12 October 2023
EMA/CHMP/488512/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Elucirem

International non-proprietary name: gadopiclenol

Procedure No. EMEA/H/C/005626/0000

Note

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

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List of abbreviations

ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
ALT	Alanine aminotransferase
APD	3-Amino-1,2 propanediol
AST	Aspartate aminotransferase
AUC	Area under the curve
BBB	Blood brain barrier
BMI	Body mass index
BQL	Below the quantification limit
BUN	Blood urea nitrogen
CA	Competent authority
CFU	Colony forming units
Clt	Total clearance
CNS	Central nervous system
CPP	Critical process parameter
CQA	Critical quality attribute
CRO	Contract research organisation
CSF	cerebrospinal fluid
CT	Computed tomography
DBP	Diastolic blood pressure
DCN	Deep cerebellar nuclei
DoE	Design of experiments
DSC-MRI	Dynamic susceptibility contrast-enhanced magnetic resonance imaging
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicine Agency
ESRD	End-stage renal disease
FAS	Full analysis set
FDA	Food and Drug Administration
FOB	Functional observation battery
GALT	Gut-associated lymphoid tissue
GBCA	Gadolinium based contrast agent
GCP	Good clinical practice
Gd	Gadolinium
GD	Gestation day
GLP	Good laboratory practice

HCC	Hepatocellular carcinoma
hERG	Human ether-à-go-go-related gene
HPLC	High-performance liquid chromatography
HR	Heart rate
IA	Intra-arterial
ICH	International Conference on Harmonization
ICP-MS	Inductively-coupled plasma – mass spectrometry
IEC	Independent ethics committee
IMP	Investigational medicinal product
IR	Infrared
IRB	Institutional review board
IU	International units
IV	Intravenous
KF	Karl Fischer titration
LA-ICP-MS	Laser ablation-inductively coupled plasma- mass spectrometry
LC	Liquid chromatography
LC-MS/MS	Liquid chromatography - mass spectrometry/mass spectrometry
LD	Lactation day
LDPE	Low density polyethylene
LLOQ	Lower limit of quantification
LOD	Limit of detection
MNPCE	Micronucleated polychromatic erythrocytes
MR / MRI	Magnetic resonance / magnetic resonance imaging
Mw	Molecular weight
NDA	New drug application
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
NO(A)EL	No observed (adverse) effect level
NSF	Nephrogenic systemic fibrosis
NZW	New Zealand white
PD	Pharmacodynamic
PFS	Pre-filled syringe
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric investigational plan
PK	Pharmacokinetics
PND	Post-natal day
PPND	pre- and postnatal development

PSP	Psediatric study plans
PTZ	Pentylenetetrazole
PV	Perivenous
QbD	Quality by design
QSAR	Quantitative structure activity relationship
QTPP	Quality target product profile
QWBA	Quantitative whole-body autoradiography
RBCs	Red blood cells
RH	Relative humidity
RP	Reversed-phase chromatography
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Sprague-Dawley
SEC	Size exclusion chromatography
SEM	Standard error of the mean
SmPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
T	Tesla
T1/2	Distribution / elimination half-life
TAMC	Total aerobic microbial count
TGF-beta	Transforming growth factor-beta
TE	Echo time
TR	Recovery time
TYMC	Total combined yeasts/moulds count
US(A)	United States (of America)
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
Vd	Apparent distribution volume
Vdss	Distribution volume at steady state
WBCs	White blood cells

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Guerbet submitted on 26 January 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Elucirem, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 April 2020.

The applicant applied for the following indication: This medicinal product is for diagnostic use only.

Elucirem is indicated for magnetic resonance imaging (MRI) in adults and children aged 2 years and older for contrast enhancement of:

- the brain, spine and associated structures to improve detection and visualisation of lesions with disruption of the blood-brain barrier (BBB), blood-spinal cord barrier (BSCB) and/or abnormal vascularity;

- other body regions (head and neck, chest including breast, abdomen including liver and kidneys, pelvis including prostate and musculoskeletal system) to improve the visualisation and assessment of pathologies.

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

An application for Vueway is submitted as a multiple, simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004.

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0151/2021 and P/0152/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIPs P/0151/2021 and P/0152/2021 were not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

the proposed indication.

1.5. Applicant's request for consideration

1.5.1. New active substance status

The applicant requested the active substance gadopiclenol contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
20 July 2017	EMEA/H/SA/3577/1/2017/I	Dieter Deforce, Susan Morgan
15 November 2018	EMEA/H/SA/3577/3/2018/II and EMEA/H/SA/3577/2/2018/III	Dieter Deforce, Mario Miguel Rosa
28 February 2019	EMEA/H/SA/3577/2/FU/1/2019/II and EMEA/H/SA/3577/4/2019/II	Minne Casteels, Karl-Heinz Huemer

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- The proposed active substance starting material. The characterisation of P03277 drug substance isomers. Strategy to register two finished product manufacturing sites for the drug product. Proposal to register the commercial active substance manufacturing site based upon data obtained at pilot scale from another site belonging to the same group of companies. The proposed stability protocol, regarding the number of batches, the manufacturing site and available data at submission.
- Sufficiency of conducted and on-going non-clinical studies to support the intended Phase 3 clinical trials in the EU, and if the overall planned non-clinical programme would be adequate to support MA approval in EU.
- Design of CNS phase III trial (GDX-44-010), including primary objectives, proposal to aggregate lesion visualisation scores per subject by using the mean of up to the three most representative lesions, doses, comparators, sample size, and non-inferiority margin.

  Design of the Body phase III trial (GDX-44-011), including primary objectives, proposal to aggregate lesion visualisation scores per subject by using the mean of up to the three most representative lesions, patient population with diseases in various body regions, the proposed minimum number of patients for certain organs/regions, acceptability to pool all patients scanned for various regions/organs as primary analysis, doses, comparators, sample size, and non-inferiority margin.

  Acceptability to perform one pivotal phase III study per indication.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Finbarr Leacy

The appointed CHMP co-rapporteur had no such prominent role in Scientific advice relevant for the indication subject to the present application.

The application was received by the EMA on	26 January 2022
The procedure started on	24 February 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 May 2022
The CHMP Co-Rapporteur's critique was circulated to all CHMP and PRAC members on	30 May 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	30 May 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 June 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	09 September 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	17 October 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 October 2022
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	10 November 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 March 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	14 April 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	26 April 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	08 September 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues	28 September 2023

to all CHMP and PRAC members on	
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Elucirem on	12 October 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	12 October 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Gadopiclenol is a non-ionic macrocyclic gadolinium (Gd) complex intended to be used in humans, as a contrast agent for Magnetic Resonance Imaging (MRI).

The applicant proposed the following indication:

This medicinal product is for diagnostic use only.

Elucirem is indicated for magnetic resonance imaging (MRI) in adults and children aged 2 years and older for contrast enhancement of:

- the brain, spine and associated structures to improve detection and visualization of lesions with disruption of the blood-brain barrier (BBB), blood-spinal cord barrier (BSCB) and/or abnormal vascularity;

- other body regions (head and neck, chest including breast, abdomen including liver and kidneys, pelvis including prostate and musculoskeletal system) to improve the visualization and assessment of pathologies.

2.1.2. Management

Gadolinium-based contrast agents (GBCAs) are widely used to provide image enhancement of magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and MR arthrography and are regarded as particularly valuable for tumour detection/anatomical characterisation.

Gadolinium-containing contrast agents (GdCAs) consist of a gadolinium ion that is bound to a carrier molecule (a chelator or chelating agent). Interactions between the gadolinium ion and water molecules alter the relaxation time of protons in the water molecules within a magnetic field, which increases the signal intensity on T1-weighted magnetic resonance (MR) imaging.

GBCAs may be categorised by their structure: whether they are linear of macrocyclic based on the chemical structure of their ligand, and whether the molecule is ionic or non-ionic. Macrocyclic agents have shown a better safety profile than linear agents due a low potential for retention of gadolinium in tissues, their stability and a low risk of dechelation. In a referral under Article 31 of Directive 20010/83/EC finalised in

2010 (EMEA/H/A-31/1097), the Committee for Medicinal Products for Human Use (CHMP) concluded that the use of GdCAs is associated with the risk of nephrogenic systemic fibrosis (NSF), a serious and life-threatening syndrome involving fibrosis of the skin, joints and internal organs in patients with renal impairment. The CHMP concluded that the risk of NSF is different for the different GdCAs, which were then categorised into three groups for NSF risk (high risk, medium risk and low risk). Further to a subsequent referral under Article 31 of Directive 20010/83/EC finalised in 2017 (EMEA/H/A-31/1437), where PRAC and CHMP concluded that there is convincing evidence of gadolinium deposition in brain tissues following use of gadolinium contrast agents and restricted the use of some linear gadolinium agents used in MRI body scans as well as suspended the authorisations of others; accumulation of gadolinium in the brain (and its retention) as well as in organs and tissues other than brain tissues are considered as important potential risk for all GdCAs. In addition, the indication of the authorised GdCAs was amended to highlight the need to carefully assess the need of enhanced imaging before using GdCAs and their product information were amended to indicate that all these products should be used at the lowest dose that provides sufficient enhancement for diagnostic purposes. Thus, the development of high-relaxivity GBCAs would allow the reduction of the injected dose with the same efficacy as the other available GBCAs.

Gadopiclenol is a macrocyclic GBCA characterised by a very high r_1 relaxivity, at least two-fold higher compared to other available GBCAs, whatever the magnetic field strength.

2.2. About the product

Mode of action

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

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

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

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

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

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

Pharmacological classification

paramagnetic contrast media, ATC code: V08CA12.

The proposed indication was:

This medicinal product is for diagnostic use only.

Elucirem is indicated for magnetic resonance imaging (MRI) in adults and children aged 2 years and older for contrast enhancement of:

- *the brain, spine and associated structures to improve detection and visualization of lesions with disruption of the blood-brain barrier (BBB), blood-spinal cord barrier (BSCB) and/or abnormal vascularity;*
- *other body regions (head and neck, chest including breast, abdomen including liver and kidneys, pelvis including prostate and musculoskeletal system) to improve the visualization and assessment of pathologies.*

The approved therapeutic indication is:

This medicinal product is for diagnostic use only.

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

- the brain, spine, and associated tissues of the central nervous system (CNS);

- the liver, kidney, pancreas, breast, lung, prostate, and musculoskeletal system.

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

The approved posology is: *The recommended dose of Elucirem is 0.1 mL/kg body weight (BW) (equivalent to 0.05 mmol/kg BW) to provide diagnostically adequate contrast for all indications.*

The dose should be calculated based on the patient's BW and should not exceed the recommended dose per kilogram of BW detailed in this section.

Table 1. Volume of Elucirem to be administered per BW

BW **kilograms (kg)**	**Volume** **millilitres (mL)**	**Quantity** **millimoles (mmol)**
10	1	0.5
20	2	1.0
30	3	1.5
40	4	2.0
50	5	2.5
60	6	3.0

70	7	3.5
80	8	4.0
90	9	4.5
100	10	5.0
110	11	5.5
120	12	6.0
130	13	6.5
140	14	7.0

2.3. Type of application and aspects on development

This is a complete independent application (see 1.2. Legal Basis).

Scientific advice from the EU Scientific Advice Working Party (SAWP) / Committee for Medicinal Products for Human Use (CHMP) were received on quality, non-clinical, and clinical aspects. See 1.6. Scientific Advice. In addition to scientific advice received from the EU SAWP, during the course of development, the applicant sought scientific advice from the following agencies: Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) in November 2014 and FDA (pre-IND and end-of-phase 2).

Compliance with CHMP guidance

The CHMP guidance applying are:

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

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as solution for injection. 1 mL of solution contains 485.1 mg gadopiclenol (equivalent to 0.5 mmol of gadopiclenol and to 78.6 mg of gadolinium).

Other ingredients are: tetraxetan, trometamol, hydrochloric acid (for pH adjustment) sodium hydroxide (for pH adjustment) and water for injections.

As described in section 6.5 of the SmPC, the product is available as

- 3 mL solution for injection in a 10 mL vial (glass type I) with elastomeric stopper.
- 7.5 mL solution for injection in a 10 mL vial (glass type I) with elastomeric stopper.
- 10 mL solution for injection in a 10 mL vial (glass type I) with elastomeric stopper.
- 15 mL solution for injection in a 20 mL vial (glass type I) with elastomeric stopper.
- 30 mL solution for injection in a 50 mL vial (glass type I) with elastomeric stopper.
- 50 mL solution for injection in a 50 mL vial (glass type I) with elastomeric stopper.

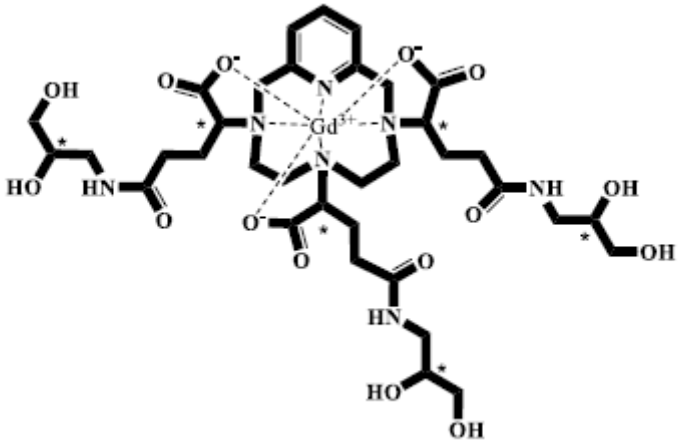
- 100 mL solution for injection in a 100 mL vial (glass type I) with elastomeric stopper.
- 7.5 mL, 10 mL or 15 mL of solution for injection in a 15 mL plastic (polypropylene) pre-filled syringe, graduated every 0.5 mL, without a needle, with an elastomeric (bromobutyl) plunger stopper and capped with an elastomeric (bromobutyl) tip cap.
- 7.5 mL, 10 mL or 15 mL of solution for injection in 15 a mL plastic (polypropylene) pre-filled syringe, graduated every 0.5 mL, with an elastomeric (bromobutyl) plunger stopper and capped with an elastomeric (bromobutyl) tip cap with administration set for manual injection (one extension line and one catheter).
- 7.5 mL, 10 mL or 15 mL of solution for injection in 15 mL plastic (polypropylene) pre-filled syringe, graduated every 0.5 mL, with an elastomeric (bromobutyl) plunger stopper and capped with an elastomeric (bromobutyl) tip cap with administration set for Optistar Elite injector (one extension line, one catheter and one empty 60 mL plastic syringe).
- 7.5 mL, 10 mL or 15 mL of solution for injection in 15 mL plastic (polypropylene) pre-filled syringe, graduated every 0.5 mL, with an elastomeric (bromobutyl) plunger stopper and capped with an elastomeric (bromobutyl) tip cap with administration set for Medrad Spectris Solaris EP injector (one extension line, one catheter and one empty 115 mL plastic syringe).

2.4.2. Active Substance

2.4.2.1. General information

Gadopiclenol is a macrocyclic non-ionic complex of gadolinium. The chemical name of gadopiclenol is *rac*-[(2*R*,2'Ξ,2''Ξ)-2,2',2''-(3,6,9-triaza-κ3*N*3,*N*6,*N*9-1(2,6)-pyridina-κN1-cyclodecaphane-3,6,9-triyl)tris(5-{[(2Ξ)-2,3-dihydroxypropyl]amino}-5-oxopentanoato-κ3O1,O1',O1'')(3−)]gadolinium corresponding to the molecular formula $C_{35}H_{54}GdN_7O_{15}$. It has a relative molecular mass of 970.11 g/mol and the following structure:

Figure 1. Active substance structure



The ligand part of the molecule is cyclic and is visually identified in bold in the structure depicted above. The molecule is globally neutral. The seven bonds established between the gadolinium ion (Gd^{3+}) and the ligand are strong resulting in a complex which is stable in aqueous solution.

The chemical structure of gadopiclenol was elucidated by a combination of infrared spectroscopy, mass spectrometry, ultraviolet spectrophotometry, elemental analysis, nuclear magnetic resonance spectroscopy (^{1}H and ^{13}C NMR), thermal analysis by differential scanning calorimetry and X-Ray diffraction. Gadopiclenol is a mixture of stereoisomers. The information provided is adequate and sufficient.

The active substance gadopiclenol is a white to off-white powder. The active substance is very hygroscopic and highly soluble in water.

Gadopiclenol contains 6 chiral centres and is a mixture of stereoisomers with no optical activity. The isomeric distribution is routinely controlled in the active substance specification. Gadopiclenol is amorphous. Polymorphism has not been observed for the active substance.

During the procedure, a Major Objection was initially raised in relation to the New Active Substance claim as the justification provided was not considered sufficient. In response, the applicant further substantiated the claim, and the MO was satisfactorily resolved. The claim is accepted.

2.4.2.2. Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site with a further site involved in manufacturing an intermediate.

Gadopiclenol is synthesised in six main steps using well defined starting materials with acceptable specifications.

During the procedure, a Major Objection was raised in relation to the initially proposed starting material. In response, the starting material was redefined. This resolved the MO.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The manufacturing process has been described in sufficient detail and has been developed together with the control strategy using a combination of conventional univariate studies and elements of QbD such as the use of risk assessment and design of experiment (DoE) studies. No design space is claimed. Critical steps in gadopiclenol manufacturing process have been identified and critical process parameters (CPP) identified for these steps have been presented; these are satisfactory. The proven acceptance range (PAR) established for each CPP are acceptable.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of active substances.

Potential and actual impurities are well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged into a multilayer low-density polyethylene (LDPE) / aluminium / LPDE bag which complies with Commission Regulation (EU) 10/2011, as amended. A multilayer LDPE bag instead of a simple polyethylene bag has been selected to increase protection of gadopiclenol from moisture since the active substance is very hygroscopic. The LDPE bag is closed by a flat clamp, placed into an additional simple monolayer LDPE bag, and then in a plastic drum.

2.4.2.3. Specification

The active substance specification includes tests for appearance (visual), identity (IR), assay (RP LC-UV), related substances (RP LC-UV), isomeric distribution (RP LC-UV), impurity APD (ionic LC conductivity), free Gd (RP LC-Fluorimetry), water content (KF), bacterial endotoxins (Ph. Eur.) and microbial enumeration (Ph. Eur.).

The proposed specification comply with Ph. Eur. and relevant ICH guidelines requirements and the proposed limits have been set considering historical batch data and stability data; this is acceptable.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The discussion and control of impurities, including of genotoxic impurities is adequate and acceptable.

Routine testing for residual solvents is not required. It has been demonstrated either by testing the active substance or by testing the intermediate that levels of the respective solvents were consistently below 10% of the applicable ICH Q3C limit.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The risk of presence of elemental impurities in gadopiclenol is very low since the final purification steps efficiently remove elemental impurities. In addition, batch analysis data for 7 batches using an ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the active substance specification.

Batch analysis data (3 batches of commercial scale) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from three pilot-scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 12 months under long term conditions (25ºC/ 60% RH) and for up to 6 months under accelerated conditions (40ºC/ 75% RH) according to the ICH guidelines were provided. The parameters tested are the same as for release (bar the identity test which was not conducted during stability studies). The analytical methods used were the same as for release and are stability indicating.

The only significant change observed was an increase of the water content from 4% to 5% (2 batches) and from 3% to 4% (1 batch). As gadopiclenol is a very hygroscopic substance, it is presumed that the increase is related to the opening and closing of the stability samples. The primary packaging (multilayer

LDPE/aluminium/LDPE) is not expected to be permeable. The water content in the active substance does not lead to any significant chemical degradation and does not negatively impact the microbial enumeration. All tested parameters were within the specification limits.

Photostability testing following the ICH guideline Q1B was performed on one batch. The active substance was found not to be light sensitive. Results on stress conditions were also provided. The active substance in solid (powder) form was exposed to dry and moist heat. The active substance in solution was exposed to aqueous acidic, basic, and oxidative conditions. While the stress degradation studies showed that specific stress conditions could lead to specific degradation products, the active substance was found to be relatively thermostable in its powder state. The isomeric distribution is stable under all stress conditions tested. The stress test study demonstrated the stability indicating power of the analytical procedures.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months without specific temperature storage conditions in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Elucirem is a diagnostic product for contrast-enhanced magnetic resonance imaging (MRI). The contrast-enhancing effect is mediated by the active substance gadopiclenol, which enhances the relaxation rates of water protons in its vicinity in the body, leading to an increase in signal intensity (brightness) of tissues.

The finished product Elucirem is a clear, colourless to pale yellow sterile aqueous solution intended for parenteral use by intravenous injection. It contains 0.5 mmol/mL of the active substance gadopiclenol per mL of solution.

The finished product is presented either in a vial (7 different fill volumes) or in a pre-filled syringe (3 different fill volumes). All presentations have the same composition.

The vial presentations are: 10-mL vial filled to 3 mL, 10-mL vial filled to 7.5 mL, 10-mL vial filled to 10 mL, 20-mL vial filled to 15 mL, 50-mL vial filled to 30 mL, 50-mL vial filled to 50 mL and 100-mL vial filled to 100 mL. The vial is a Type I clear glass vial closed with an elastomeric stopper and sealed with an aluminium crimp-on seal.

The pre-filled syringe presentations are: 15-mL syringe filled to 7.5 mL, 15-mL syringe filled to 10 mL and 15-mL syringe filled to 15 mL. The pre-filled syringes (PFS) are polypropylene plastic syringes with an elastomeric plunger stopper and capped with an elastomeric tip. A plastic plunger rod is supplied with the syringe to allow movement of the plunger stopper.

The finished product in pre-filled syringe is also available with three administration sets:

- administration set for manual injection composed of an intravenous catheter made of polyurethane and an extension line made of polyvinyl chloride.

- administration set for Optistar Elite injector composed of a 60 mL syringe made of polypropylene or polyethylene terephthalate and synthetic rubber, an intravenous catheter made of polyurethane and an extension line made of polyvinyl chloride.

- administration set for Medrad Spectris Solaris EP injector composed of a 115 mL syringe made of polyethylene terephthalate, polycarbonate and synthetic rubber, an intravenous catheter made of polyurethane and an extension line made of polyvinyl chloride.

The active substance gadopiclenol is a neutral macrocyclic gadolinium complex intended as MRI contrast medium due to its high relaxivity in water and good hydrophilicity. Due to these two properties, low volumes of finished product are necessary to achieve the targeted MRI contrast enhancement. All stereoisomers of gadopiclenol share the macrocyclic structure and therefore the stereochemistry of the asymmetric carbons has a low impact on the relaxivity value. The active substance is highly soluble in water.

The excipients used in the manufacturing are tetraxetan (DOTA), trometamol, hydrochloric acid and/or sodium hydroxide, and water for injections. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, except for tetraxetan (DOTA), which meets the compendial requirements of the USP. Tetraxetan (DOTA) is used as chelating agent as the absence of free gadolinium (Gd) all along the shelf life is a key safety parameter. Trometamol is used as buffer to maintain the pH of the solution close to physiological pH and HCl or NaOH are used to adjust the pH, if needed. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report.

No compatibility studies between the active substance and the excipients or between excipients have been conducted. However, the excipients used are well known and/or used in other gadolinium formulations and the stability of the formulation has been demonstrated (see chapter on stability below). The acceptability of the proposed excipients for the finished product has been justified for the paediatric population as per requirements of ICH Q8 and the guideline on *Pharmaceutical development of medicines for paediatric use*. No further compatibility studies were deemed necessary.

The aim of formulation development was to develop an aqueous sterile solution for injection for intravenous administration containing 0.5 mmol/mL of gadopiclenol filled into glass vials or plastic syringes with different volumes.

A quality target product profile (QTPP) was defined for the finished product based on the clinical pharmacokinetic of a non-specific contrast medium for medical imaging:

Table 2

QTPP Elements		Target	Justification
Pharmaceutical class		Contrast Agent	Gadopiclenol contains gadolinium as active moiety. It is part of Gadolinium Based Contrast Agent (GBCA) class
Dosage form		Solution for injection	In connection with the practice and the recommendations of the other products of the class
Route of administration		IV path: 1 injection before MRI examination	The current medical practice
Dosage strength		0.5 mmol/mL	Same strength as most other GBCA Injected less quantity than other GBCA Dose of 0.05 mmol/kg body weight (eq. 48.51 mg gadopiclenol/kg or 7.86 mg gadolinium/kg) corresponding to an injected volume of 0.1 mL/kg body weight
Container closure system		Vial and pre-filled syringe with different filled volumes to consider the large range of body weight of the targeted population and/or the multidose presentation	Ensures the quality of the drug product over shelf-life. Ensures the integrity of the container during storage and transportation
Stability		36 months for vial and pre-filled syringe without specific storage conditions	Equivalent to or better than other GBCAs
Drug Product Quality Attributes	Identification	Pharmaceutical Requirements: identity / assay / purity / quality See Table 2	
	Physical Attributes		
	Chemical Attributes		
	Microbial Attributes		
	Other Attributes		

Critical quality attributes (CQAs) were identified and justified. The formulation development studies have been described in detail. The justification for the changes made to the formulation during development is acceptable and the data provided on formulation development is sufficient.

