)	2.27 (0.03)	1.53 (0.02)	(1.48, 1.57)
Reader 2	555	3.46 (0.08)	2.97 (0.08)	0.49 (0.04)	(0.40, 0.57)
Reader 3	681	3.48 (0.04)	1.76 (0.04)	1.72 (0.03)	(1.67, 1.76)
Internal morphology					
Reader 1	728	3.82 (0.02)	1.99 (0.02)	1.83 (0.02)	(1.80, 1.86)
Reader 2	555	3.65 (0.07)	3.07 (0.07)	0.58 (0.04)	(0.50, 0.66)
Reader 3	681	3.67 (0.04)	1.59 (0.04)	2.09 (0.03)	(2.04, 2.14)
Degree of contrast enhancement					
Reader 1	728	3.71 (0.03)	1.02 (0.03)	2.68 (0.02)	(2.64, 2.72)
Reader 2	555	2.88 (0.06)	1.07 (0.06)	1.81 (0.04)	(1.73, 1.90)
Reader 3	681	3.37 (0.03)	1.06 (0.03)	2.33 (0.02)	(2.27, 2.36)

Source: Table 6 on page 11/15 of 'statistics-additional-ir-post-mid-cycle-review-9-may22.pdf', confirmed by the FDA statistical reviewer.
Notes: Matching and non-matching lesions are considered. The models include lesion visualization factor as dependent variable, MRI modality (pre and paired MRI) and center as fixed factors, lesion and subject as random factor.
Reader 1 is the combination of the following actual readers: H&N reader 1, body reader 1, and MSK reader 1.
Reader 2 is the combination of the following actual readers: H&N reader 2, body reader 2, and MSK reader 2.
Reader 3 is the combination of the following actual readers: H&N reader 3, body reader 3, and MSK reader 3.
Abbreviations: CI, confidence interval; CNS, central nervous system; FAS, full analysis set; LS, Least Squares; MRI, magnetic resonance imaging; SE, Standard Error

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Region-Level Analyses by Actual Reader

As discussed above, there were five anatomic regions imaged in this study: abdomen (including liver, pancreas, and kidney), head & neck, musculoskeletal system (including extremities), pelvis (including uterus, ovary, and prostate), and thorax (including breast). The lesion visualization efficacy endpoints were analyzed by anatomic region using a mixed model in FAS 1 (N=278). Note that this analysis was by actual reader since readers were not combined within an anatomic region. Paired images were superior to precontrast images in all regions for all three lesion visualization efficacy endpoints with statistical significance except for border delineation assessed by Reader 2 in musculoskeletal system examinations (Table 91). The sample size for musculoskeletal system examinations was relatively small with 17 subjects for Reader 2.

In response to the FDA IR dated June 17, 2022, the Applicant performed additional analyses of the three lesion visualization co-primary efficacy endpoints in subgroups corresponding to actual readers, i.e., head and neck, MSK, and body (thorax, abdomen, and pelvis). For body, paired images were superior to pre-contrast images for the three lesion visualization efficacy endpoints with statistical significance (Table 91).

Table 91. [Outside CNS, by Body Region] Lesion Visualization Efficacy Endpoints by Body Region - Off-Site Reading – MRI With Gadopiclenol – Paired vs Pre – Mixed Model – FAS 1

		LS Mean (SE)			95% CI
Body Region Subgroup	**n**	**Paired**	**Pre**	**Difference**	**Difference**
Head & neck					
Border delineation					
Reader 1	15	3.71 (0.10)	2.13 (0.10)	1.58 (0.14)	(1.30, 1.86)
Reader 2	19	3.53 (0.18)	2.11 (0.18)	1.42 (0.18)	(1.07, 1.77)
Reader 3	13	3.92 (0.13)	2.85 (0.13)	1.08 (0.13)	(0.82, 1.33)
Internal morphology					
Reader 1	15	3.80 (0.07)	1.87 (0.07)	1.93 (0.10)	(1.75, 2.12)
Reader 2	19	3.74 (0.14)	2.05 (0.14)	1.68 (0.16)	(1.37, 2.00)
Reader 3	13	3.92 (0.12)	2.54 (0.12)	1.38 (0.14)	(1.11, 1.66)
Degree of contrast enhancement					
Reader 1	15	3.60 (0.11)	1.00 (0.11)	2.60 (0.16)	(2.29, 2.91)
Reader 2	19	3.68 (0.16)	1.00 (0.16)	2.68 (0.22)	(2.25, 3.12)
Reader 3	13	3.92 (0.11)	1.00 (0.11)	2.92 (0.15)	(2.62, 3.22)
Musculoskeletal system (including extremities)					
Border delineation					
Reader 1	17	3.00 (0.10)	2.06 (0.10)	0.94 (0.13)	(0.68, 1.21)
Reader 2	17	2.68 (0.20)	2.44 (0.20)	0.24 (0.19)	(-0.14, 0.61)
Reader 3	21	2.81 (0.10)	2.05 (0.10)	0.76 (0.10)	(0.56, 0.96)
Internal morphology					

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		LS Mean (SE)			95% CI
Body Region Subgroup	**n**	**Paired**	**Pre**	**Difference**	**Difference**
Reader 1	17	3.00 (0.07)	2.00 (0.07)	1.00 (0.09)	(0.82, 1.18)
Reader 2	17	3.94 (0.15)	2.35 (0.15)	1.59 (0.17)	(1.26, 1.92)
Reader 3	21	2.90 (0.09)	2.05 (0.09)	0.86 (0.11)	(0.64, 1.07)
Degree of contrast enhancement					
Reader 1	17	2.82 (0.10)	1.00 (0.10)	1.82 (0.15)	(1.53, 2.11)
Reader 2	17	3.33 (0.17)	1.00 (0.17)	2.33 (0.24)	(1.87, 2.80)
Reader 3	21	3.06 (0.08)	1.00 (0.08)	2.06 (0.12)	(1.83, 2.30)
Body regions (thorax, abdomen, pelvis)					
Border delineation					
Reader 1	219	3.86 (0.03)	2.28 (0.03)	1.57 (0.04)	(1.50, 1.64)
Reader 2	194	3.54 (0.06)	3.15 (0.06)	0.40 (0.06)	(0.29, 0.51)
Reader 3	228	3.53 (0.03)	1.69 (0.03)	1.84 (0.03)	(1.78, 1.90)
Internal morphology					
Reader 1	219	3.86 (0.02)	2.00 (0.02)	1.87 (0.03)	(1.82, 1.92)
Reader 2	194	3.74 (0.05)	3.41 (0.05)	0.33 (0.05)	(0.23, 0.43)
Reader 3	228	3.78 (0.03)	1.60 (0.03)	2.17 (0.03)	(2.11, 2.24)
Degree of contrast enhancement					
Reader 1	219	3.71 (0.03)	1.00 (0.03)	2.71 (0.04)	(2.63, 2.79)
Reader 2	194	2.69 (0.05)	1.00 (0.05)	1.69 (0.07)	(1.54, 1.83)
Reader 3	228	3.33 (0.03)	1.00 (0.03)	2.33 (0.44)	(2.25, 2.40)
Abdomen (including liver, pancreas and kidney)					
Border delineation					
Reader 1	94	3.84 (0.04)	2.26 (0.04)	1.58 (0.06)	(1.47, 1.70)
Reader 2	89	3.63 (0.09)	3.37 (0.09)	0.26 (0.08)	(0.10, 0.42)
Reader 3	97	3.65 (0.05)	1.80 (0.05)	1.85 (0.05)	(1.76, 1.95)
Internal morphology					

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		LS Mean (SE)			95% CI
Body Region Subgroup	**n**	**Paired**	**Pre**	**Difference**	**Difference**
Reader 1	94	3.85 (0.03)	1.99 (0.03)	1.86 (0.04)	(1.78, 1.93)
Reader 2	89	3.78 (0.07)	3.52 (0.07)	0.25 (0.07)	(0.11, 0.40)
Reader 3	97	3.87 (0.04)	1.62 (0.04)	2.25 (0.05)	(2.15, 2.35)
Degree of contrast enhancement					
Reader 1	94	3.62 (0.04)	1.00 (0.04)	2.62 (0.06)	(2.50, 2.74)
Reader 2	89	2.42 (0.07)	1.00 (0.07)	1.42 (0.10)	(1.22, 1.62)
Reader 3	97	3.25 (0.04)	1.00 (0.04)	2.25 (0.06)	(2.14, 2.36)
Pelvis (including uterus, ovary and prostate)					
Border delineation					
Reader 1	58	3.76 (0.05)	2.21 (0.05)	1.55 (0.07)	(1.40, 1.69)
Reader 2	50	3.20 (0.11)	2.94 (0.11)	0.26 (0.11)	(0.04, 0.48)
Reader 3	58	3.34 (0.06)	1.62 (0.06)	1.72 (0.06)	(1.60, 1.84)
Internal morphology					
Reader 1	58	3.78 (0.04)	2.02 (0.04)	1.77 (0.05)	(1.67, 1.86)
Reader 2	50	3.61 (0.09)	3.41 (0.09)	0.20 (0.10)	(0.00, 0.39)
Reader 3	58	3.64 (0.06)	1.73 (0.06)	1.91 (0.07)	(1.78, 2.04)
Degree of contrast enhancement					
Reader 1	58	3.60 (0.06)	1.00 (0.06)	2.60 (0.08)	(2.45, 2.76)
Reader 2	50	2.52 (0.10)	1.00 (0.10)	1.52 (0.14)	(1.25, 1.79)
Reader 3	58	3.12 (0.05)	1.00 (0.05)	2.12 (0.07)	(1.98, 2.27)
Thorax (including breast)					
Border delineation					
Reader 1	67	3.96 (0.05)	2.38 (0.05)	1.58 (0.07)	(1.44, 1.71)
Reader 2	55	3.71 (0.11)	2.96 (0.11)	0.75 (0.10)	(0.54, 0.96)
Reader 3	73	3.51 (0.06)	1.60 (0.06)	1.91 (0.05)	(1.80, 2.02)
Internal morphology					
Reader 1	67	3.96 (0.03)	1.99 (0.03)	1.97 (0.05)	(1.88, 2.06)
Reader 2	55	3.80 (0.09)	3.24 (0.09)	0.56 (0.09)	(0.38, 0.75)
Reader 3	73	3.77 (0.05)	1.49 (0.05)	228 (0.06)	(2.17, 2.40)
Degree of contrast enhancement					
Reader 1	67	3.92 (0.05)	1.00 (0.05)	2.92 (0.07)	(2.77, 3.07)
Reader 2	55	3.28 (0.09)	1.00 (0.09)	2.28 (0.13)	(2.02, 2.53)
Reader 3	73	3.58 (0.05)	1.00 (0.05)	2.58 (0.06)	(2.46, 2.71)