The development of the manufacturing process has been described. Manufacturing process development was conducted with the use of risk management, design of experiments at lab-scale and scientific knowledge in order to identify and understand process parameters and unit operations that impact the critical quality attributes of the finished product and to develop appropriate control strategies, either by controlling a process parameter or by testing. No design space is claimed. The process parameters of the manufacturing process are appropriately justified, and critical process parameter are identified and adequately controlled. No justification is provided for the selected sterilisation method of the finished product filled in glass vials and manufactured at one manufacturing site. This is acceptable as the terminal sterilisation is performed as per Ph. Eur. 5.1.1. The overkill cycle used for the product packed in PFS or glass vials at the second manufacturing site has been adequately validated. Sufficient information has been provided to justify that the scalability of the manufacturing process does not impact the quality of the finished product.

The finished product is available in the following primary packaging:

- a 10 mL, 20 mL, 50 mL or 100 mL vial (glass type I) with elastomeric stopper.
- a 15 mL plastic (polypropylene) pre-filled syringe, graduated every 0.5 mL, without a needle, with an elastomeric (bromobutyl) plunger stopper and capped with an elastomeric (bromobutyl) tip cap.

- a 15 mL plastic (polypropylene) pre-filled syringe, graduated every 0.5 mL, with an elastomeric (bromobutyl) plunger stopper and capped with an elastomeric (bromobutyl) tip cap with administration set for manual injection (one extension line and one catheter).
- a 15 mL plastic (polypropylene) pre-filled syringe, graduated every 0.5 mL, with an elastomeric (bromobutyl) plunger stopper and capped with an elastomeric (bromobutyl) tip cap with administration set for Optistar Elite injector (one extension line, one catheter and one empty 60 mL plastic syringe).
- a 15 mL plastic (polypropylene) pre-filled syringe, graduated every 0.5 mL, with an elastomeric (bromobutyl) plunger stopper and capped with an elastomeric (bromobutyl) tip cap with administration set for Medrad Spectris Solaris EP injector (one extension line, one catheter and one empty 115 mL plastic syringe).

The materials comply with Ph. Eur. and EC requirements.

Sufficient information has been provided regarding the integrity of the container closure systems and the stability of the mechanical properties of the syringes. An in-process control for filling volume has been included in the filling step of the manufacturing process. The requirement is in line with Ph. Eur. 2.9.17.

Compatibility between the finished product solution and the administration sets has been adequately demonstrated.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

During the procedure, a major objection has initially been raised as the graduation of the pre-filled syringe was missing and then a subsequent Major Objection was raised to request more information to justify the use of a glued label. The applicant has opted for glueing the label with a printed graduation to the measuring device. This practice is not generally favoured according to the *Q&A on Quality (Part 2) for the requirements on the graduation of measuring devices for liquid dosage forms* because of the potential for dislocation of the glued label during storage and use. However, all aspects of the Major Objection were satisfactorily addressed and resolved. The requirements of the beforementioned Q&A are fulfilled.

During the procedure, a major objection was also raised on the need to provide an EU certificate issued by a notified body designated for the pre-filled syringe in question or a Notified Body Opinion (NBOP) for the pre-filled syringe confirming full compliance with the relevant General Safety and Performance Requirements (GSPRs) in Annex I of Regulation (EU) 2017/745. Following the initial response, a subsequent Major Objection was raised to request a new Notified Body Opinion which reflects the PFS as presented in the finished product at the time of placing on the market, i.e. to reflect the measuring function of the PFS. In response, a new NBOP confirming that the relevant general requirements as outlined in Chapter I, II and III of Annex I of Regulation (EU) 2017/745 are met was provided. It was determined that the applicant had identified all applicable general safety and performance requirements. For non-applicable general safety and performance requirements a justification has been provided why they are not applicable for the devices. This was sufficient to resolve the Major Objection.

In section 4.2 of the SmPC the applicant has restricted the use of the finished product packed in PFS to adults only. For paediatric patients, only the finished product packed in vials with a single use syringe of a volume adapted to the amount to be injected is recommended. This approach is more conservative compared with the SmPC of other gadolinium products with the same indication and patient target groups, which use the wording "is preferred". Furthermore, potential overdosing of 0.35 mL in case a PFS is used off-label in the

paediatric population is not expected to be clinically relevant in terms of safety since gadopiclenol can be given at half dose of gadolinium compared to other gadolinium-containing contrast agents. Overall, the approach to restrict the use of pre-filled syringes to adults is accepted.

Sufficient information for the different proposed administration sets has been submitted. Justification for the proposed 60 mL and 115 mL syringes for saline flush has been provided and is acceptable.

2.4.3.2. Manufacture of the product and process controls

Two manufacturing sites are proposed for manufacture of the vial presentation and one site is proposed for manufacture of the PFS

The manufacturing process consists of six main steps for both glass vial and plastic syringe presentations: preparation of the bulk solution, filtration, filling, sterilisation (in autoclave), visual inspection and labelling. The process is considered to be a standard manufacturing process.

The intended commercial batch size is 600 L, whereas the pilot batch size was 60 L.

The maximum holding times has been defined at both manufacturing sites from the beginning of the preparation of the bulk solution to the start of the sterilisation.

The Critical Process Parameters (CPPs) have been identified and the in-process controls are adequate for this type of manufacturing process and pharmaceutical form. Information on the validation of the test method for microbial enumeration by membrane filtration has been presented to demonstrate suitability for in-process samples before the sterilisation step in line with Ph. Eur. 2.6.12.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Validation reports have been presented for four pilot-scale batches from one manufacturing site for both container closure systems (PFS and glass vials). Validation at pilot-scale is acceptable as the manufacturing process is standard. All results have been found to be within the proposed limits. The process is considered validated at this manufacturing site. For the second manufacturing site, a validation report has been presented for three commercial-scale batches. The presented process validation data is in line with the requirements of *Guideline on Process validation for finished products for non-standard (sterile) method of manufacturing*. The validation data presented for the second manufacturing site is sufficient.

For the finished product in PFS, it has been demonstrated that transportation does not affect the quality of the finished product or the label in line with the *Guideline on quality documentation for medicinal products when used with a medical device*.

For the PES filter used for the filtration of the bulk solution, the applicant has provided the necessary filter validation studies (i.e., sorption, compatibility and extractable/leachable studies) in line with the requirements of the *Guideline on Sterilization of the Medicinal Product, active substance, excipient and primary container for non-sterilizing filters*. The sterilisation cycle for filled vials and PFS has been adequately validated at one manufacturing site.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance of the solution (visual inspection), identification of gadopiclenol (IR), DOTA-Gd (RP LC-Fluorimeter), free Gd (RP LC-Fluorimeter), degradation products and total impurities (RP LC-UV), APD (Ionic LC-Conductivity), pH (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxins (Ph. Eur.), particulate contamination (Ph. Eur.) and assay gadopiclenol (RP LC-UV).

The specification tests and acceptance limits for appearance of the solution, pH, sterility, bacterial endotoxins and particulate contamination are according to common pharmaceutical practice, information on manufacturing, ICH guidelines and/or compendial requirements for sterile finished products and, therefore, require no additional justification.

The limits for degradation products have been set in line with ICH Q3B (R2) while certain impurities limits exceeding the ICH Q3B qualification threshold have been toxicologically qualified.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Class 1 (Cd, Pb, As, Hg), Class 2A (Co, V, Ni), Class 2B (Tl, Au, Pd, Ir, Os, Rh, Ru, Se, Pt) and Class 3 (Li, Sb, Ba, Mo, Cu, Sn, Cr) elemental impurities have been considered. The potential contribution factors (active substance, the excipients, water for injections, the manufacturing equipment or both container closure systems) have been evaluated. The smallest container closure system available was used during the screening to account for the worst-case surface/volume ratio (10 mL vials filled with 3 mL volume, and 15 mL PFS filled with 7.5 mL volume). Both manufacturing sites have been covered. The ICP-MS used for the determination of elemental impurities has been validated and the maximum daily dose has been considered for the risk assessment. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary. A major objection concerning the nitrosamine risk assessment was resolved during the procedure.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The compendial methods for the sterility test and for the test for bacterial endotoxins have also been adequately validated on three batches of the finished product filled in glass vials and three batches of the finished product filled in PFS.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for four pilot-scale batches as well as two commercial-scale batches from one manufacturing site and for three commercial-scale batches from the second manufacturing site confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the release specifications, through traditional final product release testing.

2.4.3.4. Stability of the product

Stability data is available from batches from both manufacturing sites. Not all presentations were tested. A bracketing approach has been used in line with ICH Q1D whereby the extremes of fill volumes were selected for stability testing (3 mL filled in 10 mL vial and 100 mL filled in 100 mL vial / 7.5 mL filled in 15 mL syringe and 15 mL filled in 15 mL syringe). The bracketing approach is acceptable.

For the first manufacturing site, stability data from pilot-scale batches was provided. For the vial presentations, data was provided for 3 batches with a fill volume of 3 mL and 3 batches with a fill volume of 100 mL stored for up to 24 months under long term conditions (25ºC/ 40% RH) and for up to 6 months under accelerated conditions (40ºC/ NMT 25% RH) according to the ICH guidelines were. For the PFS presentations, data was provided for 3 batches with a fill volume of 7.5 mL and 3 batches with a fill volume of 15 mL stored for up to 24 months under long term conditions (25ºC/ 40% RH) and for up to 6 months under accelerated conditions (40ºC/ NMT 255% RH) according to the ICH guidelines. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition, stability studies were started with the commercial-scale validation batches from the second manufacturing site according to the ICH guidelines. For one bulk batch, stability data is available for 6 months under long term conditions (25ºC/ 40% RH) and for 6 months under accelerated conditions (40ºC/ NMT 25% RH) for the two extremes of the vial presentation (3 mL filled in 10 mL vial and 100 mL filled in 100 mL vial) and of the PFS presentation (7.5 mL filled in 15 mL syringe and 15 mL filled in 15 mL syringe). For a further bulk batch, this data is available for up to 3 months.

Samples were tested for appearance of solution, assay of gadopiclenol, mass loss, pH, APD content, free Gd, DOTA-Gd, degradation products, total impurities, particulate matter, endotoxins and sterility. The analytical procedures used are stability indicating.

All results remained within the proposed limits at shelf life under accelerated conditions.

All results remained within the proposed limits at shelf life under long-term conditions.In addition, one batch of finished product in vial was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results show that the finished product is not sensitive to light.

In-use stability studies have been conducted on one pilot-scale batch of the finished product packed in 100 mL vial with a fill volume of 100 mL. The finished product was found to be stable after 24 hours at room temperature.

Freeze-thaw studies have been conducted on one batch of finished product packed in a 15 mL PFS with a fill volume of 15 mL and one batch packed in a 100 mL glass vial with a fill volume of 100 mL. The finished product packed in glass vial has been found to be stable after 3 freeze-thaw cycles. The proposed storage claim "This medicinal product does not require any special storage conditions" for the finished product packed in glass vials is therefore acceptable. However, piston displacement was found after freezing of the pre-filled syringes. Therefore, the storage claim "Do not freeze" is acceptable for the finished product in PFS.

Based on available stability data, the proposed shelf-life of 3 years for the finished product packed in both container closure systems and without special storage conditions for the vial presentations and with the

precaution for storage 'do not freeze' for the PFS presentations as stated in the SmPC (section 6.3 and 6.4) is acceptable. For the vial presentation, the SmPC (section 6.3) states that 'Chemical and physical in-use stability has been demonstrated for 24 hours at up to 25 °C' with the addition 'From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless the opening has taken place in controlled and validated aseptic conditions.' The in-use shelf life for the vial presentations is acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The New Active Substance claim for gadopiclenol is acceptable after a Major Objection was resolved during the procedure. The active substance starting material has been re-defined during the procedure in response to a Major Objection. Regarding the finished product, a Major Objection on the nitrosamine risk assessment was resolved during the procedure. Furthermore, two Major Objections related to the syringes used for the PFS presentations were also resolved during the procedure. The medical device is acceptable.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical development programme of gadopiclenol was performed in Europe and in the USA, and included pharmacodynamics, safety pharmacology on main body systems and functions, as well as pharmacokinetic and toxicity studies in several animal species (rodent and non-rodent).

During the course of development, the applicant sought scientific advice on the non-clinical data package from the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), November 2014 and EMA's Committee for Medicinal Products for Human Use (CHMP), November 2018.

All pivotal safety pharmacology and toxicology studies serving as a basis for the non-clinical safety assessment presented in the marketing authorisation dossier for gadopiclenol, were conducted with OECD principles of Good Laboratory Practice (OECD, ENV/MC/CHEM(98)17).

During the development of gadopiclenol, different formulations were used. In early pre-phase I/II non-clinical studies (pharmacodynamics, safety pharmacology, pharmacokinetics, genotoxicity, single dose toxicity studies), formulation A was used. In pre-phase III and pre-marketing non-clinical studies (28-day toxicity studies in rats and dogs, fertility study in rats, pre- and post-natal developmental and juvenile toxicity studies), formulation B was used. This formulation was also used in phase III clinical trials and is intended to be used for commercialisation.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Relaxivity is a key physiochemical property to induce a higher signal intensity enhancement. The relaxivity values (r1 and r2) of different batches of gadopiclenol were compared with linear GBCAs (Magnevist, Omniscan, MultiHance) and other macrocyclic GBCAs (Dotarem, ProHance, Gadovist/Gadavist) in several non-GLP compliant studies. At 1.5-3 Tesla (often used in routine radiological practices), gadopiclenol has at least a 2-3 fold higher relaxivity compared to other GBCAs in water at 37°C. The relaxivity is directly proportional to the number of inner water molecules bound to the Gd ion. Due to the specific structure of gadopiclenol, water molecules occupy two coordination sites of Gd, instead of one site in the other GBCAs.

Imaging studies were performed on animals to evaluate the benefit of the high relaxivity of gadopiclenol in CNS imaging applications, as compared to marketed gadolinium products.

To evaluate the benefits of the higher relaxivity of gadopiclenol for MR imaging (T1 enhancement) of brain tumours, several studies were conducted. An initial study in female rats with a brain tumour (C6 glioma) was conducted to investigate the contrast-to-dose relationship of gadopiclenol after a dose of 0.025 to 0.2 mmol/kg. This study also included a comparison with GBCA reference products (Dotarem, MultiHance and Gadovist/Gadavist) at the usual clinical dose of 0.1 mmol/kg. The peak of the contrast-to-noise ratio (CNR) was between 5-10 minutes post-injection for all products. At 5 minutes post-injection, there was a significant linear relationship between contrast enhancement and gadopiclenol doses, although a slight saturation of the signal was observed between 0.1 mmol/kg and 0.2 mmol/kg. Gadopiclenol at 0.05 mmol/kg was as effective as the reference products at 0.1 mmol/kg and a dose of 0.075 mmol/kg of gadopiclenol allowed to increase the contrast by at least 30% compared to commercial products at 0.1 mmol/kg.

The performance of gadopiclenol in detecting very early-stage tumoural tissue and detecting more lesions have been confirmed in additional experimental imaging studies (T1 enhancement) in rats and mice with implanted brain tumours in different stages in different imaging set-ups.

As perfusion imaging is increasingly included in tumour imaging protocols, the relationship between the susceptibility effect and the dose of gadopiclenol for perfusion imaging (T2*-weighted) was determined in an experimental imaging study in rats with a brain tumour (C6 glioma) dosed with 0.025 to 0.2 mmol/kg

gadopiclenol. This study also included a comparison with GBCA reference products (Dotarem, MultiHance and Gadovist/Gadavist) at the usual clinical dose of 0.1 mmol/kg. There was a significant linear relationship between the susceptibility effect and gadopiclenol doses, although a slight saturation was observed between 0.1 mmol/kg and 0.2 mmol/kg. At 0.1 mmol/kg, gadopiclenol performed identically to the reference products in healthy- and tumour tissue. An additional study in healthy rats confirmed these results.

A final study consisted of pharmacokinetic modelling of plasma, tumour and muscle concentrations of gadopiclenol in rats with a brain tumour (C6 glioma). The correlation between measured concentration in plasma or issues by inductivity-coupled plasma-mass spectrometry (ICP-MS) and estimation of the concentration by MRI was linear, which is consistent with a passive diffusion of the drug.

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been conducted with gadopiclenol, since it is intended for diagnostic purposes only.

2.5.2.3. Safety pharmacology programme

The safety pharmacology programme covered the central nervous system, cardiovascular and respiratory systems, and renal function, in compliance with the ICH Guideline S7. No toxicokinetic assessment was done in safety pharmacology studies, but these values can be extrapolated from the single dose toxicity studies.

Cardiovascular system

To assess the potential effect of gadopiclenol on the cardiovascular system, two GLP-compliant *in vitro* assays were conducted.

In a human ether-à-go-go related gene (hERG) test, gadopiclenol was tested up to 10 mmol/mL. Gadopiclenol induced a concentration-dependent inhibition of hERG tail current amplitude, starting at the lowest concentration of 1.25 mmol/mL, which was not reversible after the washout period. The effect was statistically significant at 5 and 10 mmol/L.

To confirm the non-specific effect of gadopiclenol in the hERG study, a second GLP-compliant study was performed on rabbit Purkinje fibres at the same doses. At 10 mmol/mL gadopiclenol, a slight depolarisation was observed, however this was not considered physiologically relevant because of its low amplitude. In short, this study confirmed the non-specific effect of gadopiclenol in the hERG study.

To further assess any potential effect of gadoplicenol on the cardiovascular system, two GLP-compliant *in vivo* studies were conducted in either anaesthetised or conscious dogs.

Anaesthetised dogs were administered a single IV dose of up to 2 mmol/kg, and several ECG and haemodynamic parameters were monitored. No TK assessment was included in this study. Slight and transient variations of several haemodynamic parameters were observed at 1 and 2 mmol/kg. Additionally, QT and QTc interval durations were slightly increased at 2 mmol/kg. However, conscious telemetered dogs, administered a single IV dose of up to 2 mmol/kg, did not demonstrate any modification of arterial blood pressure or other ECG parameters. Therefore, the NOAEL in anaesthetised dogs was considered 0.5 mmol/kg and 2 mmol/kg (MoE: 13-fold, based on exposure data from single dose "expanded" toxicology study) in conscious dogs.

In addition, ECG recordings in the single-dose, 14-day and 28-day repeat-dose toxicity studies in dogs (dosing up to 4 mmol/kg/day, MoE: ≥25-fold), did not reveal any effect on the ECG waveforms and interval durations. A thorough QT study in healthy volunteers did not demonstrate any potential for gadopiclenol to induce QT prolongation and cardiac repolarisation problems.

Respiratory system

To assess the potential effects of gadopiclenol on respiratory parameters, two GLP-compliant studies were conducted in rats and guinea pigs.

Non-restrained, conscious rats administered a single IV dose of up to 5 mmol/kg gadopiclenol were monitored using the whole-body barometric plethysmography method. No TK assessment was included in this study. No-treatment related changes were observed on any of the respiratory parameters. Therefore, the NOAEL was considered 5 mmol/kg (MoE: 19-fold, based on exposure data from single dose "expanded" toxicology study) in rats.

In a second study, anaesthetised male guinea pigs were administered a single IV dose of up to 5 mmol/kg gadopiclenol. Starting at 2.5 mmol/kg, a concentration-dependent effect on bronchoconstriction was observed, which is considered adverse. Therefore, the NOAEL was considered 1.25 mmol/kg (MoE: 5-fold based on body surface area adjustment) in guinea pigs.

Although the anaesthetised guinea pigs were more sensitive to gadopiclenol, the study in conscious rats showed no adverse effects and provided a sufficient safety margin.

Central nervous system

A GLP-compliant study was performed to evaluate potential neurobehavioural effects of gadoplicenol, using the Irwin method. Conscious unfasted male SD rats were given one IV dose up to 5 mmol/kg gadopiclenol and remained under observation for 24 hours. At 5 mmol/kg, a slight treatment-related decrease in rectal temperature was observed at 0.5 hour post-dosing, but this was considered not adverse. No effect on the main central and peripheral nervous system functions were noted at any dose level. The NOAEL was considered 5 mmol/kg (MoE: 16-fold).

Another GLP-compliant study was performed to evaluate any possible proconvulsant effect of gadopiclenol, since gadopiclenol is intended for use in humans with possible blood brain barrier disruption. Wistar rats were given one IV dose up to 5 mmol/kg gadopiclenol, followed by an IV infusion of pentylenetetrazole (PTZ). In animals dosed with 5 mmol/kg gadopiclenol, a decrease in the time of PTZ-induced seizures was observed. Seizures are a known adverse effect of GBCAs. The NOAEL was considered 2.5 mmol/kg (MoE: 8-fold).

Renal system

Since the kidney is the excretory organ for GBCAs, and due to the high osmolality of gadopiclenol, the kidney is a potential target organ. Therefore, an additional safety pharmacology study was performed to assess any potential effect of gadopiclenol on renal functions.

Male rats were administered a single IV dose of up to 5 mmol/kg gadopiclenol, followed by an oral saline overload given 15 minutes post-dosing. At all dose levels, an increased urine osmolality was observed compared to controls. In addition, a dose-dependent decrease in free water clearance was observed, which was statistically significant at 2.5 and 5 mmol/kg. At 5 mmol/kg, animals had decreased sodium and chloride urinary concentrations. These changes did not result in a change in the glomerular filtration rate. The NOAEL was considered 1.25 mmol/kg (MoE: ~4-fold).

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamic drug interaction study was performed.

2.5.3. Pharmacokinetics

The PK parameters following single oral and IV administration in rats and dogs and repeated IV administration in rats were determined by measuring [^{153}Gd]-gadopiclenol by γ-counting. For toxicokinetic assessment in toxicity studies gadopiclenol was measured in plasma by the validated LC-MS/MS method over the range 0.5-100 µg/mL. The tissue content of gadolinium in selected rat tissues from toxicological studies (rat brain, kidney, cerebellum, skin, femur, liver and total plasma) was determined by the validated ICP-MS methods (ranges in µg Gd/g tissue: brain: 0.006-1.297, kidney and liver: 0.006-6.483, cerebellum: 0.006-1.297, skin: 0.006-12.156, femur: 0.006-2.341, total plasma: 12-10000).

Following IV administration of gadopiclenol to rats, systemic exposure to the total radioactivity increased in a proportional manner across the dose range of 0.6-3 mmol/kg in both sexes, indicative of linear kinetics with increasing dose. The volume of distribution at steady state was ca. 0.2 L/kg in both rats and dogs, consistent with a distribution of gadopiclenol within the extracellular water volume.

The absorption via oral route was low, with the bioavailability of ca. 3.7% relative to the IV administration based on the radiolabelled ^{153}Gd. The Tmax following a single oral administration of 0.6 mmol/kg in rats was 1 hour, with the Cmax reaching 14.7 nmol eq/g.

Following IV administration, gadopiclenol is rapidly and widely distributed across all systemic tissues without apparent sex differences. The highest gadolinium concentrations were consistently measured in kidneys, with a high degree of distribution also to the liver, skin, femur, brain and cerebellum (with the relative degree of distribution to these tissues varying between different studies). In the QWBA study with naïve rats, when expressed as a percentage of the administered dose, the highest levels 10 minutes post-dose were seen in the skin, skeletal muscles, kidneys, liver and bone mineral (23.7-34.9%, 19.2-24.2%, 8.1-8.8%, 5.7-6.1% and 2.9-4.3% of the total administered radioactive dose, respectively). The high degree of distribution to the skin and skeletal muscles possibly reflects a large surface area and a high degree of vascularity of these tissues. Low levels of radioactivity were also measured in the brain (up to 0.09% of the total administered radioactive dose 10 minutes post-dose). The radioactivity declined over the course of the study, almost disappearing at 4 hours post-dose in all tissues except those involved in the excretion (urinary and gastrointestinal tracts), with only kidneys and liver retaining the measurable low radioactivity levels at 336 hours post-dose (0.32%/0.12% and 0.02/0.01% in males/females, respectively).

It was noted that the distribution of gadopiclenol to the brain of adult rats in the QWBA study was very limited (0.09%, 10 mins post IV administration of radiolabelled gadopiclenol).

The placental transfer was evaluated in a separate QWBA study in time-mated rats administered 0.6 mmol/kg gadopiclenol on GD18. The measured levels in placenta and amniotic fluid 10 minutes post-dose (651 and 23 nmol eq/g, respectively) were comparable with other mean maternal tissue concentrations (30-1035 nmol eq/g), but were notably lower than in kidneys (21231 nmol eq/kg). The low levels of radioactivity (12 nmol eq/g) were measurable at the last time point (24 hr post-dose) in the placenta but not in the amniotic fluid.

Gadopiclenol is partially excreted in milk. Following IV administration of 0.6 mmol/kg to lactating rats 0.3% and 0.2% of the administered dose was recovered in pups 6 and 24 hours post-dose. The highest

gadopiclenol concentration was measured in mammary gland 6 hours post-dose (17 nmol equiv/g), followed by milk (15 nmol equiv/g). The mean milk : plasma ratio 6 hours post-dose was 6.7, decreasing to 3.5 at 24 hours post-dose.

The distribution of total gadolinium was also investigated by ICP-MS in a number of selected tissues in the reproductive and juvenile toxicity studies. Following single or repeated administration of 0.6 mmol/kg gadopiclenol to juvenile and adult animals, the highest gadolinium concentrations were measured in the kidneys, followed by the liver, femur, skin, cerebellum, brain and plasma. Generally, accumulation in tissues was seen following the repeated administration, with notably higher levels measured in the brain and cerebellum of adults (up to 6.3x and 9.3x increase), juvenile kidneys (up to 13.5x increase) and femur of both adults and juveniles (up to 8x increase) compared to the single administration. The gadolinium tissue concentrations were in general comparable between juvenile and adult animals, with the exception of the levels in kidneys (lower in juveniles) and brain and cerebellum (lower in adults) immediately after the single administration. The concentrations in all evaluated tissues, except of the femur and kidneys, decreased nearly to the lower limit of quantification in both adults and juveniles following the 8 weeks recovery period, indicating a significant degree of a wash-out. Somewhat lower wash-out was seen following the repeated administration (91-100%) compared to the single administration (>95%), with notably lower washout in the femur (18-28% in adults and 47-56% in juveniles) and brain and cerebellum (84-93% in adults and 76-82% in juveniles) following repeated administration. When a comparator Omniscan was administered at the same dose level, the gadolinium concentrations were lower in gadopiclenol-treated adult animals compared to Omniscan-treated adult animals in all tissues and both sexes, with the exception of kidney and liver of adult males after repeated dosing with equivalent gadolinium mean concentrations.

In the pre- and postnatal development (PPND) study, in which the dams were treated at dose levels of 2.5, 5 and 10 mmol/kg, gadolinium was quantified in almost all pups, with the highest levels again seen in the kidneys, femur, skin, liver, brain and cerebellum, followed by plasma. The levels in brain/cerebellum and plasma of the pups were up to 14% and 11%, respectively, of the levels measured in dams, whereas in other tissues the levels in pups were much lower (up to 0.96%).

In a separate juvenile toxicity study in which gadopiclenol was administered at dose levels of 0.6, 1.25 and 2.5 mmol/kg, in general comparable results were observed, with the highest gadolinium concentrations measured in kidneys, followed by the femur, the brain, the cerebellum, the liver and the skin. Generally, higher concentrations were seen following the repeated dosing (2.4-3.6x), with the exception of the brain and cerebellum, which were ca. 0.5x lower. Following the 9-week recovery period, lower wash-out was observed in the brain, cerebellum and femur (78.1-96.1%) compared to the single administration, where the wash-out of gadolinium was over 96.5%.

A GLP-compliant *in vitro* binding study indicates a very low degree of binding of [153Gd]-gadopiclenol to plasma proteins and erythrocytes in all investigated species (rat, dog, human) which appears to be independent of the concentration.

The levels of Gd distribution to the brain were noted to be higher in juvenile rats than in adult rats. In the PPND study, the Gd concentration in the brain and cerebellum of pups was higher than that in dams. In the juvenile Gd tissue deposition study, the Gd concentration in the brain and cerebellum of juvenile rats compared to adults was up to 10.4 fold higher (following a single dose on PND10 without recovery).

Available data indicate that gadopiclenol is metabolically stable when administered intravenously. The HPLC-analysis of the plasma and urine of rats and dogs following the IV administration of (153Gd)-gadopiclenol indicated the presence of only the parental compound. Following the incubation with hepatic microsomes

from rat, dog, rabbit, monkey and humans both in the presence and absence of NADPH-generating system the percentage of the remaining parental compound was in all cases ≥ 95%, with no differences in the metabolic profiles.

The main route of excretion in rats and dogs following IV administration was renal, with renal clearance representing 75-85% of the total clearance in rats and 80-90% in dogs. Faecal excretion was relatively minor and accounted respectively for means of 4.8% (M) and 8.7% (F) in rats and 6% (M) and 5% (F) in dogs. The excretion was rapid in both species, with the elimination half-life of 0.85-1.43 h in rats and 1 hour in dogs. Within 168 hours post-dose 81.7% and 78.7% of the administered radioactivity was excreted in male and female rats. In dogs, 95-99% was excreted during the first 24 hours after administration.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Multiple GLP-compliant single dose toxicity studies were conducted in rodents (dosing up to 12 mmol/kg) and Beagle dogs (dosing up to 4 mmol/kg) with intravenous (IV) administration of gadopiclenol. These studies are considered more relevant for human risk assessment since gadopiclenol will be given as a single dose in humans. Significant exposure levels were obtained in all species.

In the single-dose acute toxicity studies in rodents, gadopiclenol induced swelling of the face and/or limbs in CD-1 mice dosed with ≥ 4 mmol/kg and SD rats dosed with 12 mmol/kg, lasting 3 to 4 hours post-dosing.

In the "expanded" single dose toxicity study in SD rats, increased kidney weights were observed in animals dosed with 10 mmol/kg (margin-of-exposure (MoE): 59-fold), accompanied by non-reversible tubular vacuolation in the kidney of animals dosed with ≥ 2.5 mmol/kg (MoE: 9-fold). Tubular cell vacuolation in the kidney, accompanied by increased kidney weights, are considered class-related effects of GBCAs without clinical relevance. In addition, swelling of the limbs was observed in male rats dosed with 10 mmol/kg (MoE: 59-fold), lasting 4 hours post-dosing.

In the expanded single-dose toxicity study in Beagle dogs, reversible tubular vacuolation in the kidney was observed in animals dosed with ≥ 1 mmol/kg (MoE: 6-fold). Two high-dose males (dosed with 4 mmol/kg, MoE: 25-fold) presented with peripapillary conus or swelling of the optic nerve on day 2, without any associated histological finding.

No NOAEL was established in mice since the lowest tested dose of 4 mmol/kg already demonstrated adverse effects. The NOAEL was considered 5 mmol/kg (MoE: 19-fold) and 4 mmol/kg (MoE: 25-fold) in rats and dogs, respectively.

2.5.4.2. Repeat dose toxicity

Multiple GLP-compliant repeat-dose toxicity studies up to 28 days, including a 28-day recovery period, were conducted in SD rats (dosing up to 10 mmol/kg/day) and Beagle dogs (dosing up to 4 mmol/kg/day) with IV administration of gadopiclenol. Significant exposure levels were obtained in both species, and no differences were observed with different gadopiclenol formulations.

Swelling of the face and/or limbs was observed in SD rats dosed with 10 mmol/kg/day in the 14-day (MoE: 33-fold) and 28-day (MoE: 42-fold) study. In addition, this was also observed in dogs dosed with 4 mmol/kg/day in the 28-day study (MoE: 32-fold).

Dose-dependent increased kidney weights were observed in rats dosed with ≥ 2.5mmol/kg (MoE: 8-fold) and dogs dosed with ≥ 1 mmol/kg/day (MoE: 6-fold). This was accompanied by partially reversible tubular vacuolation in the kidney.

In rats, dose-dependent cell vacuolation findings were also present in the liver, lungs, lymph nodes, and in several other tissues throughout the body, mainly as vacuolated/granular macrophages. These microscopic findings were partially reversible after the recovery period and were considered non-adverse.

The NOAEL in the repeat-dose toxicity study was considered 2.5 mmol/kg (MoE: 9-fold) and 2 mmol/kg (MoE: 15-fold) in rats and dogs, respectively.

2.5.4.3. Genotoxicity

Gadopiclenol demonstrated no genotoxic potential in the Ames mutagenicity assay, structural chromosome aberration assay in L5178Y mouse lymphoma cells *in vitro*, or in the micronucleus assay in bone marrow cells of SD rats *in vivo* at significant exposure levels.

2.5.4.4. Carcinogenicity

No carcinogenicity assays were performed with gadopiclenol since it will be used as a single administration in humans.

2.5.4.5. Reproductive and developmental toxicity

Fertility and early embryonic development

One exploratory and one GLP-compliant definitive fertility and early embryonic development (F-EED) study were conducted with IV administration of gadopiclenol in SD rats, with dosing up to 10 mmol/kg/day. Significant exposure levels were obtained.

Clinical signs (e.g. swelling of limbs) and findings in the kidney were observed during the F-EED study, similar to the observations in the repeat-dose toxicity studies in rats. Several animals across different dose groups were found dead after dosing. The cause of death for these males and females was unclear. However, due to minor findings at necropsy and the lack of dose-response, these deaths are likely not treatment-related.

An increased amount of abnormal sperm was observed in at the highest tested dose of 10 mmol/kg/day (MoE: 63-fold). In addition, females dosed with 10 mmol/kg/day (MoE: 62-fold) demonstrated prolonged estrous cycle lengths, resulting in a reduced total amount of cycles. However, no effect on reproductive performance was observed in both sexes. Therefore, the parenteral NOAEL in rats is 5 mmol/kg/day (MoE: 26-31 fold) and the NOAEL for reproductive performance and fertility in rats is 10 mmol/kg/day (MoE: 62-63 fold).

Embryo-fetal development

One GLP-compliant exploratory and one GLP-compliant definitive embryo-fetal development (EFD) study were conducted with IV administration of gadopiclenol in both SD rats (dosing up to 10 mmol/kg/day) and NZW rabbits (dosing up to 6 mmol/kg/day). Significant exposure levels were obtained in both species.

Clinical signs (e.g. swelling of limbs) were observed in both EFD studies in rats at the highest tested dose of 10 mmol/kg/day (MoE: 52-fold), similar to the observations in the repeat-dose toxicity studies. In the exploratory EFD study in rats, a slight increase in post-implantation loss and early resorptions was observed at the highest tested dose of 10 mmol/kg/day. This was not observed in the definitive EFD study in rats. Therefore, the maternal NOAEL is 5 mmol/kg/day (MoE: 26-fold) and the NOAEL for developmental toxicity is 10 mmol/ml/day (MoE: 52-fold) in rats.

In the exploratory EFD study in rabbits, five out of six high dose (6 mmol/kg/day) females died or were euthanised in extremis between GD16-19. These animals displayed decreased activity, difficulty breathing and decreased bodyweight, and these mortalities were considered treatment-related. Macroscopic examinations demonstrated tan discoloured kidneys. In the definitive EFD study, two high dose (5 mmol/kg/day, MoE: 57-fold) females died or were euthanised in extremis on GD18 and GD25, displaying similar findings as the high-dose animals in the exploratory study. These treatment-related deaths are of low clinical relevance since these were observed at very high dose levels with sufficient safety margins. No treatment-related effects were found on uterine implantation data at any dose level. A lower fetal body weight was observed at 5 mmol/kg/day, which was attributed to the maternotoxicity. Therefore, the maternal and fetal development of NOAEL was considered 2.5 mmol/kg/day (MoE: 24-fold) in rabbits.

Pre- and postnatal development

One GLP-compliant pre- and postnatal development (PPND) study was conducted with IV administration of gadopiclenol in SD rats, with dosing up to 10 mmol/kg/day. Significant exposure levels were obtained.

Clinical signs (e.g. swelling of face and limbs) observed at ≥ 2.5 mmol/kg/day (MoE: 13-fold) were similar to the observations in the repeat-dose toxicity studies. Two 5 mmol/kg/day and two 10 mmol/kg/day females died or were euthanised in extremis, with macroscopic findings (adherences between abdominal organs and injection site, enlarged organs and/or firm area at the injection site) considered related to the administration procedure.

At ≥ 5 mmol/kg/day (MoE: 19-fold), a slightly higher percentage of pre-birth loss compared to concurrent and historical controls was observed. This was mainly driven by an individual case, and no similar observation/trend was seen in the EFD studies. The estimated live birth index was also slightly lower in these treatment groups. Because of the low magnitude of these findings, the toxicological significance was considered low. However, it is unclear whether these findings are treatment-related. Together with the clinical signs (e.g. swelling of the face and limbs), no maternal NOAEL could be established in this PPND study in rats.

In F1 pups, exposure to gadopiclenol was confirmed on PND 20/21 from dams treated at ≥ 5 mmol/kg/day (MoE: 19-fold). At these dose levels, a reduced pup body weight gain from birth, leading to reduced body weight up to 4 weeks of age for females and 15 weeks of age for males was observed. However, there was no effect on pre-weaning functional development, post-weaning behaviour or reproductive performance. Therefore, the NOAEL for post-natal development of the offspring was considered 10 mmol/kg/day (MoE: 55-fold).

Juvenile toxicity

One non-GLP exploratory and one GLP-compliant definitive juvenile toxicity study were conducted with gadopiclenol in neonatal and juvenile SD rats. Gadopiclenol was tested in neonatal and juvenile rats following a single IV administration at 10 days of age or repeated IV administrations every four days from 10 days to 30 days of age (a total of six administrations). Significant exposure levels were obtained in all studies. Gd concentrations were measured at various timepoints in several organs.

Gadopiclenol was well tolerated in juvenile animals after single and repeat-dose administration and did not induce adverse effects. Reversible decreases of ferritin in males dosed with ≥ 0.6 mmol/kg/occ (MoE: 2-fold) and in females treated with ≥ 1.25 mmol/kg/occ (MoE: 4-fold) was observed after repeated administrations. In addition, reversible decreases of serum iron in females dosed with ≥ 0.6 mmol/kg/occ (MoE: 2-fold) were observed, which was associated with reversible increased iron urinary excretion in the high-dose animals (MoE: 8-fold). These findings were not observed in adult animals in the repeat-dose toxicity studies but are of low magnitude.

Similar as in adults animals, cortical tubular vacuolation in the kidneys was noted after repeated administrations at all dose levels. This was completely reversible after the recovery period. The NOAEL in juvenile rats was considered 2.5 mmol/kg/day (MoE: 8-fold).

An additional GLP-compliant study was conducted to compare Gd distribution and tissue retention in juvenile and adult rats after single or repeated administration (every 4 days for 8 weeks, a total of 15 administrations) at 0.6 mmol/kg/occ. This study included a group of animals dosed with 0.6 mmol/kg/occ gadodiamide (Omniscan), as a comparator. The only treatment-related finding in this study was reversible tubular vacuolation in the kidneys of both juvenile and adult animals.

2.5.4.6. Toxicokinetic data

In rats, both on day 1 and following the repeated administration the exposure generally increased dose-proportionally in the range 0.6-5 mmol/kg and slightly more than dose-proportionately from 5 to 10 mmol/kg. In rabbits, the exposure generally increased dose-proportionately on day 1, but slightly more than dose-proportionately following repeated exposure, especially in the range from mid- to high dose (2.5-5 mmol/kg). In dogs, mean AUC0-t increased in a dose-related manner. The AUC0-t values on day 1 and following the repeated exposure were comparable, indicating the lack of accumulation of gadopiclenol. In the rat FEED, EFD and PPND studies at the highest dose level of 10 mmol/kg, the exposure at the end of treatment appeared to be lower than on day 1, whereas in general comparable exposure was seen at the lower two dose levels. There were no sex differences observed in any species.

2.5.4.7. Local tolerance

Local tolerance at the injection site was assessed in the single- and repeat-dose toxicity studies in rats and dogs. Some adverse effects were observed in both control and gadopiclenol-treated animals were related to the administration procedure and were not considered indicative of local toxicity caused by gadopiclenol. However, signs of intolerance (discolouration of the ears) were noted in the EFD study in rabbits after repeated administrations at the highest dose of 5 mmol/kg/day (MoE: 57), which did not resolve. In addition, dams receiving 10 mmol/kg gadopiclenol (MoE: 55-fold) in the rat PPND study had a higher incidence of injection site reactions, considered related to the treatment but exacerbated by gadopiclenol.

A dedicated study was performed in rabbits receiving a single dose via IV, perivenous (PV) or intra-arterial (IA). IV and IA administration of 0.6 mmol/kg gadopiclenol resulted in transient erythema, associated with histopathological changes after IA administration, which were completely resolved on day 4. PV administration of 0.25 mmol/kg gadopiclenol resulted in erythema and edema and associated histopathological changes, which were not resolved on day 4.

In conclusion, gadopiclenol was well tolerated following a single administration in rats (IV), dogs (IV) and rabbits (IV, IA), or following repeated IV injections in rats and dogs, but irritation was observed following single PV and repeated IV administrations in rabbits.

2.5.4.8. Other toxicity studies

Antigenicity

Repeat-dose toxicity studies did not indicate any potential for gadopiclenol to invoke antigenicity. Therefore, no dedicated antigenicity studies were performed with gadopiclenol.

Immunotoxicity

No dedicated immunotoxicity studies were performed with gadopiclenol.

Dependence

Repeat-dose toxicity studies did not indicate any potential for gadopiclenol to invoke dependency. Therefore, no dedicated dependence studies were performed with gadopiclenol.

Metabolites

No studies were performed with metabolites, since gadopiclenol is not metabolised.

Impurities

The genotoxicity of possible impurities, including those coming from the drug substance, starting materials, reagents, solvents, intermediates, by-products and degradation products, were evaluated in a series of in silico platforms. Predicted genotoxic impurities were further evaluated *in vitro*, and subsequently classified and controlled, in line with ICH Guideline M7.

Immediate hypersensitivity

To assess the potential of gadopiclenol to induce immediate hypersensitivity, male guinea pigs received two subcutaneous "induction" injections on day 1 and 7, followed by an IV challenge injection on day 21. IV injection of gadopiclenol did not induce any signs of immediate hypersensitivity in guinea pigs.

Nephrogenic systemic fibrosis

Several supportive non-GLP non-clinical studies were conducted to contribute to a better understanding of the possible relation between nephrogenic systemic fibrosis (NSF) and repeated gadopiclenol exposure. It was suggested that the low kinetic stability of the linear GBCAs (and the consequential possible release of free toxic Gd in the body) was a risk factor to trigger NSF symptoms.

Multiple studies were conducted in renally-impaired male rats with or without hyperphosphoraemia and juvenile rats dosed for 5 days with 2.5 mmol/kg/day gadopiclenol, other macrocyclic or linear GBCAs. These studies generally demonstrated numerous skin lesions with the linear GBCA. No skin lesions were observed with gadopiclenol and other macrocyclic GBCAs. The total Gd concentrations in skin and bone of gadopiclenol-

treated rats were lower than those of rats treated with the linear GBCA. There was no evidence for release of dissociated and soluble Gd in gadoplicenol-treated rats. In conclusion, these studies did not indicate a profibrotic risk associated with gadopiclenol administration.

Gd deposition

To address the concern of potential Gd deposition in the brain, multiple non-GLP non-clinical imaging studies were performed.

In the first study, healthy rats received 20 IV administrations of 0.6 mmol/kg/occ gadopiclenol or linear GBCAs over a period of 5 weeks. Repeated administration of the linear GBCAs was associated with T1 signal hyperintensity in the deep cerebellar nuclei with Gd deposition in the brain, in contrast to gadopiclenol for which no such effect on T1 signal was observed.

In a second study, healthy rats received a single IV dose 1.2 mmol/kg gadopiclenol or a linear GBCA. The tested GBCAs enhanced the 4th ventricle compartment (CSF and choroid plexus) immediately after injection with a decrease of the enhancement all along the follow-up, independent of the molecular structure of the GBCA. However, the follow-up in this study was not long enough to determine the elimination half live, and therefore not very indicative of potential deposition.

In the final study, healthy rats received 2.4 mmol/kg/week gadopiclenol or another GBCA (linear or macrocyclic) over a period of 5 weeks. Animals were sacrificed after 1, 5 or 12 months after the treatment period. In general, long-term Gd exposure was lower after gadopiclenol and other macrocyclic GBCAs as compared to the linear GBCA. In terms of speciation and Gd spatial distribution in brain and kidneys, gadopiclenol behaves like other macrocyclic GBCAs. Gd presence in tissues had no impact on renal function and was not associated with abnormalities in tissues.

2.5.5. Ecotoxicity/environmental risk assessment

Table 3. Summary of main study results

Substance (INN/Invented Name): Gadopiclenol			
CAS-number (if available): 933983-75-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	-4.2	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-4.2	not B
	BCF	Not investigated	
Persistence	ready biodegradability	not readily biodegradable	
Toxicity	NOEC algae NOEC crustacea	>100 mg/L >11 mg/L >11 mg/L	not T

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

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Raphidocelis subcapitata*	OECD 201	EC10	>100	mg/L	growth rate and yield (no effects observed)
Daphnia sp. Reproduction Test	OECD 211	EC10	>11	mg/L	mortality, reproduction and growth (no effects observed)
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	EC10	>11	mg/L	survival, reproduction and growth (no effects observed)
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	µg/L	Respiration (no effects observed)
Phase IIb Studies					
Sediment dwelling organism	OECD 218	EC10	≥3138	mg/kg	normalised to 10% o.c.

Gadopiclenol is not a PBT nor vPvB substance. Regarding the PBT assessment, the P-criteria exceed the threshold for being persistent in water. However, since the log K_{ow} < 4.5, no further assessment is needed.

2.5.6. Discussion on non-clinical aspects

At the time the pivotal safety pharmacology and toxicology studies were conducted, the sites operated in compliance with GLP. Overall, the studies can be accepted and no GLP inspections have been considered warranted.

All non-clinical pre-requisites supporting the development of gadopiclenol have been fulfilled in compliance with International Conference on Harmonization (ICH M3) and United States-Food and Drug Administration (US-FDA) requirements.

Pharmacology

The mechanism of the pharmacodynamic effect of Gd on MRI signal is well known for many decades. Gadolinium enhances MR signal by modifying relaxation times of surrounding water protons in blood and tissues, thus increasing signal intensity in T1-weighted sequences and reducing signal intensity in T2-weighed sequences. The performance of gadopiclenol in detecting very early-stage tumoural tissue and detecting more lesions have been confirmed in additional experimental imaging studies (T1 enhancement) in rats and mice with implanted brain tumours in different stages in different imaging set-ups. Overall, these results showed that gadopiclenol at half-dose (0.05 mmol/kg) was as effective as the reference products at 0.1 mmol/kg. These non-clinical studies can be considered predictive of human efficacy, which is further illustrated with consistent results from clinical trials in patients with brain lesions.

A proof of concept has been obtained for the efficacy of gadopiclenol as an MR contrast agent for brain tumour imaging in rats with implanted brain tumours and in a mouse model of brain metastasis. Since gadopiclenol is intended for diagnostic purposes only, it is considered acceptable that no secondary pharmacodynamic studies have been conducted with it.

Regarding the safety pharmacology, studies showed an acceptable tolerance of the cardiovascular system, the respiratory system as well as the central nervous system to gadopiclenol. In a hERG test, gadopiclenol induced a concentration-dependent inhibition of hERG tail current amplitude. This effect was considered due to the hyperosmolarity of the tested solutions and high molecular weight of gadopiclenol, and not a deleterious effect on cardiac repolarisation. This was also observed for other approved GBCAs. The study in conscious dogs among the 2 studies performed to further assess any potential effect of gadoplicenol on the cardiovascular system, was considered a better model to predict QT prolongation potential. With regards to the renal function, since the kidney is considered as a potential target organ for gadopiclenol, an additional safety pharmacology study was performed to assess any potential effect of gadopiclenol on renal functions. At all dose levels, an increased urine osmolality was observed compared to controls. The main findings of general toxicity studies consisted of (partial reversible) kidney tubular vacuolations. This is seen with all GBCAs and is known to be of no physiological consequence on the kidney function. In conclusion, the safety pharmacology studies showed an acceptable tolerance of the renal functions to gadopiclenol.

No pharmacodynamic drug interaction study was performed; this was found acceptable.

Pharmacokinetics

The pharmacokinetic properties of gadopiclenol were assessed in a comprehensive battery of GLP-compliant studies in rats and dogs. For most pharmacokinetic studies, radiolabelled [153Gd]-gadopiclenol was utilised, and the total radioactivity was measured by γ-counting. The exposure in the toxicological studies was assessed by measuring gadopiclenol content in plasma by a validated LC-MS/MS method. The validation was adequate regarding calibration, accuracy, precision, matrix effect and dilution integrity. Stability in a matrix

at room temperature and long-term storage stability are considered to be sufficiently covered. Furthermore, in a number of rat studies, the total content of gadolinium was determined in selected tissues from a selected number of animals by validated ICP-MS methods at final necropsy and following the recovery period, following the tissue digestion with concentrated nitric acid and subsequent dilution.

Following intravenous administration, gadopiclenol is quickly cleared from plasma and is rapidly and extensively distributed across all systemic tissues, with the distribution profiles being overall comparable between the species, between juvenile and adult animals and between the sexes.

It was noted that the distribution of gadopiclenol to the brain of adult rats in the QWBA study was very limited (0.09%, 10 mins post IV administration of radiolabelled gadopiclenol). The applicant states that gadopiclenol does not cross in the intact blood-brain barrier (BBB); but that it "is intended for use in humans as a contrast agent for CNS MR imaging in patients with possible BBB disruption." In early scientific advice requests (e.g. EMA/CHMP/SAWP/431941/2017), this was considered as part of the proposed indication "MRI in the brain (intracranial), spine and associated tissues to detect and visualise areas with disruption of the BBB and/or abnormal vascularity". However, this was not specified in the current indication. The applicant was therefore asked to provide a discussion on the limited distribution of gadopiclenol to the brain and any associated implications for clinical efficacy. The applicant has amended the indication statement to clarify that the product is intended for MRI contrast enhancement of the brain, spine and associated structures to improve the detection and visualisation of lesions with disruption of the BBB, blood-spinal cord barrier (BSCB) and/or abnormal vascularity. Therefore, the limited distribution to the brain observed in healthy animals is less of a concern, as it is assumed that increased permeability of the BBB/BSCB would allow for increased gadopiclenol distribution to the CNS. This is supported by the contrast enhancement observed following gadopiclenol administration in the rat glioma model.