Source: Table 14.2.1.10 on pages 291/1645 – 295/1645 of 'csr-section-14-4-21-00556.pdf', confirmed by the FDA statistical reviewer, and Table 3 on page 6/11 of '4_22_00242-response-to-fda-ir-statistics-17jun2022.pdf'.
Notes: Only matching lesions are considered. The models include lesion visualization factor as dependent variable, MRI modality (pre and paired MRI), body regions and MRI*body regions as fixed factors, subject as random factor.
Abbreviations: CI, confidence interval; CNS, central nervous system; FAS, full analysis set; LS, Least Squares; MRI,

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magnetic resonance imaging; SE, Standard Error

Similar to Study GDX-44-010, in a response to the FDA IR dated June 17, 2022, the Applicant performed additional analyses regarding the percentage of subjects whose number of lesions detected on paired images with gadopiclenol exceeded that of pre-contrast images, and vice versa, by meta-reader. Further, in response to the FDA IR dated June 28, 2022, the Applicant conducted the same analyses by anatomic region and by actual reader (instead of meta-reader), as well as for the combined body region (thorax, abdomen, pelvis) by actual reader. Table 92 below presents the results of these analyses, where findings of interest include:

- For meta-readers, the percentages of subjects with more lesions detected with pre-contrast images were higher than those of subjects with more lesions detected with paired images, in distinction from Study GDX-44-010.
- The percentages of subjects with more lesions detected with pre-contrast images were higher than those of subjects with more lesions detected with paired images for all anatomic regions combined, the combined body region, musculoskeletal system, and pelvis.
- The percentages of subjects with more lesions detected with pre-contrast images were lower than those of subjects with more lesions detected with paired images for head and neck, thorax, and abdomen.

Further discussion of these results is included in Section 8.3.1. Reference is also made to the Clinical review in Section 8.1.4.

Table 92. [Outside CNS, by Body Region, Comparison of Number/Percentage of Subjects With More Lesions on Paired Images Versus Pre-Contrast Images, by Reader and Across Reader] Comparison of Number of Lesions Detected With Pre and Paired Images- Head & Neck, Musculoskeletal System, Body - Extended FAS 1

	Considering the Number of Lesions Detected by Reader			Considering the Mean Number of Lesions Detected Across Readers
Body Region Subgroup	**Reader 1**	**Reader 2**	**Reader 3**	
All Anatomic Regions Combined				
N subjects	286	286	286	286
n (%) subjects with more lesions detected with pre-contrast images	71 (24.83%)	66 (23.08%)	77 (26.92%)	115 (40.21%)
n (%) subjects with more lesions detected with paired images	66 (23.08%)	38 (13.29%)	31 (10.84%)	74 (25.87%)
n (%) subjects with the same number of lesions detected with pre and paired images	149 (52.10%)	180 (62.94%)	175 (61.19%)	97 (33.92%)
n (%) subjects with missing data	0 (0.00%)	2 (0.70%)	3 (1.05%)	*
Head & Neck				
N subjects	24	24	24	24

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Body Region Subgroup	Considering the Number of Lesions Detected by Reader: Reader 1	Reader 2	Reader 3	Considering the Mean Number of Lesions Detected Across Readers
n (%) subjects with more lesions detected with pre-contrast images	3 (12.50%)	2 (8.33%)	4 (16.67%)	6 (25.00%)
n (%) subjects with more lesions detected with paired images	7 (29.17%)	4 (16.67%)	5 (20.83%)	9 (37.50%)
n (%) subjects with the same number of lesions detected with pre and paired images	14 (58.33%)	18 (75.00%)	12 (50.00%)	9 (37.50%)
n (%) subjects with missing data	0 (0.00%)	0 (0.00%)	3 (12.50%)	*
Musculoskeletal System				
N subjects	22	22	22	22
n (%) subjects with more lesions detected with pre-contrast images	0 (0.00%)	4 (18.18%)	1 (4.55%)	4 (18.18%)
n (%) subjects with more lesions detected with paired images	0 (0.00%)	2 (9.09%)	1 (4.55%)	3 (13.64%)
n (%) subjects with the same number of lesions detected with pre and paired images	22 (100.00%)	16 (72.73%)	20 (90.91%)	15 (68.18%)
n (%) subjects with missing data	0 (0.00%)	0 (0.00%)	0 (0.00%)	*
Body (thorax, abdomen, pelvis)				
N subjects	240	240	240	240
n (%) subjects with more lesions detected with pre-contrast images	68 (28.33%)	60 (25.00%)	72 (30.00%)	105 (43.75%)
n (%) subjects with more lesions detected with paired images	59 (24.58%)	32 (13.33%)	25 (10.42%)	62 (25.83%)
n (%) subjects with the same number of lesions detected with pre and paired images	113 (47.08%)	146 (60.83%)	143 (59.58%)	73 (30.42%)
n (%) subjects with missing data	0 (0.00%)	2 (0.83%)	0 (0.00%)	*
Thorax				
N subjects	77	77	77	77
n (%) subjects with more lesions detected with pre-contrast images	21 (27.27%)	19 (24.68%)	33 (42.86%)	33 (42.86%)
n (%) subjects with more lesions detected with paired images	26 (33.77%)	12 (15.58%)	5 (6.49%)	24 (31.17%)
n (%) subjects with the same number of lesions detected with pre and paired images	30 (38.96%)	46 (59.74%)	39 (50.65%)	20 (25.97%)
n (%) subjects with missing data	0 (0.00%)	0 (0.00%)	0 (0.00%)	*
Abdomen				

Reference ID: 5048631

Body Region Subgroup	Considering the Number of Lesions Detected by Reader: Reader 1	Reader 2	Reader 3	Considering the Mean Number of Lesions Detected Across Readers
N subjects	101	101	101	101
n (%) subjects with more lesions detected with pre-contrast images	24 (23.76%)	23 (22.77%)	26 (25.74%)	41 (40.59%)
n (%) subjects with more lesions detected with paired images	26 (25.74%)	14 (13.86%)	13 (12.87%)	27 (6.73%)
n (%) subjects with the same number of lesions detected with pre and paired images	51 (50.50%)	63 (62.38%)	62 (61.39%)	33 (32.67%)
n (%) subjects with missing data	0 (0.00%)	1 (0.99%)	0 (0.00%)	*
Pelvis				
N subjects	62	62	62	62
n (%) subjects with more lesions detected with pre-contrast images	23 (37.10%)	18 (29.03%)	13 (20.97%)	31 (50.00%)
n (%) subjects with more lesions detected with paired images	7 (11.29%)	6 (9.68%)	7 (11.29%)	11 (17.74%)
n (%) subjects with the same number of lesions detected with pre and paired images	32 (51.61%)	37 (59.68%)	42 (67.74%)	20 (32.26%)
n (%) subjects with missing data	0 (0.00%)	1 (1.61%)	0 (0.00%)	*

Source: Table 5 on page 7/11 of 4_22_00242-response-to-fda-ir-statistics-17jun2022.pdf and Tables 1 and 2 on pages 4/6-5/6 of 4-22-00243-statistics-ir-28jun2022.pdf.
Notes: Missing means at least one evaluation (pre or paired) is either not diagnostic or not assessable.
Percentage is calculated by dividing the frequency of each cell by the total mean number of lesions across readers, which is defined as (n lesions seen by reader 1 + n lesions seen by reader 2 + n lesions seen by reader 3)/3.
*In case of missing data for one reader, the mean is calculated on the result from the other 2 readers.
Abbreviations: CNS, central nervous system; FAS, full analysis set

Subject-Level Analyses Using Different Reader Combinations

Sensitivity analyses were performed by grouping readers from each expertise domain to yield a similar number of subjects with matching lesions for each meta-reader. The results of the sensitivity analyses were similar to those obtained with the primary analysis and are presented in Table 93 below.

Table 93. [Outside CNS, Subject-Level, Alternative Meta-Readers] Sensitivity Analysis of Co-Primary Efficacy Endpoints - Lesion Visualization Efficacy Endpoints - Off-Site Reading – MRI With Gadopiclenol – Paired vs Pre – Mixed Model – FAS 1

FAS 1 (N=278)	n	LS Mean (SE): Paired	Pre	Difference	95% CI Difference	p-value
Border delineation						
Reader 1	258	3.51 (0.03)	1.77 (0.03)	1.74 (0.03)	(1.67, 1.81)	<.0001

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FAS 1 (N=278)	n	LS Mean (SE) Paired	Pre	Difference	95% CI Difference	p-value
Reader 2	230	3.49 (0.06)	2.98 (0.06)	0.51 (0.05)	(0.40, 0.62)	<.0001
Reader 3	255	3.75 (0.03)	2.28 (0.03)	1.47 (0.04)	(1.39, 1.55)	<.0001
Internal morphology						
Reader 1	258	3.74 (0.03)	1.68 (0.03)	2.06 (0.04)	(1.98, 2.13)	<.0001
Reader 2	230	3.67 (0.05)	3.19 (0.05)	0.48 (0.05)	(0.38, 0.58)	<.0001
Reader 3	255	3.86 (0.02)	2.02 (0.02)	1.84 (0.03)	(1.78, 1.89)	<.0001
Degree of contrast enhancement						
Reader 1	258	3.32 (0.03)	1.00 (0.03)	2.32 (0.04)	(2.25, 2.39)	<.0001
Reader 2	230	2.78 (0.05)	1.00 (0.05)	1.78 (0.07)	(1.65, 1.92)	<.0001
Reader 3	255	3.68 (0.03)	1.00 (0.03)	2.68 (0.04)	(2.60, 2.76)	<.0001

Source: Table 14.2.1.34 on page 568/1645 of 'csr-section-14-4-21-00556.pdf', confirmed by the FDA statistical reviewer.
Notes: Only matching lesions are considered. The models include lesion visualization factor as dependent variable, MRI modality (pre and paired MRI) as fixed factors, subject as random factor.
Reader 1 is the combination of the following actual readers: H&N reader 1, body reader 2, and MSK reader 3.
Reader 2 is the combination of the following actual readers: H&N reader 2, body reader 1, and MSK reader 2.
Reader 3 is the combination of the following actual readers: H&N reader 3, body reader 3, and MSK reader 1.
Abbreviations: CI: Confidence Interval; CNS, central nervous system; FAS, full analysis set; H&N: head and neck; LS: Least Squares; MRI, magnetic resonance imaging; MSK: musculoskeletal; SE: Standard Error

As discussed in the introduction to this section, the sponsor performed three additional sensitivity analyses using different numbering allocations, where the number allocation was selected at random from the 34 possible combinations that had not been used for the primary analysis or the pre-defined sensitivity analysis. The results of the three additional sensitivity analyses were all statistically significant and similar to those obtained by the primary analysis and the pre-defined sensitivity analysis. These results are presented in Table 94, Table 95, and Table 96. Also note that the statistical analysis programs for these additional post hoc sensitivity analyses were not submitted.