The levels of Gd distribution to the brain were noted to be higher in juvenile rats than in adult rats. In the PPND study, the Gd concentration in the brain/cerebellum of pups was higher than that in dams (up to 14%). In the juvenile Gd tissue deposition study, the Gd concentration in the brain/cerebellum of juvenile rats compared to adults was up to 10.4-fold higher (following a single dose of PND10 without recovery. The applicant has provided a justification that the higher levels of Gd in the brain of juvenile rats are likely to be caused by immaturity of the blood-brain barrier, which achieves its full functionality only by PND 33-40. This justification was substantiated by literature references (De Schaepdrijver LM et al.; 2013)[1] and two mice studies with another GBCA, Dotarem, demonstrating that the observed effect has also been observed for other GBCA's. Furthermore, if gadopiclenol was a P-gp substrate, a higher distribution of Gd to tissues in which P-gp is expressed, such as the liver, kidneys and GIT, could be expected, which was not the case. Finally, P-gp substrates are generally hydrophobic molecules. It is therefore unlikely that gadopiclenol is a substrate for P-gp based on its physicochemical properties.

The volume of distribution in rats and dogs is consistent with the distribution of gadopiclenol into extracellular water. A very low degree of binding of [^{153}Gd]-gadopiclenol to plasma proteins and erythrocytes was observed *in vitro* in all investigated species (rat, dog, human), which appears to be independent of the concentration. The highest gadolinium levels following intravenous administration were consistently measured in kidneys, liver, skeletal muscles, skin, brain/cerebellum and bone mineral.

[1] De Schaepdrijver LM et al. (2013). Juvenile animal toxicity assessments: decision strategies and study design. Pediatr Drug Dev. 201–221.

Report 8_20_01237-2.0 on UV spectrophotometry of gadopiclenol indicates that gadopiclenol absorbs at 271 nm, which is outside the range of 290-700 nm specified in the ICH S10 guideline. Based on this, it is agreed that gadopiclenol can be considered as non-phototoxic.

Gadopiclenol can cross the placenta and is also excreted in milk. While the applicant states that gadopiclenol can penetrate the placenta only in small quantities, the radioactivity levels measured in the placenta 10 minutes post-dose were comparable with those measured in other tissues (651 nmol eq/g vs 30-1035 nmol eq/g). The measurements of gadopiclenol in milk were conducted only at two-time points, with the earliest measurement conducted at 6 hours post-dose. Considering the rapid distribution of gadopiclenol across all systemic tissues, as indicated by the QWBA studies, it is therefore questioned whether earlier higher concentrations of gadopiclenol in mammary glands and milk could not have been missed. Thus, while the applicant states that gadopiclenol is excreted in milk only in small quantities, this cannot be corroborated by the available data. Continuing or discontinuing breastfeeding for 24 hours after administration of gadopiclenol should be at the discretion of the doctor and lactating mother (see section 4.6 of the SmPC in line with CHMP Art. 31 referral for GdCA).

Since gadopiclenol is a non-ionic macrocyclic GBCA with a high kinetic stability, this suggests a lower risk for NSF induction. The proposed wording is, therefore, acceptable. It is also acknowledged that the bioavailability of gadopiclenol via the oral route is low, amounting to only 3.7% relative to IV administration. Thus it can be agreed that systemic exposure of a sucking child to gadolinium from the amounts in breast milk is likely to be negligible.

In pups, 0.3% and 0.2% of the administered dose was recovered 6 and 24 hours post-dose. In the PPND study, pup exposure to gadolinium was demonstrated in nearly all pups, with levels measured in the tissues of the pups lower than in the respective tissues of the dams. The highest levels of gadolinium in pups compared to the dams were seen in brain/cerebellum and plasma (up to 14% and 11% of the dam levels).

Gadopiclenol is metabolically stable when administered intravenously. The main route of excretion in rats and dogs following IV administration was renal, with faecal excretion accounting only for 4.8-8.7% in rats and 5-6% in dogs. The excretion was rapid, with T1/2 of 0.9-1.4 h in rats and 1 h in dogs.

Of note, four non-clinical studies (Investigation of Small Fiber Neuropathy (SFN) after single administration of gadolinium based-contrasts agents (GBCAs) in mice (ER-21-00003); Investigation of Small Fiber Neuropathy (SFN) after repeated administrations of gadolinium based-contrasts agents (GBCAs) in mice (ER-21-00007); Early (W1, M1) and long-term (M5) gadolinium retention after a dose of 0.05 mmol/kg of gadopiclenol vs 0.1 mmol/kg dose of already marketed macrocyclic GBCAs in rat (ER-21-00015); Exhaustive speciation of Gd retained after repeated injections of 0.05 mmol/kg of gadopiclenol vs 0.1 mmol/kg of gadobutrol in rat (ER-21-00011)) are currently ongoing in the context of Gd accumulation and retention in the body (see 2.7.2. and 2.7.3.), the provision of the results (final study reports) are considered post-authorisation measures as per the approved RMP v0.3.

Toxicology

General toxicology was evaluated in studies up to 28 days in duration following IV administration of gadopiclenol to mice, rats and dogs. In the single-dose acute toxicity studies in rodents, gadopiclenol induced swelling of the face and/or limbs in CD-1 mice dosed with $\geq$ 4 mmol/kg and SD rats dosed with 12 mmol/kg, lasting 3 to 4 hours post-dosing. Similarly, this was also observed in SD rats dosed with 10 mmol/kg/day in the 14-day (MoE: 33-fold) and 28-day (MoE: 42-fold) study. In addition, this was also observed in dogs dosed with 4 mmol/kg/day in the 28-day study (MoE: 32-fold). Therefore, a NOAEL of 4 mmol/kg/day in dogs, as indicated by the applicant, was not agreed. Although significant exposure margins were obtained in

all studies, the applicant was asked to discuss the potential mechanism and subsequent clinical relevance of this finding. In addition, swelling of the optic nerve was observed in two animals in the high-dose group in the expanded single-dose study in dogs. No similar observation was made in repeat-dose toxicity studies. Intravenous injection of high volumes of a hyperosmolar compound with a relatively high viscosity can lead to swelling of the face and limbs in rats and dogs and animals showed adaptation over time. Swelling of the optic nerve in dogs completely recovered and was not accompanied by any histopathological finding at necropsy. Since the finding was bilateral in one male dog and unilateral in another male dog, it is unlikely to be a systemic condition and not associated with the swelling of the face and limbs. In addition, sufficient safety margins were obtained since the No Observed Effect levels (NOELs) were 22 times and 8 times higher in dogs and rats, respectively. Therefore, it can be agreed that the clinical relevance of swelling of the face and limbs is considered negligible.

Gadopiclenol demonstrated no genotoxic potential in a standard genotoxicity assay battery. No carcinogenicity study was conducted Which was considered acceptable in line with ICH Guideline S1 since it will be used as a single administration in humans.

A fertility study was conducted in male and female rats, embryofetal development studies were performed in pregnant rats and rabbits, and a pre/post-natal development toxicity study was conducted in rats. Overall, no clear treatment-related effect on reproductive and developmental parameters were observed in the F-EED, EFD and PPND studies, and sufficient exposure levels were obtained in all studies. This is adequately reflected in SmPC Section 4.6.

Furthermore, a juvenile toxicity study in rats and a study comparing Gd tissue retention in juvenile and adult rats were conducted. Gadopiclenol was well tolerated in juvenile animals after single and repeat-dose administration. While it is agreed that the findings of decreased ferritin in males and reduced serum iron levels in females were reversible, these effects were observed at doses ≥0.6 mmol/kg, which provides (at best) a 2-fold MoE relative to clinical exposure in paediatric patients. The applicant was asked to comment on a potential relationship between gadopiclenol exposure and iron balance. The applicant has presented historical control data for serum iron, serum ferritin and urine iron levels in males and females at time points relevant to the juvenile toxicity study and argues that the effects seen were "of low magnitude with values globally in the same range of historical data". Indeed, it is noted that there is some disparity between the historical control values and the control values in this study. Given (1) this apparent variability, (2) the fact that the biggest change in treated groups vs controls was following repeat administration and gadopiclenol is intended for single dosing in the clinical setting, and (3) that the effects were reversible after the treatment-free recovery period, it can be agreed that the observed effects are unlikely to be of clinical concern despite the narrow exposure margin. The applicant further suggests that immaturity and sex differences in the postnatal development of renal functions could explain the differences observed. However, differences between males and females are still apparent at later time points following recovery. An additional GLP-compliant study was conducted to compare Gd distribution and tissue retention in juvenile and adult rats after single or repeated administration (every 4 days for 8 weeks, a total of 15 administrations) at 0.6 mmol/kg/occ. This study included a group of animals dosed with 0.6 mmol/kg/occ gadodiamide (Omniscan), as a comparator. The results on Gd retention are discussed above. The only treatment-related finding in this study (reversible tubular vacuolation in the kidneys of both juvenile and adult animals) is in line with the previous studies. These findings are similar to the single-dose toxicity studies and are considered non-adverse class-related effects of GBCAs without clinical relevance.

Gadopiclenol was well tolerated following a single or repeated intravenous administration in rats and dogs, but irritation was observed following single perivascular and repeated intravenous administrations in rabbits, indicating that misadministration must be avoided.

The genotoxicity of possible impurities was evaluated in a series of *in silico* platforms and predicted genotoxic impurities were further evaluated *in vitro* and subsequently classified and controlled. Since sufficient exposure levels were obtained in the non-clinical studies, impurities in the different batches are likely sufficiently tested. The impurity limits are considered toxicologically qualified based on the dog study.

No dedicated antigenicity, immunotoxicity, dependence or metabolite studies were conducted, this was found acceptable based on the results of the repeat dose toxicology studies and on the well-known GBCAs profile.

In the 1-year Gd retention study, for all three GBCAs tested, Gd exposition along the 12 months of follow-up was higher for females than for males (females after gadobutrol are more exposed to Gd by 66% versus males, after gadodiamide by 52% versus males and gadopiclenol by 30% versus males). The applicant was asked to discuss the observed difference between males and females and between GBCAs. The applicant has provided details on the calculations used to determine Gd exposure. The %ID/g accounts for animal body weight by dividing by the total quantity of Gd injected. The applicant notes that if the raw data in nmol/g is used, males would be considered as more exposed. Similarly, if the data are presented as nmol/organ or %ID/organ, females are less exposed than males. This is unsurprising, as these latter calculations do not account for the body weight of the animals and/or the organ weights, both of which are higher in males. Therefore, it would appear that when exposure in males is calculated by nnmol/g, nmol/organ or %ID/organ, exposure is higher than in females simply because males received a greater quantity of Gd. It is still unclear why exposure is higher in females than in males when exposure is corrected for body weight, although it is accepted that this does not appear specific to gadopiclenol. Based on similar findings for all GBCAs tested, including the approved gadobutrol, the effect is not expected to be of clinical relevance.

In addition, in the Gd speciation report of the 1-year follow-up study, the "Perspectives" list a number of outstanding analyses. An update on the outstanding analyses listed as "Perspectives" in the one-year retention study report and a number of new study reports (global speciation report for Gd DR-21-00453-RAP, Gd speciation in bone DR-21-00140-RAP and LA-ICP-MS analysis in rat tissue DR21-00449-RAP) were submitted. The data in relation to the brain appear to align with the information originally presented in the initial submission. None of the additional data would impact on the safety assessment of gadopiclenol.

In the non-clinical toxicity studies, no differences between the different formulations were observed.

Environmental Risk Assessment

Gadopiclenol is not a PBT nor vPvB substance. Regarding the PBT assessment, the P-criteria exceed the threshold for being persistent in water. However, since the log Kow < 4.5, no further assessment is needed.

In conclusion, gadopiclenol is not a PBT substance and, considering the above data, is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

There are no objections to marketing authorisation from a non-clinical point of view.

Of note, four non-clinical studies are currently ongoing in the context of Gd accumulation and retention in the body (see 2.7.2. and 2.7.3.), the provision of the results (final study reports) are considered post-authorisation measures as per the approved RMP v0.3.

2.6. Clinical aspects

2.6.1. Introduction

Gadopiclenol is an extracellular contrast agent for magnetic resonance imaging (MRI) that belongs to the class of gadolinium-based contrast agents (GBCAs). Gadolinium is tightly bound in a macrocyclic complex with a high stability in the chelate.

When placed in a magnetic field, gadopiclenol produces contrast enhancement by shortening of the relaxation times of protons in plasma, referred to as relaxivity. Both T1 and T2 relaxation times were shortened. The T1 shortening effect tends to dominate and is dependent on the relaxivity of gadopiclenol. Visualisation of normal and pathological tissue depends, in part, on the variations in the radiofrequency signal intensity that occur with differences in proton density, differences in the T1 relaxation times, and differences in the T2 relaxation times.

Gadopiclenol is recommended to be administered as an intravenous bolus injection, manually or by power injector, at a flow rate of approximately 2 mL/second. A flush of physiological saline solution after the injection is recommended. The recommended dose of gadopiclenol is 0.05mmol/kg body weight (0.1mL/kg). This dose was selected based on the pharmacodynamic parameter contrast to noise ratio (CNR). A dose of 0.05 mmol/kg was identified as optimal, yielding appropriate CNR and contrast enhancement.

GCP aspects

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

The applicant states that all the clinical studies in this programme were conducted in accordance with the principles of Good Clinical Practice (GCP), including the directions set forth in relevant regulatory guidance (such as International Council for Harmonization [ICH] E6) and the Declaration of Helsinki.

A routine GCP inspection has taken place for the clinical studies GDX-44-007 and GDX-44-011. An integrated inspection report (GCP/2022/006) on behalf of the EMA has been finalised (30/09/2022) concluded that the trials were conducted in accordance with internationally accepted ethical standards.

- **Tabular overview of clinical studies**

The clinical development programme of gadopiclenol consists of the following completed studies:

- 1 Phase I/IIa first in human study (GDX-44-003) evaluating the safety, PK and PD of gadopiclenol following single ascending dose level administration in healthy subjects (phase I) and in patients with brain lesions (phase IIa)
- 2 Phase I studies:
  - 1 Phase I study evaluating PK of gadopiclenol in patients with mild to severe renal impairment (GDX-44-005)
  - 1 Phase I thorough QT study (GDX-44-006)

- 1 Phase IIa study assessing the diagnostic performance of gadopiclenol-enhanced MRI for hepatocellular carcinoma using a standard of reference based on previous imaging and/or histology (GDX-44-008)
- 1 Phase IIB study (GDX-44-004) to determine a safe and effective dose of gadopiclenol based on a comparison of Contrast to Noise Ratio (CNR) between four doses of gadopiclenol and gadobenate dimeglumine (MultiHance) at 0.1 mmol/kg in patients with central nervous system (CNS) lesions.
- 1 Phase II study evaluating the PK profile, safety and efficacy of gadopiclenol in paediatric patients from 2 to 17 years of age (GDX-44-007)
- 2 phase III studies evaluating the safety and efficacy of gadopiclenol for CNS MRI (GDX-44-010) and MRI of other body regions (GDX-44-011) compared to gadobutrol.

A Phase I study (GDX-44-013) is ongoing to assess the PK profile and safety of gadopiclenol in Japanese healthy volunteers. A phase II study (GDX-44-015) is ongoing to assess the PK profile, safety and efficacy of gadopiclenol in paediatric patients under 2 years old.

Table 4 below presents a summary of the completed clinical studies:

Table 4. Clinical Development Programme for Gadopiclenol - Completed Studies

Study **Year** **Location**	**Study design**	**Primary Objective**	**Gadopiclenol dose (mmol/kg)**	**Number of subjects (FAS)**
GDX-44-003 2013-2015 1 centre in Europe	Phase I, double-blind, randomised, placebo-controlled	PK, PD profile and safety of gadopiclenol in healthy volunteers	0.025 0.05 0.075 0.1 0.2 0.3	6 per dose (total=36) + 18 receiving placebo
	Phase IIa, open label, single ascending dose	PK, PD profile and safety of gadopiclenol in patients with brain lesions	0.05 0.075 0.1 0.2	3 per dose (Total=12)
GDX-44-005 2016-2018 2 centres in Europe	Phase I, open-label, non-randomised, successive cohorts design,	PK (plasma and urine) and safety in patients with mild to severe renal impairment. Dialysability of gadopiclenol in patients with end stage renal disease (ESRD) requiring haemodialysis.	0.1	40

Study **Year** **Location**	**Study design**	**Primary Objective**	**Gadopiclenol dose (mmol/kg)**	**Number of subjects (FAS)**
GDX-44-006 2017-2018 1 centre in Europe	Phase I, randomised, cross-over double-blind placebo-controlled and open-label positive-controlled (moxifloxacin)	Cardiac safety (QT and QTc intervals), clinical, biological safety, plasma concentrations, and long-term elimination profile of gadopiclenol in healthy volunteers.	0.1 and 0.3	48
GDX-44-004 2016-2018 28 centres in Europe, USA, Mexico, South Korea	Phase IIb, randomised, double-blind, controlled, parallel dose groups, cross-over	To determine a safe and effective dose of gadopiclenol based on a comparison of CNR with gadobenate dimeglumine 0.1 mmol/kg	0.025 0.05 0.1 0.2	57 62 61 60 Total=240
GDX-44-008 2016-2019 2 centres in Europe	Phase IIa, exploratory, non-randomised, open-label, two cohorts, two doses	Diagnostic value for HCC of gadopiclenol-enhanced MRI in patients with small suspected nodules and chronic liver disease	0.1 0.05	30 10
GDX-44-007 2018-2020 16 centres in Europe	Phase II, open-label, uncontrolled,	PK, safety and efficacy of gadopiclenol in paediatric patients 2-17 years	0.05	60 in CNS cohort + 20 in Body cohort
GDX-44-010 2019-2020 33 centres in Europe, USA, Mexico, Taiwan, South Korea	Phase III, randomised, double-blind, controlled, and cross-over; comparator: gadobutrol 0.1 mmol/kg	Efficacy and safety of gadopiclenol in MRI for CNS imaging	0.05	256
GDX-44-011 2019-2020 33 centres in Europe, USA, Mexico, South Korea	Phase III, randomised, double-blind, controlled, and cross-over; comparator: gadobutrol 0.1 mmol/kg	Efficacy and safety of gadopiclenol in MRI for body imaging	0.05	304

Abbreviations: FAS: Full Analysis Set; PK: Pharmacokinetic; PD: Pharmacodynamic; MRI: Magnetic Resonance Imaging; CNS: Central Nervous System; CNR: Contrast to Noise Ratio; HCC: Hepatocellular carcinoma;

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The pharmacokinetics (PK) of gadopiclenol in humans were first evaluated in healthy volunteers and patients with brain lesions in the Phase I/IIa study GDX-44-003 and pharmacodynamics.

Furthermore, a PK study in paediatric patients from 2 to 17 years of age who received gadopiclenol by intravenous (IV) route at 0.05 mmol/kg was carried out according to a population PK (PopPK) approach (GDX 44-007).

Finally, in study GDX-44-005 the PK profile of gadopiclenol was studied in healthy volunteers and patients with renal impairment. In this study, a group of patients with end-stage renal disease (ESRD) was also included to assess the dialysability of gadopiclenol. An additional population PK analysis was performed, adding the healthy volunteers and patients with mild to severe renal impairment from GDX-44-005 study to the previously developed model from study GDX-44-007. The aim of this PopPK analysis was to predict PK parameters in patients with renal impairment and evaluate any difference with adults with normal renal function when exposed at the same dose.

In the GDX-44-006 study, the electrocardiographic safety of gadopiclenol at 0.1 mmol/kg and at the supra-clinical dose of 0.3 mmol/kg was studied. Plasma concentrations of gadopiclenol were measured over time to obtain values at the same timepoints as ECG measurements for these two doses and long-term elimination was evaluated in urine samples.

Absorption

Elucirem is administered only via the intravenous route. Consequently, the absolute bioavailability of gadopiclenol is 100%.

The concentration-time plots of gadopiclenol show typical pharmacokinetic profiles for an intravenously administered drug. Gadopiclenol rapidly reaches C_{max} in 0.03 – 0.08 h after intravenous administration, followed by an elimination phase right after reaching C_{max}. For the recommended dose of 0.05 mmol/kg, the mean C_{max} and AUC_{inf} for gadopiclenol are 525 µg/mL and 569 µg/mL*h, respectively.

After an intravenous dose of 0.1 to 0.2 mL/kg BW (equivalent respectively to 0.05 and 0.1 mmol/kg BW), the Cmax was 525 ± 70 µg/mL and 992 ± 233 µg/mL, respectively. The Cmax increased 1.1-fold, 1.1-fold and 1.4-fold and the AUCinf increased 1.5-fold, 2.5-fold and 8.7-fold in patients with mild, moderate and severe renal impairment, respectively after a dose of 0.2 mL/kg BW (equivalent to 0.1 mmol/kg BW).

In addition, the increase in Cmax and AUCinf is expected to be similar with a dose of 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) based on the results of pharmacokinetic population pharmacokinetic simulations.

Formulation development for gadopiclenol

Two different intravenous formulations (formulation A and B) were developed and used during the clinical studies. The amount and concentration of the active substance gadopiclenol is the same for both formulations. Both formulations are aqueous solutions. The main difference between the formulations is the amount of the chelating agent to complex free gadolinium, the amount of calcium chloride to complex the excess of the chelating agent and the buffer with an adjustment of the pH.

Pharmacokinetic data is only available for formulation A. However, based on the known differences between formulation A and B, a difference in pharmacokinetics between intravenous formulations A and B is not expected, and no bioequivalence study is required to demonstrate comparability between both formulations.

Distribution

The volume of distribution of gadopiclenol is between 13 – 18.5 L for the different doses assessed in study GDX-44-003 Phase I. The relatively low distribution volume is indicative that gadopiclenol only distributes rapidly into the extracellular fluid. In the renal impairment study GDX-44-005 a similar volume of distribution was demonstrated for the healthy volunteers (cohort 1) after a dose of 0.1 mmol/kg. After a dose of 0.1 ml/kg BW (equivalent to 0.05 mmol/kg BW) the distribution volume Vd was 12.9 ± 1.7 L.

The *in vitro* binding of (^{153}Gd)-gadopiclenol to human plasma proteins was assessed in study GDX-33-007. The results of this study showed that protein binding is negligible and independent of the gadopiclenol concentration, as (^{153}Gd)-gadopiclenol bound 0.0–1.8% to human plasma proteins and 0.0-0.1% to human red blood cells.

Elimination

Metabolism

Gadopiclenol is not metabolised as 98% of the administered dose was retrieved in the urine in unchanged form in study GDX-44-003 (phase I) and study GDX-44-005 (cohort 1).

The lack of metabolism is also confirmed by *in vitro* data of study GDX-33-008, wherein pooled human liver microsomes were incubated with ^{153}Gd-gadopiclenol. After 120 minutes, ≥95% of the ^{153}Gd-gadopiclenol remained in unchanged form. The results were similar when heat-inactivated pooled human liver microsomes (negative controls) were incubated with ^{153}Gd-gadopiclenol, indicating that ^{153}Gd-gadopiclenol is not metabolised.

Excretion

Gadopiclenol is excreted renally in an unchanged form. For the investigated 0.025 – 0.050 mmol/kg and higher doses, 98% of gadopiclenol in unchanged form was collected from the urine within 24 and 48 hours, respectively. In the renal impairment study GDX-44-005 a similar fraction excreted in the urine was demonstrated for the healthy volunteers (cohort 1) after a dose of 0.1 mmol/kg.

After a dose of 0.1 to 0.2 mL/kg BW (equivalent respectively to 0.05 and 0.1 mmol/kg BW), the mean plasma elimination half-life ($t_{1/2}$) in healthy volunteers with a normal renal function was1.5 and 1.7 hour, respectively, and the clearance was 100 ± 10 mL/min and 96 ± 12 mL/min, respectively. Urinary excretion is the major route of elimination of gadopiclenol, with approximately 98 % of the dose excreted in urine after 48 hours regardless of the dose administered.

In the renal impairment study GDX-44-005, the mean renal clearance was 94, 75, 43 and 12 ml/min for healthy volunteers and patients with mild, moderate and severe renal impairment, respectively. The renal clearance values were comparable with the mean eGFR values of the corresponding subject groups. As protein binding is negligible and as the renal clearance and eGFR values for the subjects are similar, it can be assumed that active secretion does not play a major role in the renal clearance mechanism of gadopiclenol and that gadopiclenol is cleared by glomerular filtration.

Dose proportionality and time dependencies

Gadopiclenol shows dose-proportional pharmacokinetics, as the C_{max} and AUC_{inf} increase proportional to dose in the range of 0.025 – 0.3 mmol/kg.

As gadopiclenol is not metabolised and has a single dose posology, time dependency was not investigated.

Intra- and inter-individual variability

The inter-individual variability for a 0.05 mmol/ml dose of gadopiclenol for C_{max}, AUC_{inf} and CL are 13%, 18% and 10%, respectively. Therefore, gadopiclenol is a drug substance with low variability. As no replicate PK-data are available, the intra-subject variability is not known.

Pharmacokinetics in target population

The half-life (1.8 – 2.0 h), total clearance (105.3 – 109.9 mL/min), and volume of distribution (16.8 – 18.8 L) of gadopiclenol in patients with brain lesions are comparable with that of the healthy human volunteers.

When comparing the exposure of gadopiclenol in patients with brain lesions with that of healthy human volunteers, it is noted that the C_{max} and AUC_{inf} are a bit lower in patients with brain lesions for the corresponding doses. However, considering the low number of subjects with brain lesions included in Part IIa of study GDX-44-003 and the variability of the data, C_{max} and AUC_{inf} are also comparable between healthy volunteers and patients with brain lesions.

It is further shown that the pharmacokinetics of gadopiclenol is also dose-proportional in patients with brain lesions in the dose range 0.05 – 0.2 mmol/kg.

Special populations

The potential effects of intrinsic factors on exposure to gadopiclenol were evaluated either in dedicated studies (GDX-44-005 and GDX-44-007) and/or with population pharmacokinetic analyses.

Impaired renal function

The elimination of gadopiclenol is prolonged in patients with renal impairment, proportionally to the degree of renal impairment. The $t_{1/2}$ of gadopiclenol increased from 1.9 hours in healthy volunteers to 3.3, 3.8 and 11.7 hours in patients with mild, moderate and severe renal impairment, respectively.

After intravenous administration of 0.1 mmol/kg gadopiclenol, the percentage of renal clearance in proportion to the total clearance of gadopiclenol was >97% for healthy volunteers, patients with mild renal impairment and moderate renal impairment and 86% for patients with severe renal impairment. These results show that renal excretion in unchanged form is still the main route of elimination in patients with renal impairment of any severity. The data of gadopiclenol recovered in urine showed that urinary excretion was delayed with the progression of renal impairment.

With regards to the systemic exposure to gadopiclenol, after a dose of 0.2 mL/kg BW (equivalent to 0.1 mmol/kg BW), the C_{max} increased 1.1-fold, 1.1-fold and 1.4-fold in patients with mild, moderate and severe renal impairment, respectively when compared to healthy volunteers. The AUC_{inf} increased 1.5-fold, 2.5-fold and 8.7-fold in patients with mild, moderate and severe renal impairment, respectively when compared to healthy volunteers.

PopPK analysis confirmed these results, as the median clearance and terminal half-life of gadopiclenol estimated from the final model, were comparable to those obtained in non-compartmental PK analyses. The

increase in AUC_{inf} in renal impairment patients compared to healthy volunteers was also comparable with the non-compartmental data.

Simulations with a dose of 0.05 mmol/kg in renal impairment patients showed that the concentrations of gadopiclenol at 10-30 minutes post-dose and the AUC_{inf} at the 0.05 mmol/kg dose (therapeutic dose in SmPC) can be expected to be half that of 0.1 mmol/kg (dose in renal impairment study GDX-44-005), which is in line with the dose-proportional pharmacokinetics of gadopiclenol. Furthermore, simulations showed a minor difference in median gadopiclenol concentrations at 10, 20, and 30 minutes post-injection (i.e. within the time window relevant for MRI) between healthy volunteers and patients with renal impairment with a maximum of 1.4-fold increase in median concentration for patients with severe renal impairment.

From the submitted data, it can be concluded that the exposure to gadopiclenol in terms of AUC is increased significantly (2.5 to 8.7-fold) in patients with moderate and severe renal impairment, which can potentially lead to more safety issues. At the same time, it is noted that the concentrations in the relevant timeframe in which the MRI is established, 10-30 minutes post-dose, do not increase as much as the AUC (just 1.1 to 1.5 fold).

The applicant also simulated the administration of reduced doses of 0.035-0.040 mmol/kg doses to subjects with severe renal impairment. The results showed that median C10 was 22% and 11% lower between subjects with normal renal function receiving a 0.05 mmol/kg dose and severe renal impairment patients receiving 0.035 mmol/kg and 0.040 mmol/kg, respectively. Dose reduction has less impact on the concentration at later timepoints (20 and 30 minutes). C20 with the reduced dose of 0.04 mmol/kg and C30min with the dose of 0.035 mmol/kg in patients with severe renal impairment show similar distribution as the C20 and C30 at the dose of 0.05 mmol/kg for subjects with normal renal function, respectively.

In patients with mild or moderate renal impairment, more than 90 % of the administered dose was recovered in the urine within 48 hours. In patients with severely impaired renal function about 84 % of the administered dose was recovered in the urine within 5 days.

Children with renal impairment

PopPK-simulations showed relatively small differences between adults and the paediatric population with mild, moderate and severe renal impairment.

Serum creatinine values for mild, moderate and severe impairment in the paediatric population were not available from the conducted studies, because the population in study GDX-44-007 had normal renal function. These values were estimated with the Schwarz bedside formula, using the median values for the GFR in these subgroups for adults derived from study GDX-44-005.

Dialysability of gadopiclenol

In end-stage renal disease (ESRD) patients (cohort 5), 4-hour haemodialysis effectively removed gadopiclenol from plasma as the percentage of decrease in blood concentrations was 95 to 98 % at the end of the first haemodialysis session.

Gadopiclenol plasma concentrations were below the quantification limit (BLQ) after the first 1.5 hours during the second dialysis session.

Gender

In the PopPK analyses in studies GDX-44-005 and GDX-44-007, gender was not found as a significant covariate, confirming the absence of gender effect. This can also be observed from the overlapping boxplots of all the ETAs included in the final PopPK-model vs sex (gender). The pharmacokinetic profile of gadopiclenol is linear in the studied dose range (0.05 to 0.6 mL/kg BW equivalent to 0.025 to 0.3 mmol/kg BW), without difference between males and females. Mean maximum concentration (Cmax) and Area Under the Curve (AUCinf) increased proportionally to the dose.

Weight

The effect of weight was investigated with PopPK-simulations of patients with a bodyweight ranging from 40 kg to 150 kg receiving a gadopiclenol dose of 0.1 mL/kg (equivalent to 0.05 mmol/kg). The ratios of median AUCinf of gadopiclenol between a typical healthy subject of 70 kg and subjects weighing 40 kg and 150 kg was 0.86 and 2.06, respectively. The ratios of the plasma concentrations 10, 20 and 30 minutes after administration between a typical healthy subject of 70 kg and subjects weighing 40 kg and 150 kg ranged from 0.93 to 1.26.

Impaired hepatic function and race

No study was performed to investigate the effects of impaired hepatic function and race on the pharmacokinetics of gadopiclenol, as no effect is expected due to the lack of metabolism.

Elderly

Only 10 subjects >65 years were included in the PK-trials. No dose adjustment of gadopiclenol is expected for the elderly. Gadopiclenol is not metabolised. The biggest issue for the elderly is renal impairment. Please refer to 'Impaired renal function' above.

Children

Simulations based on the final population PK model applying different body weights showed slightly lower median gadopiclenol plasma concentrations at 10, 20, and 30 minutes post-injection in children compared to adults (>18 years). The differences in C10, C20 and C30 were minor (<20%). The AUC_{inf} of gadopiclenol is 1%, 19% and 32% lower compared to adults for body weight-based dosing in the age group 12-17 years, 7-11 years and 2-6 years, respectively.

The exposures in terms of median C10, C20, C30 and AUC_{inf} seem lower in children when compared to adults. The difference in gadopiclenol concentrations (C10, C20 and C30) and AUC_{inf} is more pronounced in the youngest age group (2-6 years) and becomes less with higher age. However, due to the higher variability in children than in adults and because an overlap is observed in the concentrations and AUC_{inf} when considering the min, 2.5th percentile, median, 97.5th percentile and max of the data, the difference of exposure is not significant.

Individual parameters predicted from the population pharmacokinetic model and normalised by BW were similar between adults and children. The terminal half-life was 1.77 hour for age group 12-17 years old, 1.48 hour for age group 7-11 years old and 1.29 hour for age group 2-6 years old. The median clearance ranged from 0.08 l/h/kg (for age group 12-17 years old) to 0.12 l/h/kg (for age group 2-11 years old).

The pharmacokinetics of gadopiclenol in children aged 2 to 17 years are comparable to the pharmacokinetics in adults.

Pharmacokinetic interaction studies

No formal drug-drug interaction studies were conducted with gadopiclenol as it is to be used as single dose and is not metabolised.

Pharmacokinetics using human biomaterials

Analytical methods

The bioanalytical methods for gadopiclenol were validated in studies GDX-44-002, GDX-44-009 and GDX-44-012. The bioanalytical methods proved to be accurate, precise, specific, sensitive and reproducible in measuring gadopiclenol concentrations in human plasma, urine and dialysate.

The clinical study samples were all shipped and analysed at a single bioanalytical study site at Eurofins|ADME BIOANALYSES, 75 Chemin de Sommières 30310 Vergèze France.

There were no major protocol deviations during the clinical sample analysis, which could impact the results.

The incurred sample reanalyses met the criteria for studies GDX-44-003 (Part I and Part II), GDX-44-005 and GDX-44-007 for the human plasma, urine and dialysate samples as ≥67% of the reanalysed samples differed <20% of the original values.

Overall, within-study QCs met the acceptance criteria for within-run and between-run accuracy and precision (≤ 15%) for all studies, and sufficient chromatograms were submitted.

Stability has been proven for all clinical samples within the known long-term stability period, except 4 plasma samples of subject in study GDX-44-007. However, the concentrations measured for subject in study GDX-44-007 were only given for information due to the lack of stability data. This is acceptable.

Evaluation and Qualification of Models

The applicant conducted a population pharmacokinetic analysis to evaluate the pharmacokinetic profile of gadopiclenol in a paediatric population aged from 2 to 17 years following a single IV injection of 0.05 mmol/kg (GDX-44-007). Another analysis was done to predict PK parameters and exposure of gadopiclenol in patients with renal impairment and evaluate any difference with adults with normal renal function exposed at the same dose (GDX-44-005). The selected clinical studies are appropriate to estimate pharmacokinetic parameters.

The applicant has also submitted a separate PopPK model, including only the data of study GDX-44-003 as the first model, which was acceptable. Therefore, this model will not be discussed further in detail.

Generally, model development, covariate analysis and model validation and application seem robust and are adequately summarised for both population pharmacokinetic analyses. The pharmacokinetics of gadopiclenol was best described by a 2-compartment model parameterised in terms of clearance (CL), central volume of distribution (V1), intercompartment clearance (Q) and peripheral volume of distribution (V2). Parameters appear to be estimated with reasonably high precision.

Age, bodyweight, height, gender, eGFR and dose were tested as covariates. In study GDX-44-007 two covariates (besides bodyweight) were found to significantly impact the model, eGFR on CL and age on V1. In study GDX-44-005 only eGFR on CL appeared to have a significant impact. The correlation between age and eGFR most likely causes this discrepancy. Therefore, we consider eGFR a more mechanistic explanation for differences between individuals.

All parameters were precisely estimated, and the model provided good GOF characteristics. Diagnostic plots did not reveal significant bias or model misspecification. The models were evaluated using pcVPC/VPCs, and it can be concluded that the general pattern of concentrations as a function of time and dose, as well as the variability, could be described by the model for all populations entering the analysis.

The submitted population pharmacokinetic models are, however quite empirical. In the analysis dedicated to investigating whether the pharmacokinetics in paediatric patients behave similarly to adult patients, different interindividual and intraindividual variability parameters were estimated for adults and paediatrics. This hampers the comparison between adults and paediatrics but does not change the conclusion that paediatric patients demonstrate more variability as compared to adult patients. Second, with the PopPK model for renal impairment, two different equations were used to estimate the influence of eGFR on pharmacokinetic parameters for adults and children separately. This was done, because eGFR was approximated using two different formulas, one for adults and one for paediatric patients, which seems appropriate. However, with this approach, it is not clear how to translate the results of the renal impairment study to the paediatric population.

Therefore, the applicant implemented another PopPK-model using one single formula based on serum creatinine to describe how CL is affected by renal function for adults and children. The performance of the new popPK-model is similar to the previous model. The pcVPC showed that the model was able to capture both the central tendency and variability in paediatric patients and in adults, with normal and abnormal renal function. The IIV slightly increased for all parameters compared to the previous popPK-model with two different eGFR-formulas for adults and children. However, the new model is more useful for the clinical setting since the effects of impaired renal function, which were based on adult data, can be more easily extrapolated to the paediatric population. This is thus based on the assumption that the effect of renal impairment scales proportionally from adults to paediatrics.

Clinical implications of the results of the population pharmacokinetic model are described in the special populations (intrinsic factors) for renal impairment, children, weight and gender.

Exposure relevant for safety evaluation

The pharmacokinetics of gadopiclenol has been investigated in patients with brain lesions in study GDX-44-003 Phase IIa. The drug product has a single dose posology, so steady state is not reached. The C_{max} of gadopiclenol in patients with brain lesions is 371±118 µg/mL and the AUC_{inf} is 676±72 µg/mL.h.

2.6.2.2. Pharmacodynamics

Mechanism of action

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

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

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

Contrast-enhanced MRI utilises extracellular gadolinium-based contrast agents (GBCAs) as the clinical standard for detecting and delineating lesions and associated tissues. Following the administration of a GBCA, lesions are further characterised by their temporal and spatial patterns of signal enhancement produced by the contrast agent. The paramagnetic metal gadolinium (Gd^{3+}) is the rare earth element responsible for the enhancement effect of GBCA in MRI. The Gd ion has paramagnetic properties due to its 7 unpaired electrons leading to a high magnetic moment and very labile water coordination properties.

Complexed Gd enhances MR signal by shortening the T1 and T2 relaxation times in targeted tissues, which results in increased signal intensity in T1-weighted sequences and reduced signal intensity in T2-weighed sequences. The extent to which a contrast agent can affect the relaxation rate of tissue water (1/T1 or 1/T2) is termed relaxivity (r1 or r2). At the main magnetic field used in routine radiological practice (1.5 T), gadopiclenol has at least a two-fold higher r1 relaxivity compared to other available GBCAs (Table 5 and

Table **6**). Both relaxivities r1 and r2 display only a slight dependence on the strength of the magnetic field. The T1 shortening effect, which depends on relaxivity, is associated with improved tissue/lesion detection and visualisation and assistance in lesion characterisation.

This high relaxivity of gadopiclenol in water is due to its specific structure since the relaxivity is directly proportional to the number of water molecules linked to the gadolinium. For gadopiclenol, two H_2O molecules are linked to gadolinium to complete the nine coordinations of gadolinium (in addition of the 4 nitrogens and the 3 oxygens of the carboxylate functions) whereas only one water molecule is present for the other GBCAs approved by EMA. Due to its high relaxivity, it is anticipated that gadopiclenol can be given at a half dose of gadolinium compared to other non-specific gadolinium-containing contrast agents while providing the same contrast enhancement.

Table 5. Relaxivity at 37°C for gadopiclenol

	r_1 ($mmol^{-1}.l.s^{-1}$)			**r_2 ($mmol^{-1}.l.s^{-1}$)**		
Magnetic Field	**0.47 T**	**1.5 T**	**3 T**	**0.47 T**	**1.5 T**	**3 T**
Relaxivity in water	12.5	12.2	11.3	14.6	15.0	13.5
Relaxivity in biological medium	13.2	12.8	11.6	15.1	15.1	14.7

Table 6. Relaxivity values of gadopiclenol and marketed GBCAs in water at 1.5 T and 37°C

Relaxitivity at 1.5T	r1 (L.mmol-1.s-1)	r2 (L.mmol-1.s-1)
gadopiclenol	12.2	15.0
gadopentetic acid (Magnevist)	3.3	3.9
gadodiamide (Omniscan)	3.3	3.9
gadobenic acid (MultiHance)	3.8	4.4
gadoteric acid (Dotarem)	3.0	3.5
gadoteridol (ProHance)	2.9	3.4
gadobutrol (Gadovist/Gadavist)	3.3	3.9

Primary and Secondary pharmacology

Single ascending dose study phase 1/2a study

The pharmacodynamic effects of gadopiclenol were evaluated in a first-in-human phase 1/2a clinical study (GDX-44-003), which evaluated the safety, pharmacokinetics, and pharmacodynamics of gadopiclenol following single ascending dose level administration in healthy subjects (phase 1) and in patients with brain lesions (phase 2a).

Phase 1 was double-blind, randomised, placebo-controlled and included 54 healthy male and female subjects between 18 and 45 years old. In each dose group (0.025, 0.05, 0.075, 0.1, 0.2, and 0.3 mmol/kg), 6 subjects received gadopiclenol, and 3 received placebo (NaCl 0.9%) in intravenous injection. The last 3 subjects (2 receiving gadopiclenol and 1 receiving placebo) in the dosing groups 0.05 to 0.1 mmol/kg underwent MRI examination for pharmacodynamic assessments.

Phase 2a was open-label and included 12 patients with brain lesions, 3 per dose group (0.05, 0.075, 0.1, and 0.2 mmol/kg), who underwent MRI.

Pharmacodynamic assessments included a qualitative evaluation of the visualisation of brain structures/lesions and quantitative measurements (signal-to-noise ratio, contrast-to-noise ratio) on magnetic resonance imaging.

In the phase 1 part, the qualitative evaluation of MRI images are presented in Table 7.

Table 7. GDX-44-003 - Border Delineation, Internal Morphology and Contrast Enhancement Scores Pre-contrast and Pre+Post Contrast (PD Analysis Set – GDX-44-003 Phase I)

		Placebo N = 3		gadopiclenol					
				0.05 mmol/kg N = 2		0.075 mmol/kg N = 2		0.1 mmol/kg N = 2	
	Number of subjects (n)	Pre[a]	Pre+Post	Pre	Pre+Post	Pre	Pre+Post	Pre	Pre+Post
Border Delineation									
Choroid plexus	None	0	1	0	0	0	0	0	0
	Moderate	2	2	2	2	2	2	2	0
	Clear and complete	0	0	0	0	0	0	0	2
Nasal membrane	None	0	1	0	0	0	0	0	0
	Moderate	1	1	0	0	0	0	0	0
	Clear and complete	1	1	2	2	2	2	2	2
Pineal gland	None	0	1	0	0	0	0	0	0
	Moderate	2	2	2	2	2	2	2	2
Pituitary gland	None	0	1	0	0	0	0	0	0
	Moderate	2	2	1	1	1	1	2	0
	Clear and complete	0	0	1	1	1	1	0	2
Internal Morphology									
Choroid plexus	Poor	1	2	0	0	1	0	0	0
	Moderate	1	1	1	1	1	1	2	0
	Sufficient	0	0	1	1	0	1	0	2
Nasal membrane	Poor	0	1	0	0	0	0	0	0
	Sufficient	2	2	2	2	2	2	2	2
Pineal gland	Poor	2	3	1	0	1	1	2	0
	Moderate	0	0	1	2	1	1	0	2
Pituitary gland	Poor	1	1	0	0	0	0	0	0
	Moderate	1	2	1	1	1	1	2	0
	Sufficient	0	0	1	1	1	1	0	2
Contrast Enhancement									
Choroid plexus	None	2	3	2	0	2	0	2	0
	Weak	0	0	0	1	0	1	0	0
	Clear and bright	0	0	0	1	0	1	0	2
Nasal membrane	None	2	3	2	0	2	0	2	0
	Clear and bright	0	0	0	2	0	2	0	2
Pineal gland	None	2	3	2	0	2	0	2	0
	Weak	0	0	0	2	0	2	0	2
Pituitary gland	None	2	3	2	0	2	0	2	0
	Weak	0	0	0	1	0	0	0	0
	Clear and bright	0	0	0	1	0	2	0	2

[a] one subject did not undergo pre-contrast MRI

Quantitative evaluation of MRI images are presented in Table 8.

Table 8. GDX-44-003 - Median (Range) CNR and SNR for Visualisation of Brain Normal Structures (PD Analysis Set - GDX-44-003 Phase I)

Pre-Post variation Median (Range)	Placebo N = 3	Gadopiclenol 0.05 mmol/kg N = 2	Gadopiclenol 0.075 mmol/kg N = 2	Gadopiclenol 0.1 mmol/kg N = 2
n	2[a]	2	2	2
Choroid plexus				
CNR	0.2 (-0.40; 0.80)	6.6 (4.25; 8.85)	23.4 (20.05; 26.80)	28.9 (11.20; 46.67)
SNR	-1.0 (-4.40; 2.40)	40.5 (23.40; 57.55)	66.7 (56.00; 77.45)	69.9 (61.40; 78.39)
Nasal membrane				
CNR	-0.2 (-3.80; 3.40)	80.4 (63.70; 97.10)	44.5 (36.45; 52.60)	63.0 (56.60; 69.44)
SNR	-0.6 (-1.00; -0.20)	131.1 (108.35; 153.80)	85.4 (77.85; 93.00)	118.9 (108.62; 129.20)
Pineal gland				
CNR	-0.1 (-5.60; 5.40)	-6.7 (-19.55; 6.10)	-12.1 (-14.20; -9.95)	2.8 (-8.21; 13.80)
SNR	-0.7 (-2.20; 0.80)	42.1 (39.45; 44.75)	21.6 (13.80; 29.45)	47.5 (32.61; 62.40)
Pituitary gland				
CNR	-1.2 (-1.40; -1.00)	35.9 (24.45; 47.40)	30.0 (13.00; 47.05)	57.9 (56.20; 59.68)
SNR	0.4 (-1.40; 2.20)	91.1 (51.60; 130.50)	59.3 (56.20; 62.45)	88.3 (87.60; 89.05)

CNR: contrast-to-noise ratio; SNR: signal-to-noise ratio;
[a] one subject did not undergo pre-contrast MRI

In the phase 2 part, for qualitative evaluation of MRI images, up to 5 lesions (the largest) in each patient were selected for further evaluation (Table 9).

Table 9. GDX-44-003 - Brain Lesion Visualisation Scores by Lesion (PD Analysis Set – Phase IIa)

Number of Lesions, n	gadopiclenol 0.05 mmol/kg N = 3		gadopiclenol 0.075 mmol/kg N = 3		gadopiclenol 0.1 mmol/kg N = 2		gadopiclenol 0.2 mmol/kg N = 3	
	Pre	Pre+Post	Pre	Pre+Post	Pre	Pre+Post	Pre	Pre+Post
Number of Evaluated Lesions								
	14	14	12	12	2	2	3	3
Border Delineation Score								
Moderate	2	1	3	0	0	0	0	0
Clear and complete	12	13	9	12	2	2	3	3
Internal Morphology Score								
Moderate visibility	2	1	1	0	1	0	0	0
Sufficient visibility	12	13	11	12	1	2	3	3
Contrast Enhancement Score								
None	14	9	12	1	2	0	3	1
Weak	0	0	0	1	0	0	0	0
Clear and bright	0	5	0	10	0	2	0	2

N=number of patients; n=number of lesions with that observation
To be noted: pre- and post-contrast measurements of brain lesions in patients were done independently on 1 to 5 lesions per patient (i.e., potentially not the same lesions assessed pre- and post-contrast)

Quantitative evaluation of MRI images showed that for static imaging as measured on T1 sequence, the median pre-post variation in CNR, SNR, and signal intensity (SI) at the patient level was positive. For dynamic imaging as measured on T2* sequence, the median pre-post variation at the patient level was negative in all dose groups for CNR, in the 0.2 mmol/kg dose group for SNR and in all dose groups except 0.05 mmol/kg for SI (Table 10).

Table 10. GDX-44-003 - Median (Range) for Pre-Post Variation of CNR, SNR and SI for Visualisation of Brain Lesions at Patient Level (PD Analysis Set - GDX-44-003 Phase IIa)

Group	Parameter	Number of Patients	Median (Range) Pre-Post Variation	
			Sequence T1	Sequence T2*
gadopiclenol 0.05 mmol/kg	CNR	n = 3	1.63 (-1.16; 11.41)	-0.46 (-3.62; 4.80)
	SNR	n = 3	1.32 (0.35; 8.48)	18.51 (-1.23; 23.39)
	SI	n = 3	6.60 (-7.50; 94.00)	58.25 (2.20; 345.60)
gadopiclenol 0.075 mmol/kg	CNR	n = 3	16.72 (9.65; 18.85)	-4.71 (-10.19; 25.88)
	SNR	n = 3	38.33 (14.65; 55.96)	6.45 (-21.31; 12.54)
	SI	n = 3	279.80 (14.00; 306.60)	-251.20 (-395.20; 2.50)
gadopiclenol 0.1 mmol/kg	CNR	n = 2	41.32 (13.43; 69.20)	-3.10 (-10.54; 4.34)
	SNR	n = 2	78.80 (57.00; 100.60)	5.08 (-2.30; 12.46)
	SI	n = 2	442.50 (382.00; 503.00)	-124.00 (-218.00; -30.00)
gadopiclenol 0.2 mmol/kg	CNR	n = 3	51.93 (-3.60; 93.80)	-0.92 (-6.55; 1.97)
	SNR	n = 3	100.23 (1.20; 145.40)	-5.73 (-7.45; -1.01)
	SI	n = 3	642.00 (6.00; 727.00)	-129.00 (-196.00; -18.00)

n=number with data; CNR: contrast-to-noise ratio; SNR: signal-to-noise ratio; SI: signal intensity

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Gadopiclenol is administered only via the intravenous route. Consequently, the absolute bioavailability of gadopiclenol is 100%. C_{max} is reached in 0.03 – 0.08 h after intravenous administration. For the recommended dose of 0.05 mmol/kg, the mean Cmax and AUCinf for gadopiclenol are 525 µg/mL and 569 µg/mL*h, respectively.