Reference ID: 5048631

Table 94. [Outside CNS, Subject-Level, Alternative Meta-Readers] Post Hoc Sensitivity Analysis 1 Of Co-Primary Efficacy Endpoints - Lesion Visualization Efficacy Endpoints - Off-Site Reading – MRI With Gadopiclenol – Paired vs Pre – Mixed Model – FAS 1

FAS 1		LS Mean (SE)			95% CI	
(N=278)	n	Paired	Pre	Difference	Difference	p-value
Border delineation						
Reader 1	251	3.79 (0.03)	2.26 (0.03)	1.53 (0.04)	(1.46, 1.60)	<.0001
Reader 2	264	3.47 (0.03)	1.77 (0.03)	1.71 (0.04)	(1.63, 1.79)	<.0001
Reader 3	228	3.50 (0.06)	3.03 (0.06)	0.47 (0.05)	(0.37, 0.57)	<.0001
Internal morphology						
Reader 1	251	3.80 (0.02)	1.99 (0.02)	1.81 (0.03)	(1.76, 1.87)	<.0001
Reader 2	264	3.79 (0.03)	1.69 (0.03)	2.10 (0.03)	(2.03, 2.17)	<.0001
Reader 3	228	3.67 (0.05)	3.24 (0.05)	0.44 (0.05)	(0.34, 0.53)	<.0001
Degree of contrast enhancement						
Reader 1	251	3.64 (0.03)	1.00 (0.03)	2.64 (0.04)	(2.56, 2.72)	<.0001
Reader 2	264	3.35 (0.03)	1.00 (0.03)	2.35 (0.04)	(2.28, 2.42)	<.0001
Reader 3	228	2.79 (0.05)	1.00 (0.05)	1.79 (0.07)	(1.66, 1.93)	<.0001

Source: Table 2 on Page 5/7 of 'statistical-request-response-4-22-00154.pdf'.
Notes: Only matching lesions are considered. The models include lesion visualization factor as dependent variable, MRI modality (pre and paired MRI) as fixed factors, subject as random factor.
Reader 1 is the combination of the following actual readers: H&N reader 1, body reader 1, and MSK reader 1.
Reader 2 is the combination of the following actual readers: H&N reader 2, body reader 3, and MSK reader 2.
Reader 3 is the combination of the following actual readers: H&N reader 3, body reader 2, and MSK reader 3.
Abbreviations: CI: Confidence Interval; CNS, central nervous system; FAS, full analysis set; H&N: head and neck; LS: Least Squares; MRI, magnetic resonance imaging; MSK: musculoskeletal; SE: Standard Error

Table 95. [Outside CNS, Subject-Level, Alternative Meta-Readers] Post Hoc Sensitivity Analysis 2 of Co-Primary Efficacy Endpoints - Lesion Visualization Efficacy Endpoints - Off-Site Reading – MRI With Gadopiclenol – Paired vs Pre – Mixed Model – FAS 1

FAS 1		LS Mean (SE)			95% CI	
(N=278)	n	Paired	Pre	Difference	Difference	p-value
Border delineation						
Reader 1	226	3.49 (0.06)	3.03 (0.06)	0.46 (0.06)	(0.36, 0.57)	<.0001
Reader 2	259	3.75 (0.03)	2.25 (0.03)	1.49 (0.04)	(1.42, 1.57)	<.0001
Reader 3	258	3.51 (0.03)	1.77 (0.03)	1.74 (0.03)	(1.67, 1.81)	<.0001
Internal morphology						
Reader 1	226	3.76 (0.05)	3.23 (0.05)	0.53 (0.06)	(0.42, 0.64)	<.0001
Reader 2	259	3.78 (0.02)	2.00 (0.02)	1.77 (0.03)	(1.71, 1.83)	<.0001
Reader 3	258	3.74 (0.03)	1.68 (0.03)	2.06 (0.04)	(1.98, 2.13)	<.0001
Degree of contrast enhancement						
Reader 1	226	2.80 (0.05)	1.00 (0.05)	1.80 (0.07)	(1.66, 1.94)	<.0001
Reader 2	259	3.65 (0.03)	1.00 (0.03)	2.65 (0.04)	(2.58, 2.73)	<.0001

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FAS 1 (N=278)	n	LS Mean (SE) Paired	Pre	Difference	95% CI Difference	p-value
Reader 3	258	3.32 (0.03)	1.00 (0.03)	2.32 (0.07)	(2.25, 2.39)	<.0001

Source: Table 3 on page 6/7 of 'statistical-request-response-4-22-00154.pdf'.
Notes: Only matching lesions are considered. The models include lesion visualization factor as dependent variable, MRI modality (pre and paired MRI) as fixed factors, subject as random factor.
Reader 1 is the combination of the following actual readers: H&N reader 1, body reader 2, and MSK reader 2.
Reader 2 is the combination of the following actual readers: H&N reader 2, body reader 1, and MSK reader 3.
Reader 3 is the combination of the following actual readers: H&N reader 3, body reader 3, and MSK reader 1.
Abbreviations: CI: Confidence Interval; CNS, central nervous system; FAS, full analysis set; H&N: head and neck; LS: Least Squares; MRI, magnetic resonance imaging; MSK: musculoskeletal; SE: Standard Error

Table 96. [Outside CNS, Subject-Level, Alternative Meta-Readers] Post Hoc Sensitivity Analysis 3 of Co-Primary Efficacy Endpoints - Lesion Visualization Efficacy Endpoints - Off-Site Reading – MRI With Gadopiclenol – Paired vs Pre – Mixed Model – FAS 1 set

FAS 1 (N=278)	n	LS Mean (SE) Paired	Pre	Difference	95% CI Difference	p-value
Border delineation						
Reader 1	255	3.76 (0.03)	2.26 (0.03)	1.51 (0.04)	(1.43, 1.58)	<.0001
Reader 2	264	3.49 (0.03)	1.74 (0.03)	1.75 (0.04)	(1.68, 1.82)	<.0001
Reader 3	224	3.50 (0.06)	3.08 (0.06)	0.43 (0.05)	(0.32, 0.53)	<.0001
Internal morphology						
Reader 1	255	3.78 (0.02)	1.99 (0.02)	1.79 (0.03)	(1.73, 1.85)	<.0001
Reader 2	264	3.73 (0.03)	1.66 (0.03)	2.06 (0.04)	(1.99, 2.14)	<.0001
Reader 3	224	3.77 (0.05)	3.28 (0.05)	0.48 (0.05)	(0.38, 0.59)	<.0001
Degree of contrast enhancement						
Reader 1	255	3.65 (0.03)	1.00 (0.03)	2.65 (0.04)	(2.57, 2.73)	<.0001
Reader 2	264	3.32 (0.03)	1.00 (0.03)	2.32 (0.04)	(2.25, 2.39)	<.0001
Reader 3	224	2.81 (0.05)	1.00 (0.05)	1.81 (0.07)	(1.67, 1.95)	<.0001

Source: Table 4 on Page 7/7 of 'statistical-request-response-4-22-00154.pdf'.
Notes: Only matching lesions are considered. The models include lesion visualization factor as dependent variable, MRI modality (pre and paired MRI) as fixed factors, subject as random factor.
Reader 1 is the combination of the following actual readers: H&N reader 1, body reader 1, and MSK reader 3.
Reader 2 is the combination of the following actual readers: H&N reader 2, body reader 3, and MSK reader 1.
Reader 3 is the combination of the following actual readers: H&N reader 3, body reader 2, and MSK reader 2.
Abbreviations: CI: Confidence Interval; CNS, central nervous system; FAS, full analysis set; H&N: head and neck; LS: Least Squares; MRI, magnetic resonance imaging; MSK: musculoskeletal; SE: Standard Error

8.4. Conclusions and Recommendations

Results from two adequate and well-controlled confirmatory efficacy trials, one for lesions in the CNS and one for lesions outside the CNS, demonstrated superiority of lesion visualization on paired pre-gadopiclenol and post-gadopiclenol images over pre-gadopiclenol images alone. In the study of non-CNS lesions, analyses by anatomic region still broadly supported a benefit for gadopiclenol even with the reduced size of the resulting subgroups.

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Gadopiclenol was generally well tolerated in clinical trials. The important safety issues identified for gadopiclenol are similar to those of other GBCAs.

We find that the benefit-risk balance for gadopiclenol is favorable. The Applicant has presented sufficient evidence to support approval of gadopiclenol for MRI to detect and visualize lesions with abnormal vascularity in the CNS and in the body, including the head and neck, thorax, abdomen, pelvis, and musculoskeletal system.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting or other external consultation was needed for this NDA.

10 Pediatrics

The Applicant conducted one study (GDX-44-007) that enrolled children 2 to 17 years of age. This was an uncontrolled multicenter study of the pharmacokinetics of gadopiclenol in 80 pediatric patients that also served as a source of pediatric safety data. As discussed in Section 6.3.2, the results were sufficient to establish that no dose adjustment was needed for pediatric patients in the studied age range. This pediatric study also supported extrapolation of efficacy established in two adequate and well-controlled studies in adults to children 2 to 17 years of age. In combination with the safety data from GDX-44-007, we recommend that gadopiclenol be approved for use in children aged 2 to 17 years.