Gadopiclenol distributes into the extracellular fluids and has a volume of distribution between 13 – 18.5 L. Protein binding of gadopiclenol is negligible as it binds 0.0–1.8% to human plasma proteins and 0.0-0.1% to human red blood cells.

Of the total administered dose of gadopiclenol 98% excreted renally in unchanged form by glomerular filtration. The mean half-life of gadopiclenol is 1.5-2.1 hours in the dose range 0.025 – 0.3 mmol/kg. Gadopiclenol is not metabolised.

The pharmacokinetics of gadopiclenol is dose-proportional in the range of 0.025 – 0.3 mmol/kg. In patients with brain lesions, it is further shown that the pharmacokinetics of gadopiclenol is also dose-proportional in the dose range 0.05 – 0.2 mmol/kg. In short, the pharmacokinetics in patients with brain lesions and healthy human volunteers can be considered comparable.

No dosage adjustment is necessary in elderly patients but caution should be exercised with regards to potential renal impairment (see below).

The applicant also simulated the administration of reduced doses of 0.035-0.040 mmol/kg doses to subjects with severe renal impairment. As the concentration at the 10 minutes timepoint is essential for achieving efficacy for gadopiclenol, dose reduction to 0.035 mmol/kg or 0.040 mmol/kg can lead to less efficacy. This could increase the risk to use an additional dose of gadopiclenol in patients with severe renal impairment, which increases their overall gadopiclenol exposure beyond 0.05 mmol/kg. Therefore, it is acknowledged that

a dose reduction to prevent any safety issues can lead to reduced efficacy in this special populations group. The SmPC-recommendation to not alter the dose for the mild, moderate and severe renal impairment group is understandable from this point of view. ESRD (<15 mL/min GFR) patients are being recommended the full dose, and it is not ascertained how many days before dialysis they will undergo gadopiclenol contrast-enhanced MRI. In study GDX-44-005 the first 4-hour haemodialysis session was performed between 1 and 2 hours after gadopiclenol administration. However, it is specified in the SmPC that gadopiclenol should be used in patients with severe renal impairment "after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI". It is also specified that "haemodialysis shortly after gadopiclenol administration may be useful at removing it from the body". No dosage adjustment is necessary for patients with any level of renal impairment. Gadopiclenol should only be used in patients with severe renal impairment (GFR < 30 mL/min/1.73 m2) and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI (see section 4.4). If it is necessary to use gadopiclenol, the dose should not exceed 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW). More than one dose should not be used during a scan. Because of the lack of information on repeated administration, gadopiclenol injections should not be repeated unless the interval between injections is at least 7 days.

The impact of renal impairment in the paediatric population is comparable with the adult population. Thus, the same dosing regimes can be used in the paediatric population with renal impairment.

Maturation of the renal functions was not considered, as the renal function is assumed to be mature in paediatric subjects ≥2 years of age. This is considered acceptable. However, this conclusion on the extrapolation should be drawn carefully as no paediatric patients with renal impairment were included in the studies. The paediatric population with renal impairment is only based on simulations without any real-world data.

In children, based on the final population PK model, comparable plasma gadopiclenol concentrations within the time window relevant for MRI are predicted to be achieved with body weight-based dosing in the paediatric population aged 2 to 17 years. So, there is no indication for dose adaptation based on age in addition to body weight-based dosing. It is concluded that the dose of 0.05 mmol/kg for adults can be extrapolated to the paediatric population of 2-17 years of age. More than one dose should not be used during a scan. It should be noted that some issues were raised regarding less efficacy of gadopiclenol in the children population when compared to adults in the clinical part of this report. This could be due to the lower C10, C20 and C30 gadopiclenol concentrations in children and the higher variability of the concentrations in children. Based on the PK-data, one would expect that the efficacy in the youngest age group (2-6 years) should be the worst. However, this is contradictory to the observed efficacy data in which gadopiclenol seems to perform better in the age group of 2-6 years old than the higher age groups.

Regarding weight considerations, as with patients with severe renal impairment, dose reduction in obese patients is not recommended because this could result in less efficacy.

No dosage adjustment is considered necessary for patients with hepatic impairment. Caution is recommended, especially in the case of perioperative liver transplantation period (see above "renal impairment").

Pharmacodynamics

Gadopiclenol is a non-ionic macrocyclic gadolinium (Gd) complex to be used as a contrast agent for magnetic resonance imaging. Gadopiclenol has an at least two-fold higher relaxivity compared to other available gadolinium-based contrast agents (GBCAs). This high relaxivity of gadopiclenol in water is due to its specific

structure since the relaxivity is directly proportional to the number of water molecules linked to the gadolinium. For gadopiclenol, two H2O molecules are linked to gadolinium to complete the nine coordinations of gadolinium (in addition of the 4 nitrogens and the 3 oxygens of the carboxylate functions). In contrast, only one water molecule is present for the other GBCAs approved by EMA. Due to its high relaxivity, it is argued that gadopiclenol can be given at half dose gadolinium compared to other GBCAs, while providing the same contrast enhancement.

The pharmacodynamic effects of gadopiclenol were evaluated in a first-in-human Phase 1/2a study GDX-44-003 following single ascending dose level administration in healthy subjects (phase 1) and in patients with brain lesions (phase 2a). In healthy subjects, quantitative evaluation of the gadopiclenol-enhanced MRI images showed increases in both CNR and SNR for the choroid plexus, nasal membrane and the pituitary gland at the all 3 tested doses (0.05, 0.075 and 0.1 mmol/kg) compared with pre-enhanced MRI, while the dose-response effect was observed only for choroid plexus. For the pineal gland, negative pre-post variations were observed and may be due to difficulties in placing large enough ROI on the small pineal gland to include sufficient pixels in order to calculate CNR or may be related to calcification, which is often observed for this structure and leads to poor and inhomogeneous image enhancement. Qualitative evaluation of the MRI images also showed improvements in the visualisation of normal brain structure after gadopiclenol administration. In patients with brain lesions, gadopiclenol-enhanced MRI images showed increases in CNR, SNR, and SI (T1 sequence) at all 4 doses tested (0.05, 0.075, 0.1, 0.2 mmol/kg). Additionally, increased CNR/SNR on gadopiclenol-enhanced MRI led to improvement on clarity of visualisation of the brain lesions. Overall, the results of this first-in-human study showed proof of concept of clinical efficacy.

The dose-finding phase 2b study GDX-44-004 showed a linear dose-response relationship between increasing doses of gadopiclenol (0.025, 0.05, 0.1, and 0.2 mmol/kg) and increases in CNR for all 3 independent off-site readers.

2.6.4. Conclusions on clinical pharmacology

Generally, the pharmacokinetics and pharmacodynamics of gadopiclenol have been sufficiently evaluated.

2.6.5. Clinical efficacy

This application is based on efficacy data obtained from the following studies:

- Phase 2b dose finding study (GDX-44-004)
- Phase 2a proof of concept study on liver imaging for hepatocellular carcinoma (HCC) (GDX-44-008)
- Two pivotal phase 3 studies conducted with the same study design, in order to assess the safety and efficacy of gadopiclenol at 0.05 mmol/kg for CNS MRI in one study (GDX-44-010) and MRI of other body regions in the second study (GDX-44-011)
- Phase 2 study in the paediatric population (GDX-44-007)

An overview of the clinical efficacy studies is provided in Table 4.

2.6.5.1. Dose response studies

In the multi-centre, double-blind, randomised, controlled, parallel dose groups cross-over phase 2b dose-finding study (GDX-44-004), four doses of gadopiclenol (0.025, 0.05, 0.1, and 0.2 mmol/kg) compared to gadobenate dimeglumine (MultiHance) at 0.1 mmol/kg based on CNS in 280 patients with central nervous system (CNS) lesions. Patients were randomly assigned in a 1:1:1:1 ratio to one of four doses of gadopiclenol and to one of two series of 2 MRIs performed with the different contrast agents: gadopiclenol at visit 2 and gadobenate dimeglumine at visit 4 or vice versa. The two visits were separated by a washout period of 2 days minimum and up to 14 days. Patients with brain metastasis were included at a minimum of 20% in the second subset. The primary evaluation criterion was the CNR, which was calculated by patient, and by independent blinded reader, in averaging the CNR for maximum 3 enhanced lesions. For the primary analysis, only lesions that matched on both MRIs after lesion tracking were considered. Of the 252 patients randomised, 215 (85.3%) completed the study. In total, 37 patients discontinued the study, with "withdrawal of subject's consent" (n= 8) and "other reason" (n=22) as the most common reasons. For the primary criterion CNR, there was a significant increase in CNR for gadopiclenol at 0.1 mmol/kg and 0.2mmol/kg compared with gadobenate dimeglumine at 0.1 mmol/kg for all 3 readers. gadopiclenol at 0.1 and 0.2 mmol/kg demonstrated superiority for CNR compared to gadobenate dimeglumine at 0.1mmol/kg for all 3 readers (Table 11). Gadopiclenol at 0.05mmol/kg showed a similar CNR compared to gadobenate dimeglumine at 0.1mmol/kg.

Table 11. CNS - GDX-44-004 - Primary criterion: Contrast to Noise Ratio - Off-Site Readings - Mixed Models - Holm's Step-Down Method - Per Protocol Set (N=207)

Dose of gadopiclenol	n	LS Mean (SE) of CNR			95% CI difference	p-value
		gadopiclenol	gadobenate dimeglumine	Difference		
Reader 1						
0.2 mmol/kg	44	49.99 (7.96)	35.55 (7.96)	14.45 (3.37)	[7.64 ; 21.25]	<0.0001
0.1 mmol/kg	51	35.94 (2.71)	27.28 (2.71)	8.66 (2.55)	[3.52 ; 13.79]	0.0007
0.05 mmol/kg	**56**	**31.78 (3.58)**	**29.60 (3.58)**	**2.18 (2.42)**	**[-2.67 ; 7.03]**	**0.1858**
0.025 mmol/kg	54	21.13 (2.65)	31.72 (2.65)	-10.59 (2.00)	[-14.59 ; -6.58]	-*
Reader 2						
0.2 mmol/kg	41	103.18 (10.94)	64.81 (10.94)	38.37 (9.76)	[18.62 ; 58.12]	0.0002
0.1 mmol/kg	43	72.17 (6.29)	52.79 (6.29)	19.38 (3.94)	[11.42 ; 27.34]	<0.0001
0.05 mmol/kg	**47**	**51.02 (5.09)**	**49.11 (5.09)**	**1.91 (4.56)**	**[-7.28 ; 11.10]**	**0.3384**
0.025 mmol/kg	44	43.15 (7.57)	57.29 (7.57)	-14.14 (4.55)	[-23.33 ; -4.95]	-*
Reader 3						
0.2 mmol/kg	42	125.08 (14.08)	73.12 (14.08)	51.96 (10.68)	[30.36 ; 73.55]	<0.0001
0.1 mmol/kg	45	94.17 (7.99)	64.94 (7.99)	29.23 (6.53)	[16.05 ; 42.41]	<0.0001
0.05 mmol/kg	**51**	**67.05 (6.43)**	**64.58 (6.43)**	**2.47 (5.40)**	**[-8.39 ; 13.32]**	**0.3249**
0.025 mmol/kg	49	46.74 (10.04)	70.70 (10.04)	-23.96 (4.88)	[-33.78 ; -14.13]	-*

CI: Confidence Interval; LS: Least Squares; SE: Standard Error.

Only matching lesions are considered. The models include CNR as dependent variable, contrast agent group and period as fixed factors, the unenhanced value as baseline (covariable) data and subject as random factor.

*The testing procedure was stopped the first time a non-significant comparison occurred.

The secondary efficacy criteria CNR based on cerebrospinal fluid, lesion-to-brain ratio (LBR) and contrast enhancement percentage showed the same pattern for all three blinded readers: superiority of gadopiclenol at 0.1 and 0.2 mmol/kg and similar results for gadopiclenol at 0.05 mmol/kg as compared to gadobenate dimeglumine at 0.1 mmol/kg (Table 12, Table 13 and Table 14).

Table 12. CNS- GDX-44-004 – Contrast to Noise Ratio Based on CSF - Off-Site Readings - Mixed Models - Holm's Step-Down Method - Per Protocol Set (N=207)

Dose of P03277 compared to Multihance	n	LS Mean (SE) of CNR			95% CI difference	p-value
		P03277	Multihance	Difference		
Reader 1						
0.2 mmol/kg	44	39.56 (3.10)	24.36 (3.10)	15.20 (2.46)	[10.23 ; 20.16]	<0.0001
0.1 mmol/kg	51	32.61 (2.45)	24.45 (2.45)	8.15 (2.07)	[3.98 ; 12.32]	0.0001
0.05 mmol/kg	**56**	**28.97 (2.59)**	**24.47 (2.59)**	**4.50 (1.79)**	**[0.91; 8.08]**	**0.0074**
0.025 mmol/kg	54	15.68 (1.67)	26.88 (1.67)	-11.20 (1.41)	[-14.04 ; -8.37]	1.0000
Reader 2						
0.2 mmol/kg	41	51.70 (3.90)	33.90 (3.90)	17.80 (3.34)	[11.05 ; 24.55]	<0.0001
0.1 mmol/kg	43	41.33 (3.13)	29.98 (3.13)	11.36 (3.03)	[5.23 ; 17.49]	0.0003
0.05 mmol/kg	**47**	**32.81 (2.59)**	**29.71 (2.59)**	**3.10 (1.96)**	**[-0.86 ; 7.05]**	**0.0611**
0.025 mmol/kg	44	18.81 (2.54)	32.58 (2.54)	-13.77 (2.50)	[-18.82 ; -8.73]	-
Reader 3						
0.2 mmol/kg	42	37.38 (3.42)	27.38 (3.42)	10.01 (3.03)	[3.88 ; 16.13]	0.0010
0.1 mmol/kg	45	34.79 (2.81)	26.62 (2.81)	8.17 (2.12)	[3.90 ; 12.44]	0.0002
0.05 mmol/kg	**51**	**25.14 (2.21)**	**23.49 (2.21)**	**1.65 (1.89)**	**[-2.15 ; 5.44]**	**0.1938**
0.025 mmol/kg	49	16.35 (2.22)	27.75 (2.22)	-11.40 (1.93)	[-15.28 ; -7.51]	-

Table 13. CNS- GDX-44-004 - Lesion to Brain Ratio - Off-Site Readings - Mixed Models - Holm's Step-Down Method - Per Protocol Set (N=207)

Dose of gadopiclenol compared to gadobenate dimeglumine	n	LS Mean (SE)			95% CI difference	p-value
		gadopiclenol	gadobenate dimeglumine	Difference		
Reader 1						
0.2 mmol/kg	44	2.94 (0.17)	2.02 (0.17)	0.92 (0.14)	[0.63 ; 1.21]	<0.0001
0.1 mmol/kg	51	2.50 (0.11)	2.01 (0.11)	0.49 (0.07)	[0.34 ; 0.64]	<0.0001
0.05 mmol/kg	**56**	**2.09 (0.10)**	**2.03 (0.10)**	**0.06 (0.05)**	**[-0.04 ; 0.16]**	**0.1079**
0.025 mmol/kg	54	1.58 (0.06)	2.04 (0.06)	-0.46 (0.03)	[-0.53 ; -0.39]	-
Reader 2						
0.2 mmol/kg	41	3.05 (0.19)	2.04 (0.19)	1.01 (0.17)	[0.66 ; 1.36]	<0.0001
0.1 mmol/kg	43	2.80 (0.13)	2.21 (0.13)	0.59 (0.10)	[0.38 ; 0.80]	<0.0001
0.05 mmol/kg	**47**	**2.10 (0.09)**	**2.11 (0.09)**	**-0.00 (0.03)**	**[-0.07 ; 0.06]**	**0.5370**
0.025 mmol/kg	44	1.62 (0.06)	2.07 (0.06)	-0.45 (0.04)	[-0.54 ; -0.37]	-
Reader 3						
0.2 mmol/kg	42	2.85 (0.15)	1.96 (0.15)	0.90 (0.11)	[0.67 ; 1.13]	<0.0001
0.1 mmol/kg	45	2.57 (0.11)	1.99 (0.11)	0.57 (0.08)	[0.41 ; 0.74]	<0.0001
0.05 mmol/kg	**51**	**2.03 (0.09)**	**2.00 (0.09)**	**0.03 (0.04)**	**[-0.04 ; 0.11]**	**0.1841**
0.025 mmol/kg	49	1.55 (0.06)	1.98 (0.06)	-0.43 (0.04)	[-0.52 ; -0.35]	-

CI: Confidence Interval; LS: Least Squares; SE: Standard Error.Only matching lesions are considered. The models include Lesion to Brain Ratio (LBR) as dependent variable, contrast agent group and period as fixed factors, the unenhanced value as baseline (covariable) data and subject as random factor

Table 14. CNS - GDX-44-004 - Contrast Enhancement Percentage - Off-Site Readings - Mixed Models - Holm's Step-Down Method - Per Protocol Set (N=207)

Dose of gadopiclenol compared to gadobenate dimeglumine	n	LS Mean (SE)			95% CI difference	p-value
		gadopiclenol	gadobenate dimeglumine	Difference		
Reader 1						
0.2 mmol/kg	44	3.13 (0.31)	1.83 (0.31)	1.30 (0.18)	[0.93 ; 1.67]	<0.0001
0.1 mmol/kg	51	2.58 (0.19)	1.94 (0.19)	0.64 (0.12)	[0.40 ; 0.88]	<0.0001
0.05 mmol/kg	**56**	**2.08 (0.22)**	**2.12 (0.22)**	**-0.04 (0.11)**	**[-0.25 ; 0.17]**	**0.6464**
0.025 mmol/kg	54	1.42 (0.15)	2.25 (0.15)	-0.84 (0.07)	[-0.98 ; -0.70]	-
Reader 2						
0.2 mmol/kg	41	3.31 (0.33)	1.86 (0.33)	1.45 (0.25)	[0.95 ; 1.94]	<0.0001
0.1 mmol/kg	43	2.96 (0.27)	2.00 (0.27)	0.96 (0.25)	[0.46 ; 1.45]	0.0002
0.05 mmol/kg	**47**	**2.23 (0.20)**	**2.09 (0.20)**	**0.14 (0.13)**	**[-0.13 ; 0.41]**	**0.1475**
0.025 mmol/kg	44	1.44 (0.17)	2.32 (0.17)	-0.88 (0.09)	[-1.06 ; -0.70]	-
Reader 3						
0.2 mmol/kg	42	3.26 (0.29)	1.94 (0.29)	1.33 (0.22)	[0.88 ; 1.77]	<0.0001
0.1 mmol/kg	45	2.70 (0.18)	1.88 (0.18)	0.82 (0.13)	[0.56 ; 1.07]	<0.0001
0.05 mmol/kg	**51**	**2.16 (0.23)**	**2.16 (0.23)**	**-0.00 (0.07)**	**[-0.15 ; 0.15]**	**0.5103**
0.025 mmol/kg	49	1.42 (0.15)	2.16 (0.15)	-0.74 (0.10)	[-0.93 ; -0.55]	-

Regarding lesion visualisation criteria, the mean sum of scores for up to 3 lesions tended to be higher with gadopiclenol at 0.1, and 0.2 mmol/kg compared to gadobenate dimeglumine at 0.1 mmol/kg (Table 15) and showed a linear relationship between doses of gadopiclenol and CNR for all three off-site readers independently analysed. There was no significant difference between gadopiclenol at 0.05 mmol/kg and gadobenate dimeglumine at 0.1 mmol/kg.

Table 15. CNS - GDX-44-004 - Lesion Visualisation criteria: Sum of Scores - Off-Site Readings - Mixed Models - Full Analysis Set (N=240) - Subjects with Data Available for the 2 MRI

Dose of gadopiclenol compared to gadobenate dimeglumine	Reader	n	LS Mean (SE)			95% CI difference
			Gadopiclenol	Gadobenate dimeglumine	Difference	
Border delineation						
0.2 mmol/kg	1	46	6.20 (0.52)	5.83 (0.52)	0.37 (0.14)	[0.08 ; 0.66]
	2	46	2.74 (0.23)	2.87 (0.23)	-0.13 (0.18)	[-0.49 ; 0.23]
	3	44	5.27 (0.46)	5.04 (0.46)	0.23 (0.32)	[-0.42 ; 0.88]
0.1 mmol/kg	1	53	5.21 (0.35)	5.13 (0.35)	0.07 (0.07)	[-0.07 ; 0.22]
	2	53	2.28 (0.22)	2.09 (0.22)	0.19 (0.13)	[-0.07 ; 0.45]
	3	53	4.37 (0.31)	3.97 (0.31)	0.41 (0.25)	[-0.10 ; 0.91]
0.05 mmol/kg	**1**	**58**	**5.02 (0.36)**	**5.07 (0.36)**	**-0.05 (0.15)**	**[-0.35 ; 0.25]**
	2	**57**	**2.22 (0.21)**	**2.38 (0.21)**	**-0.16 (0.14)**	**[-0.45 ; 0.13]**
	3	**57**	**4.76 (0.41)**	**5.05 (0.41)**	**-0.29 (0.20)**	**[-0.69 ; 0.12]**
0.025 mmol/kg	1	55	4.82 (0.34)	4.62 (0.34)	0.20 (0.13)	[-0.07 ; 0.47]
	2	55	2.45 (0.20)	2.26 (0.20)	0.19 (0.19)	[-0.20 ; 0.58]
	3	55	3.98 (0.30)	4.59 (0.30)	-0.61 (0.23)	[-1.07 ; -0.14]
Internal morphology						
0.2 mmol/kg	1	46	6.17 (0.49)	5.91 (0.49)	0.26 (0.11)	[0.03 ; 0.49]
	2	46	2.15 (0.19)	2.48 (0.19)	-0.33 (0.19)	[-0.72 ; 0.06]
	3	44	5.27 (0.46)	5.07 (0.46)	0.21 (0.32)	[-0.44 ; 0.86]
0.1 mmol/kg	1	53	5.36 (0.36)	5.19 (0.36)	0.17 (0.10)	[-0.03 ; 0.36]
	2	53	1.85 (0.18)	1.79 (0.18)	0.06 (0.16)	[-0.26 ; 0.37]
	3	53	4.39 (0.31)	4.00 (0.31)	0.39 (0.25)	[-0.12 ; 0.90]
0.05 mmol/kg	**1**	**58**	**5.00 (0.37)**	**4.96 (0.37)**	**0.04 (0.15)**	**[-0.27 ; 0.34]**
	2	**57**	**2.06 (0.22)**	**2.12 (0.22)**	**-0.06 (0.18)**	**[-0.42 ; 0.30]**
	3	**57**	**4.76 (0.41)**	**5.03 (0.41)**	**-0.27 (0.20)**	**[-0.68 ; 0.14]**
0.025 mmol/kg	1	55	4.71 (0.33)	4.60 (0.33)	0.11 (0.13)	[-0.16 ; 0.38]
	2	55	2.16 (0.20)	2.11 (0.20)	0.05 (0.18)	[-0.31 ; 0.41]
	3	55	4.01 (0.31)	4.60 (0.31)	-0.59 (0.23)	[-1.06 ; -0.12]
Degree of contrast enhancement						
0.2 mmol/kg	1	46	6.00 (0.46)	5.02 (0.46)	0.98 (0.18)	[0.61 ; 1.35]
	2	46	5.43 (0.47)	4.76 (0.47)	0.67 (0.37)	[-0.07 ; 1.42]
	3	44	5.28 (0.45)	4.84 (0.45)	0.44 (0.32)	[-0.20 ; 1.09]
0.1 mmol/kg	1	53	5.24 (0.32)	4.64 (0.32)	0.60 (0.14)	[0.32 ; 0.88]
	2	53	4.40 (0.32)	3.69 (0.32)	0.70 (0.28)	[0.14 ; 1.27]
	3	53	4.43 (0.31)	4.02 (0.31)	0.41 (0.24)	[-0.08 ; 0.89]
0.05 mmol/kg	**1**	**58**	**4.81 (0.36)**	**4.88 (0.36)**	**-0.07 (0.14)**	**[-0.35 ; 0.22]**
	2	**57**	**4.40 (0.41)**	**4.42 (0.41)**	**-0.02 (0.21)**	**[-0.44 ; 0.40]**
	3	**57**	**4.69 (0.40)**	**4.87 (0.40)**	**-0.18 (0.22)**	**[-0.61 ; 0.26]**
0.025 mmol/kg	1	55	4.15 (0.33)	4.38 (0.33)	-0.23 (0.15)	[-0.54 ; 0.07]
	2	55	4.10 (0.38)	4.46 (0.38)	-0.36 (0.33)	[-1.02 ; 0.30]
	3	55	3.74 (0.29)	4.44 (0.29)	-0.70 (0.21)	[-1.11 ; -0.28]

LS: Least Square; SE: Standard Error; CI: Confidence Interval. The models include sum of scores of lesion visualisation factor as dependent variable, contrast agent group and period as fixed factors and subject as random factor.