A deferral of pediatric studies in children 0 years to less than 2 years of age has been granted. The protocol for a study in this age group (GDX-44-015) was submitted to IND 123673 on October 15, 2021. Briefly, this study plans to enroll (b) (4) patients aged from birth to 23 months old who have known or highly suspected abnormalities of any anatomic region and who are scheduled for a clinically indicated contrasted MRI. Patients will receive a single MRI with 0.05 mmol/kg gadopiclenol and pharmacokinetic data will be collected for the primary endpoint analysis. Secondary safety and unblinded local reader efficacy data will also be obtained. The design overall is very similar to GDX-44-007, and it is anticipated that the results will be sufficient to determine whether gadopiclenol can be used in children aged 0 to 2 years.

11 Labeling Recommendations

Because of nearly identical content and to simplify future maintenance of the labeling, the single-dose and pharmacy bulk package versions of the prescribing information, which were submitted as separate documents, were combined. Other noteworthy labeling recommendations that differed from the Applicant's originally proposed prescribing information are listed below.

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Section 1: INDICATIONS AND USAGE

- (b) (4)
-

Section 5: WARNINGS AND PRECAUTIONS

- A warning for interference with visualization of lesions visible with non-contrast MRI was added. Reference is made to sections 8.1.2 and 8.1.4 for analyses and discussion of this point.
- (b) (4)

Section 6: ADVERSE REACTIONS

- The population for which adverse reaction results is presented (b) (4) patients who received gadopiclenol at the recommended dose of 0.05 mmol/kg. This change is intended to better convey the adverse reaction profile expected in clinical use.

Section 8: USE IN SPECIFIC POPULATIONS

- The basis for approval in pediatric patients was added.
- A subsection for geriatric use was added.

Section 10: OVERDOSAGE

- Information regarding the adverse reactions observed after administration of 0.3 mmol/kg gadopiclenol was added.

Section 11: DESCRIPTION

- (b) (4) were removed as this information is not necessary for safe use of the drug.

Section 12: CLINICAL PHARMACOLOGY

- Discussion of relaxivity was reduced because it is not needed for safe use of the drug.
- (b) (4) was removed because it is not needed for safe use of the drug.
- A subsection for cardiac electrophysiology was added to discuss the high-level results of the thorough QT study.
- A statement was added to describe the residual uncertainty regarding the extent of gadolinium retention that occurs after gadopiclenol administration. Refer to section 8.2.5 for discussion of this point.
- Pharmacokinetics results were reorganized to more clearly present the clinically relevant information.

Section 14: CLINICAL STUDIES

- (b) (4) (b) (4) brief summaries of the relevant comparisons were added to the text.
- (b) (4) replaced with a table showing lesion visualization results by anatomic region. (b) (4) Note that because this

was not the prespecified primary analysis for GDX-44-011, p-values were not included in the table.

- (b) (4)

Section 17: PATIENT COUNSELING INFORMATION

- Multiple subsections were modified for clarity.

12 Risk Evaluation and Mitigation Strategies (REMS)

A risk evaluation and mitigation strategy was not needed for this NDA.

13 Postmarketing Requirements and Commitment

To address the issue of gadolinium retention, we recommend the postmarketing requirements below for gadopiclenol. These postmarketing requirements are the same as those of other approved GBCAs. Because clinical consequences of gadolinium retention have not been established in patients with normal renal function, these data are not required prior to approval.

Perinatal Toxicity Study in Mice: This study will examine the safety of gadopiclenol following perinatal exposure through repeated dosing in pregnant dams. The study will provide safety data assessing behavioral, neurological, and histopathology findings. The study will examine the pharmacokinetics of the GBCA including gadolinium retention in the brain and other organs/tissues.

Juvenile Toxicity Study in Mice: This study will examine the safety of gadopiclenol in juvenile animals, following repeated administration. The study will provide safety data assessing behavioral, neurological, and histopathology findings. The study will also examine the pharmacokinetics of the GBCA including gadolinium retention in the brain and other organs/tissues.

Clinical Longitudinal Cohort Trial: This prospective longitudinal cohort trial with one or more matched control group(s) will evaluate the effects of repetitive gadopiclenol administration on a comprehensive battery of neurobehavioral testing over the course of at least five administrations. The trial should be sufficiently powered to exclude a prespecified magnitude of decline. As a secondary objective, trial patients should also have the option of providing blood and urine samples at the time of reimaging, so that normative estimates of gadolinium concentration across an extended range of post-administration timepoints may be documented.

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We also note that results of a deferred pediatric study under the Pediatric Research Equity Act in patients aged 0 years to less than 2 years will be required. The protocol for this study was submitted to IND 123673 on October 15, 2021.

14 Division Director (Clinical) Comments

I concur with the unanimous recommendation by the NDA review team for the approval of gadopiclenol, a macrocyclic, non-ionic gadolinium-based MRI contrast agent intended to detect and visualize lesions with abnormal vascularity in the CNS (brain, spine, and associated tissues) and the body (head and neck, thorax, abdomen, pelvis, and musculoskeletal system). I concur that the nonclinical pharmacology and toxicology characterization of gadopiclenol is acceptable and that the selection of the optimal dose is supported by the phase 2 data.

I concur that the Applicant has provided substantial evidence of the efficacy of gadopiclenol in adults based on two mutually supportive, adequate, and well-controlled clinical trials, one in the CNS and the other in the body. The study designs, efficacy endpoints, and image reading procedures for the two studies are standard for a lesion visualization claim and are similar to those used in studies of other approved agents in the class. I note that FDA verified the primary and sensitivity analyses of the efficacy data as well as the quality and integrity of the data. I concur that extrapolation of efficacy to pediatric patients from 2 to 17 years of age is supported by the PK and safety study that demonstrated no change to the dosing recommended for adults (0.05 mmol/kg) is needed for pediatric patients. I concur that the safety profile of gadopiclenol is acceptable and consistent with the profile of other approved GBCAs and that the benefit-risk balance of gadopiclenol is favorable.

I concur with combining the PIs for the single-dose and pharmacy bulk package presentations into a single PI. I also concur that (b) (4) I concur that a (b) (4)

I concur that the extent and clinical significance of gadolinium retention levels remain undefined for gadopiclenol and the GBCA class in general and require further post-marketing study. I further concur with the requirement for two postmarketing clinical studies of gadopiclenol. One longitudinal cohort study with one or more matched control groups will evaluate the effects of repetitive gadopiclenol administration on a comprehensive battery of neurobehavioral testing over the course of at least five administrations. A second study is required to evaluate PK, safety, and image quality of a single dose of gadopiclenol in pediatric patients 0 to <2 years of age.

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I also concur with the requirement for two postmarketing nonclinical studies of repeated administrations of gadopiclenol in mice. The first study will examine the safety of gadopiclenol following perinatal exposure through repeated dosing in pregnant dams to assess developmental and reproductive outcomes including a behavioral and functional assessment in the offspring. The second study will examine the safety of gadopiclenol in juvenile animals following repeated administration. Both studies will evaluate behavioral, neurological, and histopathology findings and the pharmacokinetics of gadopiclenol including gadolinium retention in the brain and other organs.

15 Office Director (or Designated Signatory Authority) Comments

I concur with the recommendation of the Division of Imaging and Radiation Medicine and the multi-disciplinary review team to approve NDA 216986 for Elucirem (Gadopiclenol) as a GBCA for use with MRI for detection and visualization of lesions with abnormal vascularity in the CNS and in the body as provided in the approved indication statement. I concur with the proposed labeling and the PMRs.

16 Appendices

16.1. References

Fretellier, N, M Rasschaert, J Bocanegra, P Robert, C Factor, A Seron, JM Idee, and C Corot, 2021, Safety and Gadolinium Distribution of the New High-Relaxivity Gadolinium Chelate Gadopiclenol in a Rat Model of Severe Renal Failure, Invest Radiol, 56(12):826-836.

Robic, C, M Port, O Rousseaux, S Louguet, N Fretellier, S Catoen, C Factor, S Le Greneur, C Medina, P Bourrinet, I Raynal, JM Idee, and C Corot, 2019, Physicochemical and Pharmacokinetic Profiles of Gadopiclenol: A New Macrocyclic Gadolinium Chelate With High T1 Relaxivity, Invest Radiol, 54(8):475-484.

Rohrer, M, H Bauer, J Mintorovitch, M Requardt, and HJ Weinmann, 2005, Comparison of magnetic properties of MRI contrast media solutions at different magnetic field strengths, Invest Radiol, 40(11):715-724.

Rudnick, MR, I Wahba, and D Miskulin, 2022, Nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy in advanced kidney disease, UpToDate, Post, T., Waltham, MA: UpToDate.

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16.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): GDX-44-007

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 24		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): GDX-44-010

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 40		
Number of investigators who are Sponsor employees (including both full-time and part-time		

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employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): GDX-44-011

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 18		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____		

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Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

16.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

16.3.1. Summary of Bioanalytical Method Validation and Performance

Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes, plasma, feces, and urine concentrations of gadopiclenol were measured in the clinical pharmacology studies (GDX-44-003, GDX-44-005, GDX-44-007). The plasma and urine concentrations of gadopiclenol were measured using a validated assay.

For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total plasma concentrations of gadopiclenol were measured in the clinical pharmacology studies since the plasma protein binding of gadopiclenol is ≤1.8% at clinically relevant concentrations. There is no active metabolite of gadopiclenol expected.

What bioanalytical methods are used to assess concentrations?

The concentrations of gadopiclenol were quantified in human plasma and urine using liquid chromatography with tandem mass spectrometry (LC-MS/MS) detection methods. The bioanalytical method performance summary tables in human plasma, urine, and dialysate with their performance in the respective clinical studies (Studies GDX-44-003, GDX-44-005, and GDX-44-007 for plasma and urine, Study GDX-44-005 for dialysate) are presented in Table 97, Table 99, and Table 100, respectively.

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The modifications and cross-validation results of the method for determination of gadopiclenol in human plasma are described in Table 98. The methods for urine and dialysate were not modified.