All three readers preferred gadopiclenol at 0.2 mmol/kg compared to gadobenate dimeglumine (75.0%, 85.4% and 58.3% of images). When comparing images with gadopiclenol at the same dose of 0.1 mmol/kg as gadobenate dimeglumine, they also mostly preferred images with gadopiclenol (45.2%, 50.9%, or 86.8% of images) or expressed no preference (49.1%, 49.1%, or 9.4% of images). With gadopiclenol at a dose of 0.05 mmol/kg, the three readers predominantly reported no preference for images with gadopiclenol or gadobenate dimeglumine (46.5% to 77.6%, respectively). Images with gadobenate dimeglumine were mostly preferred to images with gadopiclenol at a dose of 0.025 mmol/kg (69.1%, 90.9% and 61.8% of images).

The most frequent reasons for preference were superior contrast enhancement and better delineation of normal structure and lesion.

2.6.5.2. Main study(ies)

Two pivotal phase III studies were conducted with the same study design in order to assess the safety and efficacy of gadopiclenol at 0.05 mmol/kg for CNS MRI in one study (GDX-44-010) and MRI of other body regions in the second study (GDX-44-011) compared to gadobutrol (Gadovist/Gadavist) at 0.1 mmol/kg.

The applicant sought Special Protocol Assessment (SPA) with FDA and obtained an agreement on the design and planned analyses of the two Phase III pivotal studies. These protocols were also submitted to EMA, who made several important recommendations. The main comments were:

1) to obtain a standard of truth for a subset of patients, in order to address the concerns on the potential false positives with gadopiclenol.

2) to further evaluate the impact of gadopiclenol on diagnostic thinking, and on the patient treatment plan, with the aim to better understand the differences of gadopiclenol over gadobutrol.

Following these comments, the statistical analysis plan was revised when possible, and several additional analyses were added:

Secondary analysis of the primary criteria: global analysis with all readers in the same model, analysis including non-matching lesion, analysis including drop-out patients

Secondary criteria:

- analysis on patient's treatment plan: analysis with the nature (non-malignant/ malignant/not assessable) of the diagnosis done at unenhanced MRI as a covariate; descriptive statistics on therapeutic management based on unenhanced MRI in addition to those based on combined unenhanced and enhanced MRI.

- number of lesions: analysis by region/organ adding the region/organ as covariate (GDX-44-011 study)

However, some comments could not be fully addressed. No standard of truth could be added for any subset of patients. Based on Guerbet experience in previous studies, the expected CNS study population should include about 20% to 30% of glial tumours with high grade III/IV, i.e., 50-60 patients, for some of whom it would be possible to confirm the diagnosis with surgery. This number of patients will still not be sufficient to conclude on the impact of gadopiclenol on diagnostic thinking, and it will be even more difficult to link its value to the clinical outcome, considering the many confounders involved in the therapeutic plans of patients. It will be difficult to conduct such a study due to a lack of sensitivity as well as ethical reasons. For the Body trial (GDX-44-011), the CHMP recommended obtaining a standard of truth for a subset of patients, then generalising it to others for which it cannot be obtained. Meanwhile, the CHMP acknowledged that extending one organ to other body regions will be very difficult due to the different lesion types and organ specificities.

Gadopiclenol was compared in cross-over studies to a widely accepted GBCA for the claimed indication in current practice. The aim of the phase III studies was to demonstrate a similar diagnostic efficacy with the potential safety advantages from a reduced exposure to gadolinium by comparing gadopiclenol administered at half dose (0.05 mmol/kg) to an approved contrast agent belonging to the same class of GBCA (macrocyclic) at the current clinical dose of 0.1 mmol/kg. This was considered acceptable by the EMA. The potential issues of false positives with gadopiclenol due to lack of standard of truth could be limited by assessing the primary endpoint on matching lesions, that is, lesions seen with both contrast agents (excluding false positives of gadopiclenol). The number of lesions detected was similar with both contrast agents.

- ***Study GDX-44-010- Efficacy and Safety of Gadopiclenol for Central Nervous System (CNS) Magnetic Resonance Imaging (MRI) (the PICTURE Study)***

Methods

GDX-44-010 was a prospective, multi-centre, randomised, double-blind, controlled and cross-over Phase III study to evaluate the safety and efficacy of gadopiclenol at 0.05 mmol/kg compared with gadobutrol at 0.1 mmol/kg for CNS MRI in 256 adult patients with brain or spine lesions.

- **Study Participants**

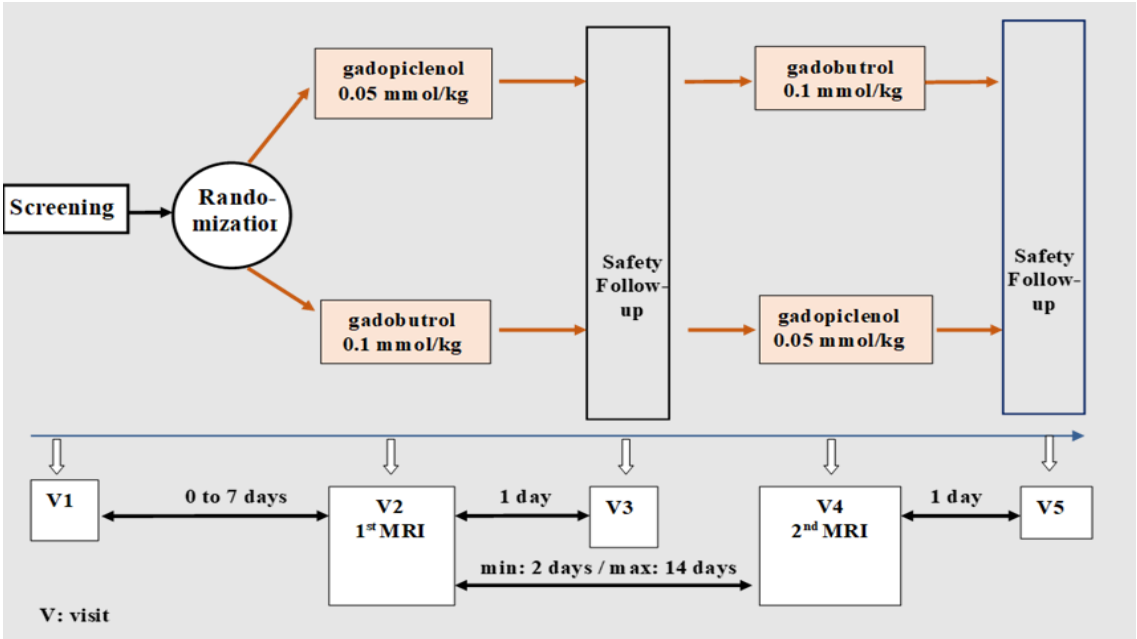
The main inclusion criteria were female or male adult patients presenting at the time of inclusion with known or highly suspected CNS lesion(s) with focal areas of disrupted BBB (e.g., primary and secondary tumours) based on results of a previous imaging procedure such as CT or MRI, which should have been performed within 12 months prior to ICF signature. If the patient was treated (either with radiation, surgery, biopsy or other relevant treatments) between previous imaging evaluation and trial MRI, there should still be a high suspicion of the remaining lesion(s) on the basis of available clinical information. Additionally, eligible subjects were patients scheduled for a CNS contrast-enhanced MRI examination for clinical reasons and agreed to have a second contrast-enhanced MRI examination for the purpose of the trial.

Following recommendations for GBCAs, patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and patients with known sensitivity to gadolinium were excluded. Additionally, patients presenting extracranial lesions and/or extradural lesions, patients presenting with an acute relapse of multiple sclerosis, patients with NYHA class III/IV, and patients with known liver failure or liver transplantation were excluded from the study.

- **Treatments**

To avoid bias, two MRI examinations were performed for each patient, which were randomised in a 1:1 ratio for the order of receiving the contrast agents (first gadopiclenol then gadobutrol or vice versa). The interval between the 2 MR examinations was at least 2 days to avoid carry-over effects but no more than 14 days to minimise the risk of measurable disease progression or lesion evolution. MRI imaging was performed with magnetic field strength of 1.5T or 3T (commonly used strength in clinical practice). The design of the study (Figure 2)included 5 visits, i.e. a screening visit (V1), 2 safety visits (V3 and V5) and 2 MRI visits (V2 and V4).

Figure 2. CNS - GDX-44-010 Study Design (and GDX-44-011 study)



Reading of images

For each investigational site, at least one experienced radiologist was appointed at the start of the trial to read all images of patients included at the site (on-site read). On-site image evaluations were image evaluations performed by blinded investigators involved in the conduct of the protocol or in the care of the patients.

Additionally, image evaluations were performed off-site in a blinded manner by three independent readers who had no contact with patients or investigators (off-site read). Blinded images were prospectively evaluated in a centralised manner. All images were sent to a core laboratory, which prepared the images for evaluation. The file headers of all the images transmitted in DICOM format were edited to remove patient or centre identification. For all images, any sequence information was removed. A complete audit trail of any changes to the file headers was maintained.

The global matched-pairs assessment for overall diagnostic preference was performed by 3 additional independent blinded radiologists.

Lesions tracking for exact matching of lesions by reader between imaging modalities (Pre-contrast and Paired [pre- and post-contrast]), or between the two MR examinations with gadopiclenol and gadobutrol was performed by an independent radiologist (so-called concordance reader). Once the concordance process was done, correspondence/tracking lesion tables were obtained so that lesions could be compared for analysis within readers or for the inter- and intra-reader. Only matching lesions were considered for the evaluation of the primary criteria.

Imaging procedure

MR equipment: For a single patient, the same MR equipment had to be used for the two MRI examinations required by the protocol.

MRI sequences: The same parameter setting for the same sequence had to be used for unenhanced images and for contrast-enhanced images in each patient. The required sequences and parameters for MRI with gadopiclenol and gadobutrol had to be as similar as possible as follows:

For brain (axial orientation and whole brain are required):			
Unenhanced:	2D T1-weighted SE/TSE images	**Contrast-enhanced:**	2D T1-weighted SE/TSE images
	3D T1-weighted GRE images		
	2D T2-FLAIR		3D T1-weighted GRE images
	T2-weighted TSE images		

For spine:			
Unenhanced:	T2-weighted TSE images (sagittal)	**Contrast-enhanced:**	T1-weighted SE/TSE (axial)
	T1-weighted SE/TSE images (sagittal)		T1-weighted SE/TSE (sagittal)

- **Objectives**

Primary objective 1:

- To demonstrate the superiority of gadopiclenol-enhanced MRI at 0.05 mmol/kg body weight (BW) compared to unenhanced MRI for patient referred for contrast-enhanced MRI of CNS, in terms of 3 lesion visualisation co-primary criteria (border delineation, internal morphology and degree of contrast enhancement) using the patient as his/her own control.

To be successful, 2 out of 3 blinded readers had to meet the alternative hypothesis for the three co-primary criteria simultaneously in the gadopiclenol group: a statistically significant (one-sided $p \geq 0.025$) positive difference in mean scores.

Primary objective 2:

- To demonstrate the non-inferiority of gadopiclenol at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg in terms of 3 lesion visualisation co-primary criteria (border delineation, internal morphology, degree of contrast enhancement) for patient referred for contrast-enhanced MRI of CNS.

The Student's t-based two-sided 95% confidence intervals (95%CI) of the difference between gadopiclenol and gadobutrol was constructed for each of 3 co-primary criteria using matching lesions only. Non-inferiority between gadopiclenol and gadobutrol was concluded if the lower bound of the 95%CI was above the non-inferiority margin set to 0.35 for at least 2 out of 3 blinded readers and for the 3 co-primary criteria simultaneously.

Of note: For FDA, the primary objective 1 had to be achieved. The primary objective 2 served as one of the secondary objectives. For EMA, both primary objectives 1 and 2 had to be achieved.

The primary criterion was "lesion visualisation" (based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement) on Paired images (Pre- and Post-contrast) versus Pre-contrast images or Paired images with gadopiclenol versus Paired images with gadobutrol assessed by three independent off-site blinded readers on a 4-point scale. The evaluation for the primary criterion was performed for up to the 3 most representative lesions (defined according to lesion size and contrast enhancement) and a mean of scores was calculated for each of the lesion visualisation co-primary criteria and for each reader.

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).

The mean of scores for each of the lesion visualisation co- primary criteria 1 ranged from 1 to 4.

Secondary objectives:

- To assess the following parameters with gadopiclenol and gadobutrol:
    - Lesion visualisation assessment by investigator (on-site read)
    - Improvement in lesion visualisation scores at patient-level
    - Technical adequacy of images (on-site and off-site read)
    - Number, size and location of lesions (on-site and off-site read)
    - Diagnostic confidence (on-site and off-site read)
    - Impact of contrast-enhanced MRI on patient treatment plan (on-site read)
    - Quantitative criteria (off-site read):
        - Contrast to Noise Ratio (CNR)
        - Percentage enhancement (E%) of lesion(s)
        - Lesion to Background Ratio (LBR)
        - Overall diagnostic preference (off-site read).
- To assess the safety profile of gadopiclenol and gadobutrol.

- **Outcomes/endpoints**

The Table 16 below summarises the definitions of the efficacy endpoints in GDX-44-010 (and GDX-44-011)

Table 16. CNS - Definitions of Efficacy Endpoints in GDX-44-010 and GDX-44-011

	GDX-44-010
Control	"Pre contrast" / Gadobutrol
Primary criteria	**Lesion visualisation criteria (border delineation, internal morphology, degree of contrast enhancement)** Paired images [Pre- and Post-contrast] with gadopiclenol versus Pre-contrast images Paired images with gadopiclenol versus Paired images with gadobutrol
Efficacy endpoints	
Lesion visualisation (lesion border delineation, internal morphology and degree of contrast enhancement)	The mean of scores for each of the 3 lesion visualisation co-criteria was 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). **The mean of scores for each visualisation endpoint could range from 1 to 4.** For each reader, only matching lesions were considered.
	Border delineation: defined as the distinction of lesion from surrounding tissues, structures, or edema; and the detection of extent of the lesion (for extra-axial lesions, this pertains to the definition of the space in which the lesion is present, and for intra-axial lesions, it pertains to the invasion of white matter, gray matter, or both; the neuroanatomical distribution of the lesion; and its mass effect). This criterion was assessed through the following scale: 1 = none: no or unclear delineation 2 = moderate: some areas of clear delineation but also with some significant areas of non-distinct delineation 3 = good: almost clear but not complete delineation 4 = excellent: border outline is sharp with clear and complete delineation **Internal morphology:** identification of lesion architecture and the intra-lesion features such as necrosis, haemorrhage and vascularity. This criterion was assessed through the following scale: 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 haemorrhage or cyst formation. **Degree of contrast enhancement:** This criterion 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

	GDX-44-010
Control	"Pre contrast" / Gadobutrol
Technical adequacy of images	For each contrast agent, images were evaluated as technically adequate for diagnosis using a 4-point scale and as assessable or not by investigators and independent blinded readers. The technical adequacy of images was rated on a 4-point scale: 1 = non diagnostic 2 = poor 3 = fair 4 = good Images were evaluated as assessable or not and if not, the reason had to be recorded: 1 = Artifacts due to patient 2 = Artifacts due to machine 3 = Injection technical failure 4 = Inadequate anatomic coverage 5= Other, specify
Number, size and location of lesions	■ Number of lesions on Pre and Paired images ■ For each of the 3 most representative lesions: ■ The largest diameter of the lesion ■ The location of the lesion
Diagnostic confidence	defined as the degree of confidence that the information on the images represents the true and complete clinical picture of a subject. The degree of confidence was rated on a 5-point scale: 1 = nil: Very uncertain 2 = poor: Uncertain 3 = moderate: Moderately certain 4 = high: Good certainty 5 = excellent: Very certain When the investigator/independent blinded reader chose 'not assessable' for diagnosis, by definition the confidence level was 1 (= very uncertain).
Impact of contrast-enhanced MRI on patient treatment plan	At the end of visit 2 and at the end of visit 4**,** after having completed all the sequences of images required by the protocol (Paired images), the investigator had to document if the subject treatment plan could have been changed based on the images obtained (yes/no) and if yes, he/she had to specify the therapeutic management proposed based on radiological assessment (based on unenhanced MRI and based on combined unenhanced and enhanced MRI): - Surgery - Biopsy - Chemotherapy - Radiotherapy - Other treatment: specify
Overall diagnostic preference	Evaluation was performed in a global matched-pairs fashion. For each randomised patient, Paired images from the first MR examination, labeled as examination 1, were displayed simultaneously with the corresponding Paired images from the second MR examination, labeled as examination 2. The assessment was performed with 3-point scale: 1: for which examination 1 is preferred to examination 2 0: for which no preference is observed 2: for which examination 2 is preferred to examination 1 Readers needed to select one or more of the following six reasons for this preference: - Contrast enhancement was superior, - Delineation of normal structure was better - Delineation of at least one lesion was better - Internal structure of lesions was better visualised - More lesions were identified - Diagnostic confidence was greater (one or more reason(s) were to be specified: detection of lesions, characterisation of disease, assignment of a grade to disease (i.e., high or low grade in the case of intraaxial gliomas), definition of extent of disease, or other reasons that had to be specified on the eCRF).

	GDX-44-010
Control	"Pre contrast" / Gadobutrol
Improvement in lesion visualisation scores at patient-level	For each contrast agent and for the 3 co-primary criteria, the lesion score was calculated and compared between Pre and Paired images. If the lesion score of Paired images was greater than those of Pre images then the Paired images were classified as "Better". If the mean score of Paired images was equal or less than those of Pre images then the Paired images were classified as "Not Better".
Quantitative parameters	Quantitative criteria were calculated by patient and by independent blinded reader and the result was provided by examination for each reader by averaging the parameter for maximum 3 most representative lesions. Only lesions that matched on both MRIs after lesion tracking were considered.
Contrast to Noise Ratio (CNR)	$CNR = \frac{SI_{lesion} - SI_{ht}}{SD_{noise}}$ SI_{lesion} = Signal intensity of lesion. SI_{ht} = Signal intensity of healthy tissue (brain or spinal cord). SD_{noise} = Standard Deviation of background noise.
Percentage enhancement (E%) of lesion(s)	$E\% = \frac{SI_{post} - SI_{pre}}{SI_{pre}} x100$ SI_{post} = Signal intensity of lesion on post injection images. SI_{pre} = Signal intensity of lesion on pre injection images.
Lesion to Background Ratio (LBR)	$LBR = \frac{SI_{lesion}}{SI_{ht}}$ SI_{lesion} = Signal intensity of lesion. SI_b= Signal intensity of background (healthy tissue in brain or spinal cord).

Inter and intra-reader variability assessment

The assessments of inter- and intra-reader variability was done in the final analysis.

- Inter-reader variability was evaluated on the whole set of study subjects, since each case was read by different readers.
- Intra-reader variability: individual readers performed repeat image evaluations of 10% of cases randomly determined. The cases used for intra-reader variability assessment were re-introduced randomly and re-read during the course of the reading. To minimise recall bias, intra-reader variability was assessed approximately after the first 50 cases had been reviewed and no sooner than two weeks from the original reviews of these patients. Results of the original reviews for these cases were not available to the reader. Only the first evaluation of a given image set was included in the efficacy analysis.

- **Sample size**

Two coprimary objectives are used in the pivotal study GDX-44-010. The sample size for each of the objectives was determined as follows:

Number of patients for the primary objective 1:

Expecting that for each co-primary criteria, the difference in mean scores will be 0.35 (["Paired" –"Pre"] within patient mean of lesion scores) with 1.5 standard deviation, a sample of 200 patients in the gadopiclenol group will have 90% power when using a single group superiority t-test with a 0.025 one-sided significance level.

As a 20% drop-out rate is expected, sample size increases to 250 patients with CNS lesions. The success hypothesis used in the sample calculation ("Paired" lesion score mean is at least 0.35 higher than "Pre" lesion

score mean) is based upon Gutierrez et al.; 2015[2] where the minimal observed difference mean was 0.41 with a SD ranging from 0.5 to 0.8.

Table 17.Mean (SD) of the difference between combined unenhanced and gadobutrol-enhanced imaging vs unenhanced imaging (N= 336).

Reader	Border delineation	Internal morphology	Degree of Contrast Enhancement
1	0.67 (0.66)	0.62 (0.47)	1.26 (0.61)
2	0.72 (0.78)	0.82 (0.61)	1.59 (0.77)
3	0.43 (0.50)	0.41 (0.52)	1.06 (0.51)

Considering that in the current trial the scale used is not exactly the same (4-point scale instead of 3-point scale for one parameter) and to account a possible greater heterogeneity, the difference is set to 0.35 with 1.5 standard deviation.

Number of patients for the primary objective 2:

Non-inferiority margin:

For EMA, both primary objectives 1 and 2 are to be achieved; therefore this trial will provide a direct demonstration of the superiority of gadopiclenol images over unenhanced images (objective 1). So, it can be considered as three-armed trial design with unenhanced images as placebo as described in EMA guideline on the choice of the non-inferiority margin [11]. As such, it is not necessary to define a value for non-inferiority margin to establish that gadopiclenol has efficacy over unenhanced images.

A 10% non-inferiority margin was considered clinically as an unimportant difference and, therefore relevant to establish acceptable efficacy relative to gadobutrol (objective 2). Based on the Guerbet Phase IIb GDX-44-004 clinical trial results of lesion visualisation criteria, the mean score for each of the 3 co-criteria is expected to be equal to 3.5, so the margin is set to 0.35 (10%).

Sample size hypothesis:

The standard deviation on lesion visualisation criteria for gadopiclenol is estimated on the basis of the Guerbet Phase IIb GDX-44-004 clinical trial results on lesion visualisation criteria presented in the table below.

[2] Gutierrez JE, Rosenberg M, Seemann J, et al. Safety and Efficacy of Gadobutrol for Contrast-enhanced Magnetic Resonance Imaging of the Central Nervous System: Results from a Multicentre, Double-blind, Randomized, Comparator Study. Magnetic Resonance Insights 2015;8:1–10

Table 18. Mean (SD) of the combined and gadopiclenol-enhanced imaging (N=61)

Reader	Border delineation	Internal morphology	Degree of Contrast Enhancement
1	3.37 (0.55)	3.34 (0.64)	3.23 (0.80)
2	1.97 (0.74)	1.71 (0.75)	3.76 (0.58)
3	3.72 (0.49)	3.72 (0.49)	3.68 (0.50)

Considering that the results for gadobutrol would be similar (meaning that the standard deviation of the difference is expected ranging from $\sqrt{}2*0.50=0.7$ to $\sqrt{}2*0.80=1.15$) and taking into account a possible greater heterogeneity of patient population to be included in the trial, the expected standard deviation of difference between gadopiclenol and gadobutrol is estimated to 1.75.

For this 2x2 cross-over design, the statistical analysis is based on the observed Student's t-based two-sided. 95% confidence interval (95%CI) of the gadopiclenol-gadobutrol difference for each co-primary criteria. An enrolment of 200 patients is deemed necessary for the lower limit of the 95% CI to exceed the non-inferiority margin set to 0.35. Assuming 80% power and for each co-primary criterion, the expected difference in mean scores is 0 with an expected standard deviation of 1.75.

If one assumes a patient drop-out rate of 20%, a minimum enrolment of 250 patients with CNS lesions is planned. Therefore, a total number of 250 patients will allow sufficient power to meet both primary objectives.

- **Randomisation and Blinding (masking)**

At visit 2, the patients were randomly assigned to one series of 2 MRIs (gadopiclenol-gadobutrol or gadobutrol-gadopiclenol) in a 1:1 ratio. The randomisation to determine the order of injection at visit 2 and visit 4 was done via Interactive Web Response System (IWRS) and performed in blocks to prevent unequal treatment allocation.

The trial design and the injection of the IMPs required identifying two separate teams in each trial site. One managed the blinded data and another one was unblinded and was in charge of the IMPs preparation and administration. The unblinded staff had to document in a separate patient's file all the unblinded information related to the IMPs and had to complete the dedicated restricted field in clinical eCRF pages.

During the course of the trial, the two teams did not exchange any information regarding the IMPs (nature of IMP injected, order of administration). The unblinded documentation was stored, and shielded from the view of the blinded staff.

The investigator and the patient remained blinded to IMPs allocation (nature of the IMPs and order of the IMP injection). A designated unblinded site staff member was in charge of preparing and administering the IMPs.

3 independent blinded radiologists performed the blinded centralised image evaluations (off-site read) and the global matched-pairs assessment was performed by 3 additional independent blinded radiologists. An

imaging electronic Case Report Form (eCRF) was used to ensure that the images were properly aligned and to ensure that the independent blinded readers documented all necessary data for the trial purpose.

- **Statistical methods**

For the pivotal Phase III studies (GDX-44-010 for CNS MRI and GDX-44-011 for Body MRI), two primary objectives were defined in order to fulfil all requirements from FDA and EMA and are described below.

For FDA, the primary objective 1 had to be achieved.

For EMA, both primary objectives 1 and 2 had to be achieved.

A FAS and PPS were defined for each objective, including patients with a valid primary criterion assessment for comparison of gadopiclenol Pre contrast and Paired images (FAS 1) and comparison of gadopiclenol and gadobutrol Paired images (FAS 2).