Table 97. Summary Method Performance of a Bioanalytical Method to Measure Gadopiclenol in Human Plasma

Method Information	**Summary**		
Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a LC-MS/MS analytical method for P03277 assay in sodium heparinized human plasma and in human urine (GDX-44-002) Amendments to final report (1, 2, 3)		
Method description	Protein precipitation		
Materials used for calibration curve & concentration	Human plasma 5 – 10 – 50 – 100 – 300 – 625 – 1250 – 1875 – 2250 – 2500 µg/mL		
Validated assay range	5 – 2500 µg/mL		
Material used for QCs & concentration	Human plasma 5 – 15 – 1250 – 2000 µg/mL		
Minimum required dilutions (MRDs)	Not applicable		
Source & lot of reagents (LBA)	Not applicable		
Regression model & weighting	Linear $1/x^2$		
Validation Parameters	**Method Validation Summary**		**Source Location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	10	GDX-44-002 validation report
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.52 to 2.39%	GDX-44-002 validation report
	Cumulative precision (%CV) from LLOQ to ULOQ	≤7.20%	GDX-44-002 validation report
QCs performance during accuracy & precision	**<u>Cumulative accuracy (%bias) in 18 QCs</u>** QCs:	-2.08 to 2.28%	GDX-44-002 validation report

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Method Information	Summary		
	Inter-batch %CV QCs:	≤10.72%	GDX-44-002 validation report
	Total error QCs:	Not applicable	
Selectivity & matrix effect	Number of total lots tested: 6. No matrix effect observed. State any issue: Not applicable		GDX-44-002 validation report
Interference & specificity	Number of total lots tested: 6. No interference observed. State any issue: Not applicable		GDX-44-002 validation report
Hemolysis effect	Number of total lots tested:1. No hemolysis effect observed. State any issue: Not applicable		GDX-44-002 validation report
Lipemic effect	Number of total lots tested:1. No lipemic effect observed. State any issue: Not applicable		GDX-44-002 validation report
Dilution linearity & hook effect	Not applicable		
Bench-top/process stability	Stable 4 hours 20 minutes at room temperature		GDX-44-002 validation report
Freeze-Thaw stability	Stable after 3 freeze cycles at -20°C and -80°C and thaw at room temperature		GDX-44-002 validation report
Long-term storage	Stable 203 days at -20°C and 40 days at -80°C.		GDX-44-002 validation report
Parallelism	Not applicable		
Carry over	None		GDX-44-002 validation report

Reference ID: 5048631

Method Information	Summary	
	Method Performance in GDX-44-003 Study	
Assay passing rate	(Including incurred sample reanalysis (ISR)) 1052 samples assayed 100% assay passing rate	GDX-44-003 PK report
Standard curve performance	• Cumulative bias range: -1.77 to 2.43% • Cumulative precision: ≤6.23% CV	GDX-44-003 PK report
QC performance	• Cumulative bias range: -2.26 to 4.33% • Cumulative precision: ≤13.50% CV • TE: ≤ x% (LBA only) Not applicable	GDX-44-003 PK report
Method reproducibility	Incurred sample reanalysis was performed in 16.1% of study samples and 75% of samples met the pre-specified criteria	GDX-44-003 PK report
Study sample analysis/ stability	Samples were analyzed within the long term stability period validated, i.e., 203 days at -20°C.	
	Method Performance in GDX-44-005 Study	
Assay passing rate	(Including incurred sample reanalysis (ISR)) 802 samples assayed 100% assay passing rate	GDX-44-005 PK report
Standard curve performance	• Cumulative bias range: -2.65 to 2.05% • Cumulative precision: ≤7.30% CV	GDX-44-005 PK report
QC performance	• Cumulative bias range: 1.58 to 2.46% • Cumulative precision: ≤10.04% CV • TE: ≤ x% (LBA only) Not applicable	GDX-44-005 PK report
Method reproducibility	Incurred sample reanalysis was performed in 10.8% of study samples and 88.5% of samples met the pre-specified criteria	GDX-44-005 PK report
Study sample analysis/ stability	Longest storage duration at -20°C of study samples: 188 days Long term stability validated at -20°C: 203 days	
	Method Performance in GDX-44-007 Study	
Assay passing rate	(Including incurred sample reanalysis (ISR)) 271 samples assayed 100% assay passing rate	GDX-44-007 PK report
Standard curve performance	• Cumulative bias range: -1.76 to 1.49% • Cumulative precision: ≤6.23% CV	GDX-44-007 PK report
QC performance	• Cumulative bias range: 1.21 to 1.96% • Cumulative precision: ≤4.64% CV • TE: ≤ x% (LBA only) Not applicable	GDX-44-007 PK report

Reference ID: 5048631

Method Information	Summary	
Method reproducibility	Incurred sample reanalysis was performed in 13.4% of study samples and 100% of samples met the pre-specified criteria	GDX-44-007 PK report
Study sample analysis/ stability	Longest storage duration at -20°C of study samples: 673 days Long term stability validated at -20°C: 651 days (based on incurred stability sample results)	

Source: Table 1 in Response to Clinical Pharmacology Information Request received on 7/25/2022
Abbreviations: CV, coefficient of variation; LC/MS-MS, liquid chromatography/ tandem mass spectrometry; LLOQ, lower limit of quantification; LQC, low quality control; QC, quality control; TE, total error; ULOQ, upper limit of quantification

Table 98. Summary of Method PKH/MOA/482 Modifications and Cross-Validation Results

Method Information	Summary		
Bioanalytical method validation report name and hyperlink	Partial validation of a LC-MS/MS analytical method aimed to quantify P03277 in Li-heparin human plasma (GDX-44-012)		
Changes in method	Minor modification of the last step of the extraction method: add 450 µL of methanol/UHQ water (90/10) to 50 µL of extract instead of 900 µL of methanol/UHQ water (90/10) to 100 µL of extract.		
New validated assay range if any	Not applicable		
Validation Parameters	**Cross-Validation Performance**		**Source Location**
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-7.25 to 4.36%	GDX-44-002 validation report
	Cumulative precision (%CV) from LLOQ to ULOQ	Not applicable 1 run performed	GDX-44-002 validation report
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in QCs	2.22 to 16.03%	GDX-44-002 validation report
	Inter-batch %CV	≤6.37%	GDX-44-002 validation report
	Percent total error (TE): Not applicable	≤ x%	

Reference ID: 5048631

Method Information	**Summary**		
Cross-validation	Numbers of spiked or incurred samples analyzed and result	0	-
List other parameters	Not applicable		
Bioanalytical method validation report name and hyperlink	Partial validation of a LC-MS/MS analytical method aimed to quantify P03277 in Li-heparin human plasma (GDX-44-012)		
Changes in method	Modification of anticoagulant counter ion (Li instead of Na)		
New validated assay range if any	Not applicable		
Validation Parameters	**Cross-Validation Performance**		**Source Location**
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-3.40 to 3.79%	GDX-44-012 validation report
	Cumulative precision (%CV) from LLOQ to ULOQ	≤8.13%	GDX-44-012 validation report
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in QCs	0.57 to 3.54%	GDX-44-012 validation report
	Inter-batch %CV	≤6.52%	GDX-44-012 validation report
	Percent TE: Not applicable	Not applicable	
Cross-validation	Numbers of spiked or incurred samples analyzed and result	0	
List other parameters	Not applicable		

Source: Table 2 in Response to Clinical Pharmacology Information Request received on 7/25/2022
Abbreviations: CV, coefficient of variation; LC/MS-MS, liquid chromatography/ tandem mass spectrometry; LLOQ, lower limit of quantification; LQC, low quality control; QC, quality control; TE, total error; ULOQ, upper limit of quantification

Reference ID: 5048631

Table 99. Summary Method Performance of a Bioanalytical Method to Measure Gadopiclenol in Human Urine

Method Information	**Summary**		
Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a LC-MS/MS analytical method for P03277 assay in sodium heparinized human plasma and in human urine (GDX-44-002) Amendments to final report (1, 2, 3)		
Method description	Protein precipitation		
Materials used for calibration curve & concentration	Human urine 5 – 10 – 50 – 100 – 300 – 625 – 1250 – 1875 – 2250 – 2500 µg/mL		
Validated assay range	5 – 2500 µg/mL		
Material used for QCs & concentration	Human urine 5 – 15 – 1250 – 2000 µg/mL		
Minimum required dilutions (MRDs)	Not applicable		
Source & lot of reagents (LBA)	Not applicable		
Regression model & weighting	Linear $1/x^2$		
Validation Parameters	**Method Validation Summary**		**Source Location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	10	GDX-44-002 validation report
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.27 to 2.71%	GDX-44-002 validation report
	Cumulative precision (%CV) from LLOQ to ULOQ	≤4.13%	GDX-44-002 validation report
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 18 QCs** QCs:	0.21% to 2.75%	GDX-44-002 validation report
	Inter-batch %CV QCs:	≤4.80%	GDX-44-002 validation report

Reference ID: 5048631

Method Information	Summary	
	Total error Not applicable QCs: Not applicable	
Selectivity & matrix effect	Number of total lots tested: 6. No matrix effect observed. State any issue: Not applicable	GDX-44-002 validation report
Interference & specificity	Number of total lots tested: 6. No interference observed. State any issue: Not applicable	GDX-44-002 validation report
Hemolysis effect	Not applicable	
Lipemic effect	Not applicable	
Dilution linearity & hook effect	Not applicable	
Bench-top/process stability	Stable 4 hours 10 minutes at room temperature.	GDX-44-002 validation report
Freeze-Thaw stability	Stable after 3 freeze cycles at -20°C and -80°C and thaw at room temperature.	GDX-44-002 validation report
Long-term storage	Stable 188 days at -20°C and 41 days at -80°C.	GDX-44-002 validation report
Parallelism	Not applicable	
Carry over	None	GDX-44-002 validation report
	Method Performance in GDX-44-003 Study	
Assay passing rate	(including incurred sample reanalysis (ISR)) 303 samples assayed 100% assay passing rate	GDX-44-003 PK report
Standard curve performance	• Cumulative bias range: -2.60 to 2.46% • Cumulative precision: ≤4.75% CV	GDX-44-003 PK report
QC performance	• Cumulative bias range: -1.27 to 1.63% • Cumulative precision: ≤4.57% CV • TE: ≤ x% (LBA only) Not applicable	GDX-44-003 PK report

Reference ID: 5048631

Method Information	Summary	
Method reproducibility	Incurred sample reanalysis was performed in 12.2% of study samples and 87% of samples met the pre-specified criteria	GDX-44-003 PK report
Study sample analysis/ stability	Samples were analyzed within the long term stability period validated, i.e., 188 days at -20°C.	
	Method Performance in GDX-44-005 Study	
Assay passing rate	(including incurred sample reanalysis (ISR)) 334 samples assayed 99.7% assay passing rate	GDX-44-005 PK report
Standard curve performance	• Cumulative bias range: -1.87 to 2.23% • Cumulative precision: ≤6.96% CV	GDX-44-005 PK report
QC performance	• Cumulative bias range: -3.27 to -0.40% • Cumulative precision: ≤8.92% CV • TE: ≤x% (LBA only) Not applicable	GDX-44-005 PK report
Method reproducibility	Incurred sample reanalysis was performed in 11.3% of study samples and 91.2% of samples met the pre-specified criteria	GDX-44-005 PK report
Study sample analysis/ stability	Longest storage duration at -20°C of study samples: 186 days Long term stability validated at -20°C: 188 days	
	Method Performance in GDX-44-007 Study	
Assay passing rate	(including incurred sample reanalysis (ISR)) 256 samples assayed 100% assay passing rate	GDX-44-007 PK report
Standard curve performance	• Cumulative bias range: -1.11 to 1.54% • Cumulative precision: ≤6.65% CV	GDX-44-007 PK report
QC performance	• Cumulative bias range: -1.59 to 1.98% • Cumulative precision: ≤7.53% CV • TE: ≤ x% (LBA only) Not applicable	GDX-44-007 PK report
Method reproducibility	Incurred sample reanalysis was performed in 10.3% of study samples and 78.26% of samples met the pre-specified criteria	GDX-44-007 PK report
Study sample analysis/ stability	Longest storage duration at -20°C of study samples: 592 days Long term stability validated at -20°C: 440 days (using incurred stability sample results)	

Source: Table 3 in Response to Clinical Pharmacology Information Request received on 7/25/2022
Abbreviations: CV, coefficient of variation; LC/MS-MS, liquid chromatography/ tandem mass spectrometry; LLOQ, lower limit of quantification; LQC, low quality control; QC, quality control; TE, total error; ULOQ, upper limit of quantification

Reference ID: 5048631

Table 100. Summary Method Performance of a Bioanalytical Method to Measure Gadopiclenol in Dialysate

Method Information	**Summary**		
Bioanalytical method validation report name, amendments, and hyperlinks	Validation of a LC-MS/MS analytical method for P03277 assay in dialysate (GDX-44-009)		
Method description	Dilution		
Materials used for calibration curve & concentration	Dialysate 0.5 – 1 – 4 – 20 – 80 – 250 – 450 – 500 µg/mL		
Validated assay range	0.5-500 µg/mL		
Material used for QCs & concentration	Dialysate 0.5 – 1.5 – 250 – 400 µg/mL		
Minimum required dilutions	Not applicable		
Source & lot of reagents (LBA)	Not applicable		
Regression model & weighting	Linear $1/x^2$		
Validation Parameters	**Method Validation Summary**		**Source Location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	GDX-44-009 validation report
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-1.13 to 2.03%	GDX-44-009 validation report
	Cumulative precision (%CV) from LLOQ to ULOQ	≤4.20%	GDX-44-009 validation report
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 18 QCs** QCs:	0.86 to 4.85%	GDX-44-009 validation report
	Inter-batch %CV QCs:	≤6.17%	GDX-44-009 validation report

Reference ID: 5048631

Method Information	Summary	
	Total error QCs: Not applicable	
Selectivity & matrix effect	Number of total lots tested: 6. No matrix effect observed. State any issue: Not applicable	GDX-44-009 validation report
Interference & specificity	Not applicable	
Hemolysis effect	Not applicable	
Lipemic effect	Not applicable	
Dilution linearity & hook effect	Not applicable	
Bench-top/process stability	Stable 21 hours 30 minutes at room temperature.	GDX-44-009 validation report
Freeze-Thaw stability	Stable after 3 freeze cycles at -20°C and thaw at room temperature.	GDX-44-009 validation report
Long-term storage	Stable 787 days at -20°C.	GDX-44-009 validation report
Parallelism	Not applicable	
Carry over	None	GDX-44-009 validation report
	Method Performance in GDX-44-005 Study	
Assay passing rate	(including incurred sample reanalysis) 104 samples assayed 100% assay passing rate	GDX-44-005 PK report
Standard curve performance	• Cumulative bias range: -5.92 to 4.21% • Cumulative precision: ≤6.61% CV	GDX-44-005 PK report
QC performance	• Cumulative bias range: -1.65 to -0.20% • Cumulative precision: ≤5.39% CV • TE: ≤ x% (LBA only) Not applicable	GDX-44-005 PK report

Reference ID: 5048631

Method Information	Summary	
Method reproducibility	Incurred sample reanalysis was performed in 30% of study samples and 100% of samples met the pre-specified criteria	GDX-44-005 PK report
Study sample analysis/ stability	Longest storage duration at -20°C of study samples: 122 days Long term stability validated at -20°C: 787 days	

Source: Table 4 in Response to Clinical Pharmacology Information Request received on 7/25/2022
Abbreviations: CV, coefficient of variation; LC/MS-MS, liquid chromatography/ tandem mass spectrometry; LLOQ, lower limit of quantification; LQC, low quality control; QC, quality control; TE, total error; ULOQ, upper limit of quantification

16.3.2. Office of Clinical Pharmacology: Pharmacometric Review

16.3.2.1. Applicant's Population Pharmacokinetics Analysis for Study GDX-44-005

Title: Population pharmacokinetics (PPK) analysis of P03277 in healthy volunteers and in patients with impaired renal function

Objective: To update the existing PPK model for gadopiclenol with data obtained from Study GDX-44-005, the dedicated renal impairment study.

Data: Three clinical studies were included in the PPK analysis, GDX-44-003, GDX-44-005, and GDX-44-007 (Table 101). There were five cohorts in Study GDX-44-005 by renal function category: mild, moderate, or severe impairment, end-stage renal disease (ESRD), and normal. The ESRD cohort was excluded from the PPK analysis to avoid potential misspecification of the elimination due to the hemodialysis session. Adult subjects from Study GDX-44-003 and pediatrics from Study GDX-44-007 used to set up a previous gadopiclenol PPK model were considered as reference population. For Study GDX-44-003, subjects (b) (6) and (b) (6) were excluded from the analysis due to incorrect dose administration. For Study GDX-44-007, PK data of ID Numbers (b) (6), as well as the first time point of ID Numbers (b) (6), and (b) (6) were considered outliers and therefore excluded from the analysis.

Reference ID: 5048631

Table 101. Summary of Studies Included in the Population Pharmacokinetics Analysis

Study Protocol	N	Dose (mmol/kg)	N_DV	PK Sampling Time
GDX-44-007, Phase 2, PK, safety and efficacy study in pediatrics ages 2-17	59	0.05	218	Pre-dose, 0.167, 0.625, 2.5, and 7.5 h after dose
GDX-44-003, Phase 1/2a, PK, PD and tolerance study in healthy subjects and patients with lesions	46	0.025, 0.05, 0.075, 0.1, 0.2, and 0.3	506	Pre-dose, 0.033, 0.083, 0.167, 0.333, 0.5, 0.75, 1, 2, 4, 6, 8, 12, and 24 h after dose
GDX-44-005, Phase 1, PK, dialysability, and safety in healthy subjects and in patients with impaired renal function	32	0.1	403	Pre-dose, 0.033, 0.083, 0.167, 0.333, 0.5, 0.75, 1, 2, 4, 6, 8, 12, and 24 h after dose
Total	137		1127	

Source: Applicant's PPK dataset "gd_3_5_7.xpt."
Abbreviations: N_DV, number of PK samples; PD, pharmacodynamics; PK, pharmacokinetics

A summary of the demographics of the PPK dataset is provided in Table 102 and Table 103.

Table 102. Baseline Characteristics of Subjects With Normal Renal Function in Population Pharmacokinetics Analysis

		Pediatric Patients (N=59)		Adult Patients (N=54)	
Parameter		**Mean (SD)**	**Median (range)**	**Mean (SD)**	**Median (range)**
Age (years)		9.1 (4.6)	9.0 (2.0-17.0)	32.9 (12.0)	27.5 (18.0-58.0)
Body Weight (kg)		38.8 (21.2)	33.5 (10.4-89.0)	74.8 (12.4)	72.6 (51.4-100)
Height (cm)		136 (26.5)	135 (88.0-187)	171 (9.4)	170 (151-188)
BMI (kg/m^2)		19.1 (4.8)	18.6 (11.9-32.3)	25.6 (3.4)	25.5 (18.7-34.8)
eGFR (mL/min/1.73 m^2)		111.2 (22.4)	108 (64-173)	108 (13.2)	108 (80-133)
Sex	Male (%)		54.2		50.0
	Female (%)		45.8		50.0

Source: Applicant's PPK dataset "gd_3_5_7.xpt."
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation

Table 103. Baseline Characteristics of Subjects in GDX-44-005 (Dedicated Renal Impairment Study)

Parameter		All (N=32)	Normal (N=8)	Mild (N=8)	Moderate (N=8)	Severe (N=8)
Gender	Female n (%)	17 (53.1)	3 (37.5)	7 (87.5)	5 (62.5)	2 (25.0)
	Male n (%)	15 (46.9)	5 (62.5)	1 (12.5)	3 (37.5)	6 (75.0)
Age (years)	Mean (SD)	50.6 (16.5)	31.4 (14.4)	47.4 (12.3)	61.1 (9.7)	62.6 (4.7)
	Median (Range)	57 (18-71)	26.5 (18-57)	49 (30-66)	65.5 (43-71)	61 (57-71)

Reference ID: 5048631

Parameter		All (N=32)	Normal (N=8)	Mild (N=8)	Moderate (N=8)	Severe (N=8)
Height (cm)	Mean (SD)	165.5 (8.0)	167.3 (6.5)	163.6 (9.9)	163.5 (8.2)	167.6 (7.6)
	Median (Range)	165 (147-181)	166 (160-178)	160 (147-180)	164 (154-181)	170 (156-176)
Weight (kg)	Mean (SD)	72.7 (11.7)	65.8 (11.5)	75.2 (7.8)	71.9 (14.6)	77.8 (10.3)
	Median (Range)	73 (51-96)	65 (51-87)	74 (63-87)	72(51-96)	77 (61-89)
BMI (kg/m^2)	Mean (SD)	26.6 (4.5)	23.5 (3.5)	28.2 (2.5)	27.0 (5.7)	27.9 (4.8)
	Median (Range)	27 (19-36)	23 (19-28)	29 (22-30)	26 (21-36)	29 (21-36)
eGFR (mL/min/1.73 m^2)	Mean (SD)	61.5 (35.5)	109.3 (13.1)	72.6 (8.6)	47.0 (8.6)	17.0 (3.5)
	Median (Range)	58 (14-133)	108 (86-133)	74 (59-86)	48 (34-57)	15 (14-22)

Source: Table 3 of Applicant's PPK Analysis Report for GDX-44-005.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; SD, standard deviation

Methods: The PPK analysis was performed by NONMEM (version 7.4.3) using the first order conditional estimate method with interaction option. A two-compartment model parameterized by CL, Q, V_1, and V_2 was used to describe the PK data and all parameters were scaled by body weight using a power of 0.75 for CL and Q, and 1 for V_1 and V_2. Given that the eGFR was estimated using the Schwartz equation for children and the CKD-EPI equation for adults which could not be continuously linked, the covariate effect of eGFR on CL was characterized in different format for adult and pediatric subjects.

$Q = \theta_2 \cdot (BW/70)^{0.75} \cdot \exp(\eta_2)$

$V_1 = \theta_3 \cdot (BW/70) \cdot \exp(\eta_3)$

$V_2 = \theta_4 \cdot (BW/70) \cdot \exp(\eta_4)$

For adults: $CL = \theta_1 \cdot (BW/70)^{0.75} \cdot (\theta_5 \cdot \exp(-\exp(-\theta_6 \cdot ((eGFR/98.5) - \theta_7))) \cdot \exp(\eta_1)$

For pediatrics: $CL = \theta_1 \cdot (BW/70)^{0.75} \cdot (eGFR/108)^{\theta_8} \cdot \exp(\eta_1)$

Results: The parameter estimates are listed in Table 104. Goodness-of-fit plots for the final model are shown in Figure 14.

Reference ID: 5048631

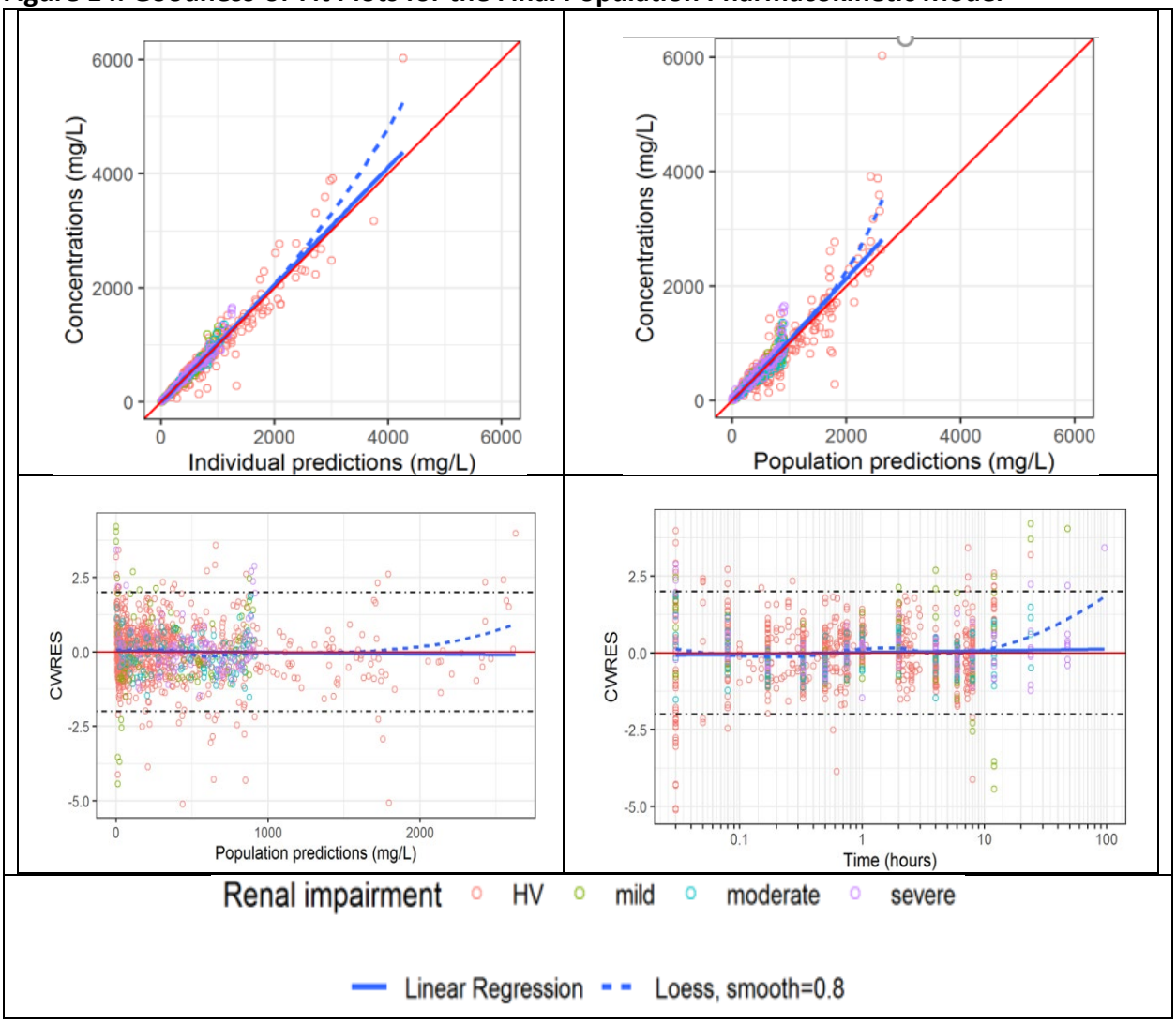
Table 104. Parameter Estimates for Gadopiclenol Population PK Model

Parameter	Estimate (%RSE)	95% CI	CV%
$CL(L/h) = \theta_1(Weight/70)^{0.75}*(\theta_5*EXP(-EXP(-\theta_6*((eGFR/98.5) - \theta_7)))*EXP(\eta_1)*$ Iadult			
$CL(L/h) = \theta_1(Weight/70)^{0.75}*(eGFR/108)^{\theta_8}*EXP(\eta 1)*$ Ichildren			
θ_1: CL typical value	5.15 (2.3)	(4.91, 5.39)	
θ_5: Asymptotic (maximal) effect of eGFR on adults CL	1.53 (7.3)	(1.31, 1.75)	
θ_6: growth rate of adults CL	2.34 (10.7)	(1.85, 2.83)	
θ_7: inflexion point of adults CL	0.523 (9.5)	(0.426, 0.62)	
θ_8: Exponent for eGFR on children CL	0.396 (30.1)	(0.163, 0.629)	
η_1 (IIV CL)	0.0259 (21.4)	(0.015, 0.0368)	16.2
$Q (L/h) = \theta_2(Weight/70)^{0.75}*EXP(\eta_2)$			
θ_2: Q typical value	4.71 (9)	(3.88, 5.54)	
η_2 (IIV Q)	0.186 (34.6)	(0.06, 0.312)	45.2
$V_1 (L) = \theta_3(Weight/70)*EXP(\eta_3)$			
θ_3: V_1 typical value	7.47 (3.3)	(6.99, 7.95)	
η_3 (IIV V_1)	0.0516 (17.3)	(0.0341, 0.0691)	23.0
$V_2 (L) = \theta_4(Weight/70)*EXP(\eta_4)$			
θ_4: V_2 typical value	4.88 (4.5)	(4.44, 5.32)	
η_4 (IIV V_2)	0.18 (36.1)	(0.0528, 0.307)	44.4
Residual error			
ε_1: proportional component	0.021 (12.3)	(0.0159, 0.0261)	14.6

Source: Table 5 of Applicant's PPK Analysis Report for GDX-44-005.
Abbreviations: CI, confidence interval; CV%, coefficient of variation; PK, pharmacokinetics; RSE, relative standard error

Reference ID: 5048631

Figure 14. Goodness-of-Fit Plots for the Final Population Pharmacokinetic Model



Source: Figures 1,4, 9, and 10 of Section 15.4.2 of Applicant's PPK Analysis Report for GDX-44-005.
Abbreviations: CWRES, conditional weighted residuals; HV, healthy volunteer

Reviewer's Comments on Applicant's PPK Analysis: *The Applicant's analysis for Study GDX-44-005 is generally acceptable for describing the PK of gadopiclenol in adults with normal and impaired renal functions as well as in pediatric subjects. In this NDA submission, the Applicant submitted another PPK report titled "Pharmacokinetics, safety and efficacy of a new gadolinium-based contrast agent, gadopiclenol, in pediatric patients from 2 to 17 years of age undergoing contrast-enhanced MRI, the Phase II Clinical Study (GDX-44-007)" based on dataset "gdx_pool_v3.xpt", where PPK data of 59 pediatric patients and 46 adults were included. Since the GDX-44-007 PPK report was generated previously, and all data of "gdx_pool_v3.xpt" were included for GDX-44-005 PPK analysis, no separate review for the GDX-44-007 PPK report is included.*

Reference ID: 5048631

16.3.2.2. FDA Reviewer's Analysis

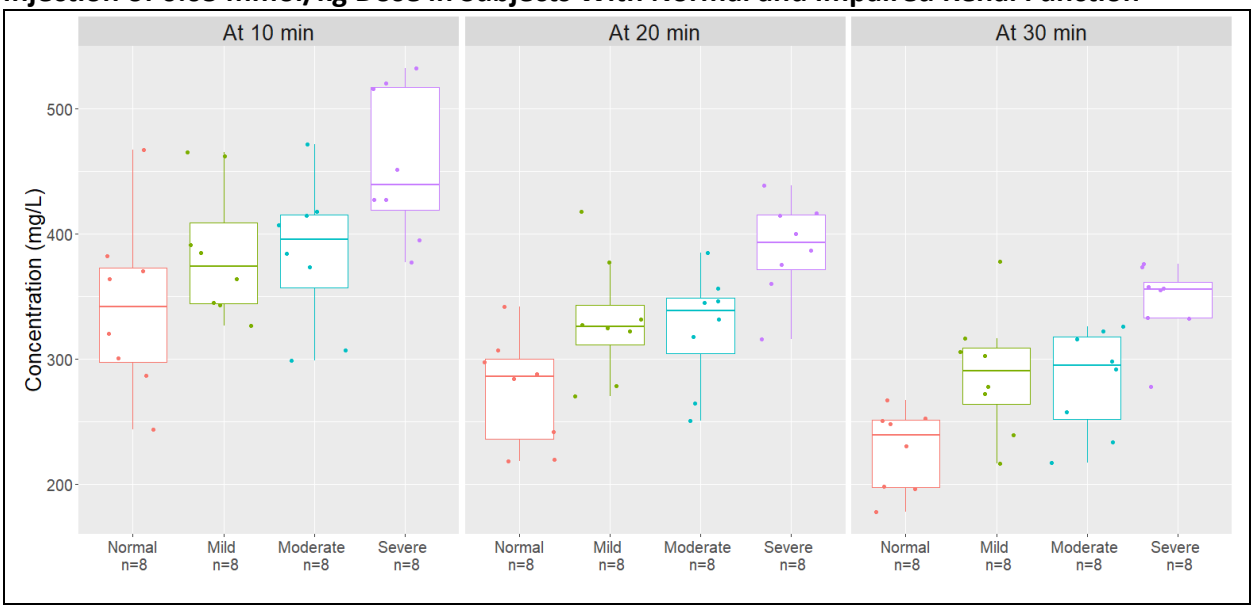
Objectives: To predict and compare the following gadopiclenol exposure metrics based on individual subject's PK parameters obtained from the Applicant's PPK analysis:

- Plasma concentration at 10, 20, and 30 min after i.v. injection of 0.05 mmol/kg dose in adult subjects with normal and impaired renal function.
- Plasma concentration at 10, 20, and 30 min in adult subjects with severely impaired renal function after i.v. injection of 0.035 mmol/kg, a 30% reduced dose to match the exposure with other renal groups.
- AUC comparison between adult subjects with different renal functions.
- Comparison of plasma concentration at 10, 20, and 30 min across different age groups after i.v. injection of 0.05 mmol/kg dose.
- Comparison of plasma concentration at 10, 20, and 30 min across different body weight groups after i.v. injection of 0.05 mmol/kg dose

Method: R version 4.1.0 was used for calculation and plotting.

Results: The predicted concentration results are shown in Figure 15 to Figure 18 and Table 105 and Table 106.

Figure 15. Gadopiclenol Plasma Concentration at 10, 20, and 30 min After Intravenous Injection of 0.05 mmol/kg Dose in Subjects With Normal and Impaired Renal Function



Source: Reviewer's Analysis Based on Applicant's Final PPK Model for Study GDX-44-005.

Reference ID: 5048631

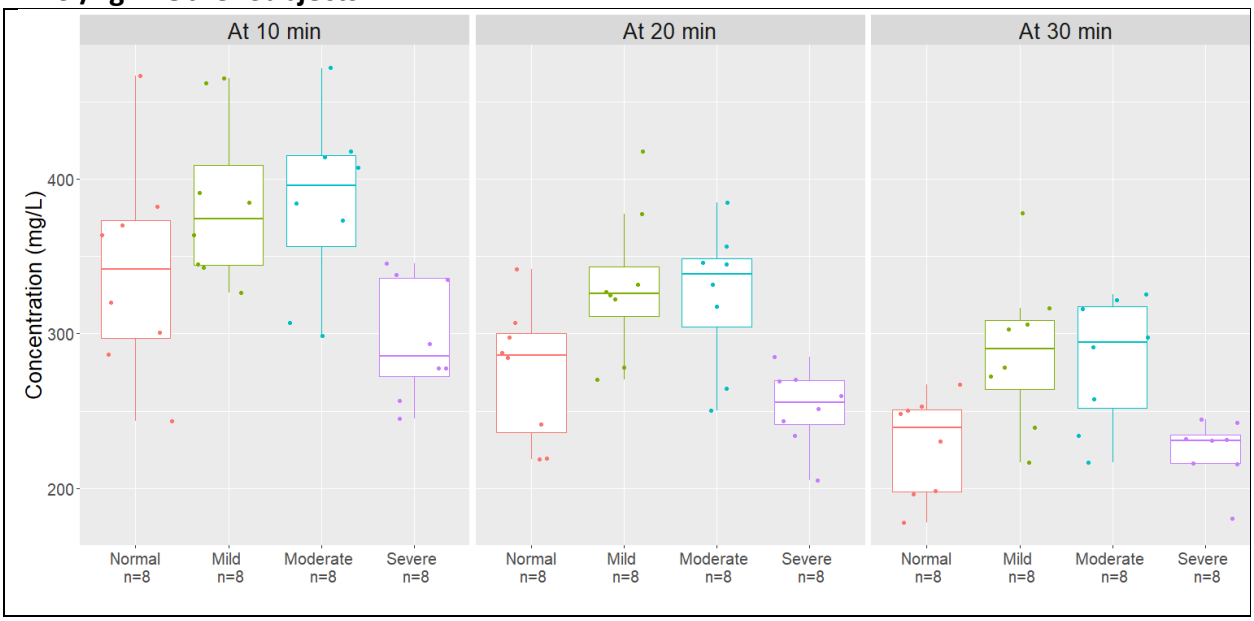
Table 105. Gadopiclenol Concentrations in Impaired Renal Function Relative to Normal Renal Function at 10, 20 and 30 min After Intravenous Injection of 0.05 mmol/kg Dose

	Concentration at		
Renal Function	**10 min**	**20 min**	**30 min**
Mild renal impairment	↑13%	↑21%	↑27%
Moderate renal impairment	↑12%	↑18%	↑24%
Severe renal impairment	↑33%	↑41%	↑52%

Source: Reviewer's Analysis Based on Applicant's Final PPK Model for Study GDX-44-005.

Due to higher gadopiclenol concentration at 10 to 30 min and about 9 times higher AUC in subjects with severe renal impairment compared to subjects with normal renal function, a potential dose reduction was evaluated through PK simulation for subjects with severe renal impairment. With 30% dose reduction in subjects with severe renal impairment, the predicted concentrations are shown in Figure 16 and Table 106. Although the predicted concentrations during the time window of 10 to 30 min in severe renal impairment subjects are closer to other groups, the AUC would still be 7 times higher than subjects with normal renal function.

Figure 16. Gadopiclenol Plasma Concentration at 10, 20, and 30 min After Intravenous Injection of 0.035 mmol/kg Dose in Subjects With Severe Renal Impairment and 0.05 mmol/kg in Other Subjects



Source: Reviewer's Analysis Based on Applicant's Final PPK Model for Study GDX-44-005.

Table 106. Gadopiclenol Concentration in Severe Renal Impairment Relative to Normal Renal Function at 10, 20 and 30 min After Intravenous Injection of 0.035 mmol/kg, a 30% Reduction in Dose

	Concentration at		
Renal Function	**10 min**	**20 min**	**30 min**
Severe Renal Impairment	↓13%	↓8%	↓1%

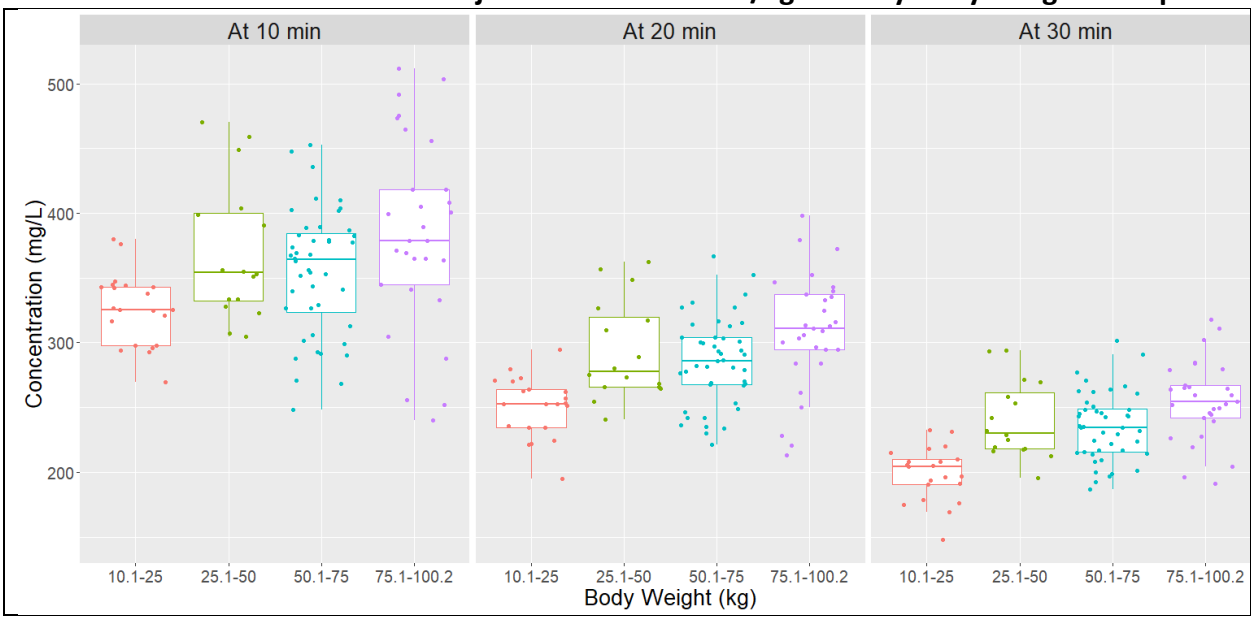
Source: Reviewer's Analysis Based on Applicant's Final PPK Model for Study GDX-44-005.

Based on subjects from Study GDX-44-007 and GDX-44-003, predicted gadopiclenol plasma concentration at 10, 20, and 30 min after i.v. injection of 0.05 mmol/kg dose increased with age and body weight but the difference may not be clinically meaningful (Figure 17 and Figure 18).

Figure 17. Gadopiclenol Plasma Concentration at 10, 20, and 30 min in Patients With Normal Renal Function After Intravenous Injection of 0.05 mmol/kg Dose by Age Group

Source: Reviewer's Analysis Based on Applicant's Final PPK Model for Study GDX-44-005.

Figure 18: Gadopiclenol Plasma Concentration at 10, 20, and 30 min in Patients With Normal Renal Function After Intravenous Injection of 0.05 mmol/kg Dose by Body Weight Group



Source: Reviewer's Analysis Based on Applicant's Final PPK Model for Study GDX-44-005.

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