Superiority of Paired versus Pre-contrast images of gadopiclenol regarding lesion visualisation co-primary criteria (primary objective 1)

Each co-primary criterion (border delineation, internal morphology and degree of contrast enhancement) was analysed on the FAS 1 using a general linear model for each reader independently, modelling the patient's score as a function of the MRI modality ("Pre" MRI and "Paired" MRI) with adjustment on repeated measures on the patient due to the pairing of MRI modalities in patients. The difference "Paired" - "Pre" for each of 3 co-primary criteria was analysed using two-sided paired t-tests on matching lesions. Results are presented per off-site reader.

In order to statistically demonstrate the superiority of the Paired MRI over the Pre-contrast MRI, two out of three readers had to meet the alternative hypothesis for the 3 co-primary criteria in the gadopiclenol group i.e., a statistically significant (one-sided p-value ≤0.025) positive difference in mean scores in border delineation, internal morphology and degree of contrast enhancement of lesions.

Non-inferiority of gadopiclenol versus gadobutrol regarding lesion visualisation co-primary criteria (primary objective 2 – for EMA only)

In the framework of the co-primary criteria (EMA request), this analysis was performed using the PPS 2.

With primary objective 1, this trial provides a direct demonstration of the superiority of gadopiclenol images over unenhanced images. It can be considered as a three-armed trial design with unenhanced images as placebo as described in the EMA "guideline on the choice of the non-inferiority margin". As such, it was not necessary to define a value for the non-inferiority margin to establish that gadopiclenol has efficacy and that the non-inferiority margin is only based on clinical relevance.

A 10% non-inferiority margin was considered a clinically insignificant difference and relevant to establish acceptable efficacy relative to gadobutrol (objective 2). Based on the Phase IIb GDX-44-004 clinical trial results of lesion visualisation criteria, the mean score for each of the 3 co-criteria was expected to be equal to 3.5, so the margin was set to 0.35 (10%).

Each co-primary criterion was analysed using a general linear model for each reader independently, modelling the patient's score as a function of period (MRI 1 or MRI 2) and contrast agent (gadopiclenol and gadobutrol) with repeated measures on the patient due to the pairing of contrast agents in patients.

The Student's t-based 95% confidence interval (95% CI) of the difference between gadopiclenol and gadobutrol was constructed for each of the 3 co-primary criteria on matching lesions. Results are presented

per off-site reader. Non-inferiority between gadopiclenol and gadobutrol could be concluded if the lower bound of the 95% CI was above the non-inferiority margin (-0.35) for at least two out of three readers and for the 3 co-primary criteria.

As supportive analyses, the superiority analysis (primary criteria 1) was repeated using the PPS1, and the non-inferiority analysis (primary criteria 2) was repeated using the FAS 2.

To test assay sensitivity, the difference "Paired"-"Pre" for each of the 3 co-primary criteria was analysed for MRI with gadobutrol using the same analysis as described for superiority on the FAS 2.

The primary analysis 2 was repeated with only one global model putting all off-site readers together and so including the reader as a covariate using the FAS 2.

The primary analyses 1 and 2 were repeated including also non-matching lesions and including drop-out patients.

For subgroups analyses, sensitivity analyses of the superiority analysis (on the FAS 1) and of the non-inferiority analysis (on the FAS 2) were conducted using the same linear model with each of main demographic parameters and magnetic field as additional factors. Each demographic parameter and applied magnetic field strength were analysed independently using the model of the primary analyses. Results of the model (difference of the least square means) were tabulated and presented graphically by means of forest plot.

For the analysis of lesion visualisation at lesion level (off site reading), each lesion visualisation criterion was analysed by reader using a general linear model, modelling the lesion score as a function of the centre, period and on the one hand, contrast agent group (gadopiclenol and gadobutrol) with repeated measures on the lesion due to the pairing of contrast agents in lesions and on the other hand, modality of the MRI (Pre and Paired images) with repeated measures on the lesion due to the pairing of MRI modalities in lesions. Matching and non-matching lesions were kept in the analysis. The Student's t-based 95% CIs of the difference were constructed for each of the three lesion visualisation criteria for the difference between gadopiclenol and gadobutrol and for the difference between Paired and pre-contrast images.

For each off-site and on-site reader, the number of lesions identified per patient was modelled by a multivariate model using a negative binomial generalised linear mixed model with fixed effects for period (MRI 1 or MIR 2) and contrast agent group or MRI modality (Pre or paired). The difference between contrast agent groups using extended FAS 2 and between MRI modality using extended FAS 1 in the mean of lesions detected and associated 95% CI were computed.

The impact on patient treatment plan was fitted by a multiple logistic regression model for correlated data. The model included the factors contrast agent group and tumour classification before administration (malignant / not malignant / not assessable). The differences between contrast agent groups in proportions and associated 95% CI were computed globally and for each tumour classification.

Differences in mean Contrast to Noise Ratio (CNR) and Lesion to Background Ratio (LBR) between contrast agents were tested using a paired Student's t-test. The models included the contrast agent group, the period and the unenhanced value (Pre) as covariates. Differences in Percentage of Enhancement of lesions (E%) between contrast agents were tested using a Student's t-test. The models included the contrast agent group as independent variable and the period as covariate.

For each off-site reader, the overall diagnostic preference (assessed in a global matched-pairs fashion) was tabulated and gadopiclenol was compared to gadobutrol by a Wilcoxon signed-rank test.

Furthermore, a pooling of data from these two studies for CNS MRI (GDX-44-004 and GDX-44-010), taking into account all the patients who received gadopiclenol at 0.05 mmol/kg, has been performed and pooled results were analysed for common criteria: lesion visualisation co-criteria, CNR, LBR, E%, impact on the subject treatment plan.

Data sets analysed

Nine patient sets were defined:

- Screened patients Set (SPS), including all patients having signed the inform consent form
- Safety Set (SS), including all patients having received at least one injection of Investigational Medicinal Product (IMP) regardless of the quantity
- All Randomised Set (ARS), including all patients having performed at least one MRI examination with the injection of IMP.
- Extended Full Analysis Sets (FAS):
- Extended FAS 1, including all patients who have both gadopiclenol Pre contrast and Paired images assessable
- Extended FAS 2, including all patients who have both gadopiclenol and gadobutrol Paired images assessable
- Full Analysis Sets (FAS), including all patients who have a valid primary criterion assessment
- FAS 1: all patients who have both Pre and Paired images with gadopiclenol assessable for primary criteria 1 for at least one matching lesion for at least one off-site reader
- FAS 2: all patients who have Paired images for both gadopiclenol and gadobutrol assessable for primary criteria 2 for at least one matching lesion for at least one off-site reader
- Per-Protocol Set (PPS), including all patients who have no major protocol deviations and a valid primary criterion assessment:
- PPS 1: all patients from FAS 1 who have no major protocol deviations for primary criteria 1

PPS 2: all patients from FAS 2 who have no major protocol deviations for primary criteria 2

These population sets were used for the different statistical analyses as follows (Table 19):

Table 19. Statistical analyses use of population datasets

Analyses Sets	Screened patients Set	Safety Set	All Randomized Set	Extended Full Analysis Set		Full Analysis Set		Per Protocol Set	
				Extended FAS 1	Extended FAS 2	FAS 1	FAS 2	PPS 1	PPS 2
Disposition	✓								
Protocol deviations	✓								
Demographics and Population characteristics		✓				✓	✓		
Compliance						✓	✓		
Efficacy evaluation									
primary analysis of primary criteria 1						✓			
secondary analysis of primary criteria 1				✓		✓		✓	
primary analysis of primary criteria 2									✓
secondary analysis of primary criteria 2			✓		✓		✓		
Secondary criteria			✓	✓	✓	✓	✓		
Safety evaluation		✓							

In a non-inferiority analysis, the use of the FAS is not conservative and analysis should be conducted to detect differences. There was a risk that patients with major protocol deviations would lead to similar results in both contrast agent groups. This is why the primary noninferiority analysis (primary criteria 2) is performed using the PPS, which exhibit the most the difference between effects of study drug and comparator under the intended scientific model of the study.

Results

- **Participant flow**

Among the 260 patients screened for the GDX-44-010 study, 256 (98.5%) were randomised, of which 128 in each arm (Table 20). Overall, fourteen 14 patients prematurely discontinued the study: 6 before receiving the first contrast agent and 8 before receiving the second contrast agent.

Table 20. Overall Disposition – Screened patients set (N=260)

	gadopiclenol / gadobutrol (N=128)	gadobutrol / gadopiclenol (N=128)	Total* (N=260)
Visit 1: screening			260 (100%)
Screened patients			260 (100%)
Visit 2	128 (100%)	128 (100%)	258 (99.2%)
Randomized patients[1]	128 (100%)	128 (100%)	256 (98.5%)
Patients receiving the first contrast agent administration[2]	125 (97.7%)	125 (97.7%)	250 (97.7%)
Visit 3 (Safety visit)	125 (97.7%)	125 (97.7%)	250 (97.7%)
Visit 4	120 (93.8%)	122 (95.3%)	242 (94.5%)
Patients receiving the second contrast agent administration[2]	120 (93.8%)	122 (95.3%)	242 (94.5%)
Visit 5 (Safety visit)	120 (93.8%)	122 (95.3%)	242 (94.5%)
Patients who completed the trial	120 (93.8%)	122 (95.3%)	242 (94.5%)

Percentage of total randomized patients calculated on the number of screened patients. Other percentages are calculated on the number of randomized patients.
* Total number of patients includes not randomized patients. Therefore, total number of patients may be different from sum of the first 2 columns.
1 According to contrast agents allocated by randomization.
2 According to contrast agents actually received.

Table 21. Reasons for Premature Discontinuation –- Randomised Patients (N= 256)

	gadopiclenol / gadobutrol (N=128)	gadobutrol / gadopiclenol (N=128)	Total (N=256)
Premature discontinuation from the trial	**8 (6.3%)**	**6 (4.7%)**	**14 (5.5%)**
Premature discontinuation from the trial before receiving the first contrast agent	**3 (2.4%)**	**3 (2.4%)**	**6 (2.4%)**
Reasons of premature discontinuation			
n	3	3	6
Inclusion criteria not met / non-inclusion criteria met	0	1 (33.3%)	1 (16.7%)
Withdrawal of patient's consent	1 (33.3%)	2 (66.7%)	3 (50.0%)
Adverse event other than COVID-19	2 (66.7%)	0	2 (33.3%)
Premature discontinuation from the trial before receiving the second contrast agent *	**5 (4.0%)**	**3 (2.4%)**	**8 (3.2%)**
Reasons of premature discontinuation			
n	5	3	8
Withdrawal of patient's consent	0	1 (33.3%)	1 (12.5%)
Adverse event other than COVID-19	2 (40.0%)	0	2 (25.0%)
COVID-19 pandemic preventing patient from following protocol schedule	2 (40.0%)	1 (33.3%)	3 (37.5%)
Other reason	1 (20.0%)	1 (33.3%)	2 (25.0%)
Premature discontinuation from the trial after receiving the second contrast agent	**0**	**0**	**0**

%: (n row / n randomized) * 100, except for reasons of premature discontinuation where percentages are computed on number of patients prematurely discontinued from the trial.

Major protocol deviations

Major protocol deviations were reported for 27 randomised patients (10.5%), impacting both primary criteria or one of the 2 primary criteria specifically (Table 22). The most frequent major deviations were MRI with gadobutrol not performed (11 patients, including 2 due to COVID-19 pandemic), MRI with gadopiclenol not performed (8 patients, including 1 due to COVID-19 pandemic), or no matching lesions between both examinations identified for any of the 3 off-site readers between Pre and Paired images with gadopiclenol (for primary criteria 1, 8 patients) or between Paired images with gadopiclenol and with gadobutrol (primary criteria 2, 3 patients).

Table 22. Major Protocol Deviations – Randomised Patients (N= 256)

	gadopiclenol / gadobutrol (N=128)		**gadobutrol / gadopiclenol (N=128)**		**Randomized (N=256)**	
	n (%) patients	n events	n (%) patients	n events	n (%) patients	n events
At least one major protocol deviation (all deviations)	16 (12.5%)	22	11 (8.6%)	14	27 (10.5%)	36
At least one major protocol deviation related to both criteria 1 and criteria 2	6 (4.7%)	6	6 (4.7%)	6	12 (4.7%)	12
- Patient having performed MRI examination but not administered with gadopiclenol	1 (0.8%)	1	0	0	1 (0.4%)	1
- Gadopiclenol volume actually administered is different from the theoretical one of more than 20%	2 (1.6%)	2	0	0	2 (0.8%)	2
- MRI examination with gadopiclenol not performed*	2 (1.6%)	2	5 (3.9%)	5	7 (2.7%)	7
- MRI examination with gadopiclenol not performed due to COVID-19 pandemic	0	0	1 (0.8%)	1	1 (0.4%)	1
- Suspicion of lack of efficacy for gadopiclenol	1 (0.8%)	1	0	0	1 (0.4%)	1
At least one major protocol deviation related to criteria 1	6 (4.7%)	6	2 (1.6%)	2	8 (3.1%)	8
- Not matching lesion: among patients with gadopiclenol MRI examination available, those with no matching enhancing lesions on Paired and Pre contrast images for all off-site readers	6 (4.7%)	6	2 (1.6%)	2	8 (3.1%)	8
At least one major protocol deviation related to criteria 2	10 (7.8%)	10	6 (4.7%)	6	16 (6.3%)	16
- Not matching lesion: among patients with both MRI examinations available, those with no matching enhancing lesions at both examination for all off-site readers	1 (0.8%)	1	2 (1.6%)	2	3 (1.2%)	3
- Gadobutrol volume actually administered is different from the theoretical one of more than 20%	1 (0.8%)	1	1 (0.8%)	1	2 (0.8%)	2
- MRI examination with gadobutrol not performed*	6 (4.7%)	6	3 (2.3%)	3	9 (3.5%)	9
- MRI examination with gadobutrol not performed due to COVID-19 pandemic	2 (1.6%)	2	0	0	2 (0.8%)	2

One patient may have more than one deviation.
*for other reason than Covid-19 pandemic.

Impact of COVID-19 pandemic

When the pandemic disruption occurred in March 2020, a total of 210 patients out of the 250 expected were already enrolled in the trial. COVID-19 pandemic led to enrolment pause in 77% of participating sites, leading

to a 2 months delay in the planning. However, the trial was completed with the planned sample size despite the disruption that occurred, and the objectives were achieved. The study is considered with minimal disruption:

- No protocol amendments were implemented as a result of the pandemic.
- No modifications of trial visits or trial procedures were necessary.
- No changes in vendors or other third parties.
- No change in statistical analysis. As the final number of patients was obtained and the number of protocol deviations was limited, statistical power was adequate and the trial was able to meet its objectives. There was no impact on the statistical hypothesis.
- Quality Tolerance Limits were assessed as originally planned for the trial and were not exceeded.

Patient disposition / data sets analysed

The All randomised Set included 251 patients; however, one patient did not receive the contrast injection and only pre-contrast images were available for this patient. The extended FAS included 246 patients who had both gadopiclenol Pre contrast and Paired images assessable (extended FAS 1) and 241 patients who had both gadopiclenol and gadobutrol Paired images assessable (extended FAS 2).
FAS 1 and FAS 2 included both 239 patients; however, those were not exactly the same patients (6 patients included in FAS 1 are not included in FAS2 and in the same way 6 patients included in FAS 2 are not included in FAS 1). The PPS included 237 patients for analysis of primary criterion 1 (PPS 1) and 236 patients for analysis of primary criterion 2 (PPS 2)

Table 23. Analysis Data Sets: full analysis and per protocol sets – Screened patients set (N=260)

	gadopiclenol / gadobutrol (N=128)	gadobutrol / gadopiclenol (N=128)	Total (N=260)
All Randomized Set	126 (98.4%)	125 (97.7%)	251 (96.5%)
Extended Full Analysis Set 1	124 (98.4%)	122 (97.6%)	246 (98.0%)
Extended Full Analysis Set 2	119 (94.4%)	122 (97.6%)	241 (96.0%)
Full Analysis Set 1	119 (94.4%)	120 (96.0%)	239 (95.2%)
Per Protocol Set 1	117 (98.3%)	120 (100%)	237 (99.2%)
Full Analysis Set 2	119 (94.4%)	120 (96.0%)	239 (95.2%)
Per Protocol Set 2	117 (98.3%)	119 (99.2%)	236 (98.7%)

Percentages for the extended FAS 1, extended FAS 2, FAS 1 and FAS 2 are based upon number of patients in the All Randomized Set.
Percentages for the Per Protocol Set are based on number of patients in the corresponding Full Analysis Set.

- **Recruitment**

This study was conducted at 33 centres in 11 countries (2 in Belgium; 1 in Taiwan; 4 in France; 1 in Germany; 5 in Hungary; 4 in Italy; 2 in Republic of Korea; 1 in Poland; 3 in Spain; 8 in United States of America; 2 in Mexico).

Out of the 239 randomised patients of FAS 1, 166 (69.5%) were from Europe.

The study period was from 03 June 2019 – 11 September 2020.

- **Conduct of the study**

The protocol version v1.0 dated 20 December 2018 was amended once specifically for France (Protocol 1.0_FRA1.0 dated 21 May 2019) upon the request of French Competent Authorities (ANSM). This amendment 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: Patient with known liver failure or liver transplantation.

- **Baseline data**

The demographics and baseline characteristics were similar between randomisation groups (Table 24).

Table 24. Demographic Data – FAS 1 (N= 239) and FAS 2 (N= 239)

	FAS 1 (N= 239)			FAS 2 (N= 239)		
	gadopiclenol / gadobutrol (N=119)	gadobutrol / gadopiclenol (N=120)	Total (N=239)	gadopiclenol / gadobutrol (N=119)	gadobutrol / gadopiclenol (N=120)	Total (N=239)
Age (years)						
n	119	120	239	119	120	239
Mean (SD)	58.4 (13.4)	56.1 (14.2)	57.2 (13.8)	58.5 (13.1)	56.6 (14.1)	57.5 (13.6)
Median	61.0	56.5	59.0	61.0	58.0	59.0
Min. ; Max.	22 ; 84	18 ; 82	18 ; 84	23 ; 84	18 ; 82	18 ; 84
Age by category						
<65 years	76 (63.9%)	77 (64.2%)	153 (64.0%)	77 (64.7%)	75 (62.5%)	152 (63.6%)
≥ 65 years	43 (36.1%)	43 (35.8%)	86 (36.0%)	42 (35.3%)	45 (37.5%)	87 (36.4%)
Sex						
n	119	120	239	119	120	239
Male	58 (48.7%)	57 (47.5%)	115 (48.1%)	56 (47.1%)	56 (46.7%)	112 (46.9%)
Female	61 (51.3%)	63 (52.5%)	124 (51.9%)	63 (52.9%)	64 (53.3%)	127 (53.1%)
If Female: Childbearing potential						
n	61	63	124	63	64	127
Woman of childbearing potential using effective contraception	10 (16.4%)	23 (36.5%)	33 (26.6%)	10 (15.9%)	23 (35.9%)	33 (26.0%)
Post-menopausal (with minimum 12 months of amenorrhea)	37 (60.7%)	31 (49.2%)	68 (54.8%)	39 (61.9%)	33 (51.6%)	72 (56.7%)
Surgically sterilized	14 (23.0%)	9 (14.3%)	23 (18.5%)	14 (22.2%)	8 (12.5%)	22 (17.3%)
Weight at Visit 2 (kg)						
n	119	119	238	119	119	238
Mean (SD)	78.2 (19.3)	78.2 (21.1)	78.2 (20.2)	77.9 (19.5)	78.2 (21.0)	78.0 (20.2)
Median	75.0	76.0	76.0	75.0	76.0	75.0
Min. ; Max.	36 ; 125	45 ; 162	36 ; 162	36 ; 125	45 ; 162	36 ; 162
Missing data	0	1	1	0	1	1
Weight at Visit 4 (kg)						
n	114	120	234	119	120	239
Mean (SD)	77.9 (19.5)	78.4 (20.8)	78.1 (20.1)	77.9 (19.6)	78.3 (20.8)	78.1 (20.2)
Median	74.5	76.0	75.5	74.0	76.0	75.0
Min. ; Max.	36 ; 126	45 ; 159	36 ; 159	36 ; 126	45 ; 159	36 ; 159
Missing data	5	0	5			
Height (cm)						
n	119	120	239	119	120	239
Mean (SD)	166.9 (10.6)	168.6 (9.4)	167.7 (10.0)	166.7 (10.6)	168.5 (9.5)	167.6 (10.1)
Median	165.0	168.0	167.0	165.0	168.0	167.0
Min. ; Max.	144 ; 197	148 ; 194	144 ; 197	144 ; 197	148 ; 194	144 ; 197
BMI at Visit 2 (kg/m²)						
n	119	119	238	119	119	238
Mean (SD)	27.97 (6.15)	27.32 (6.13)	27.64 (6.13)	27.85 (5.95)	27.32 (6.13)	27.58 (6.03)
Median	27.43	26.17	26.79	27.43	26.17	26.79
Min. ; Max.	15.6 ; 48.4	16.5 ; 51.7	15.6 ; 51.7	15.6 ; 48.4	16.5 ; 51.7	15.6 ; 51.7
Missing data	0	1	1	0	1	1
BMI at Visit 4 (kg/m²)						
n	114	120	234	119	120	239
Mean (SD)	27.88 (6.00)	27.40 (6.08)	27.63 (6.03)	27.86 (5.95)	27.39 (6.08)	27.62 (6.01)
Median	27.12	26.23	26.72	27.14	26.23	26.77
Min. ; Max.	15.6 ; 48.4	16.5 ; 50.8	15.6 ; 50.8	15.6 ; 48.4	16.5 ; 50.8	15.6 ; 50.8
Missing data	5	0	5			

	FAS 1 (N= 239)			FAS 2 (N= 239)		
	gadopiclenol / gadobutrol (N=119)	gadobutrol / gadopiclenol (N=120)	Total (N=239)	gadopiclenol / gadobutrol (N=119)	gadobutrol / gadopiclenol (N=120)	Total (N=239)
Ethnicity						
n	119	120	239	119	120	239
Not Hispanic Or Latino	113 (95.0%)	109 (90.8%)	222 (92.9%)	113 (95.0%)	109 (90.8%)	222 (92.9%)
Hispanic Or Latino	6 (5.0%)	11 (9.2%)	17 (7.1%)	6 (5.0%)	11 (9.2%)	17 (7.1%)
Race (multiple choices)						
n	119	120	239	119	120	239
White	101 (84.9%)	98 (81.7%)	199 (83.3%)	102 (85.7%)	97 (80.8%)	199 (83.3%)
Asian	10 (8.4%)	8 (6.7%)	18 (7.5%)	10 (8.4%)	9 (7.5%)	19 (7.9%)
Black Or African American	2 (1.7%)	2 (1.7%)	4 (1.7%)	1 (0.8%)	2 (1.7%)	3 (1.3%)
Native Hawaiian Or Other Pacific Islander	0	1 (0.8%)	1 (0.4%)	0	1 (0.8%)	1 (0.4%)
American Indian Or Alaska Native	5 (4.2%)	11 (9.2%)	16 (6.7%)	5 (4.2%)	11 (9.2%)	16 (6.7%)
Other	1 (0.8%)	0	1 (0.4%)	1 (0.8%)	0	1 (0.4%)
Geographical Region						
n	119	120	239	119	120	239
North America	17 (14.3%)	24 (20.0%)	41 (17.2%)	16 (13.4%)	22 (18.3%)	38 (15.9%)
Latin America	5 (4.2%)	11 (9.2%)	16 (6.7%)	5 (4.2%)	11 (9.2%)	16 (6.7%)
Asia Pacific	9 (7.6%)	7 (5.8%)	16 (6.7%)	9 (7.6%)	8 (6.7%)	17 (7.1%)
European countries	88 (73.9%)	78 (65.0%)	166 (69.5%)	89 (74.8%)	79 (65.8%)	168 (70.3%)

SD: Standard Deviation, BMI: Body Mass Index
%: (n row / n non missing) * 100.
For the item "Race", a patient may have more than one answer. Hence, sum of percentages may be above 100% for this item

- **Numbers analysed**

Study disease

By inclusion criteria, the patients presented with known or highly suspected CNS lesion(s) with focal areas of disrupted BBB (e.g., primary and secondary tumours). The disease diagnosis are summarised in Table 25. In both FAS 1 and FAS 2 patients, the most frequent diseases were meningioma (29.3 to 29.7%), metastases to the central nervous system (18.0 to 19.2%), glioblastoma (10.5 to 10.9%) and acoustic neuroma (8.4 to 8.8%).

Table 25. Trial Disease Diagnosis According to Primary SOC and PT - FAS 1 (N= 239) and FAS 2 (N=239)

	FAS 1			FAS 2		
	gadopiclenol / gadobutrol (N=119)	gadobutrol / gadopiclenol (N=120)	Total (N=239)	gadopiclenol / gadobutrol (N=119)	gadobutrol / gadopiclenol (N=120)	Total (N=239)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**108 (90.8%)**	**111 (92.5%)**	**219 (91.6%)**	**109 (91.6%)**	**111 (92.5%)**	**220 (92.1%)**
Meningioma	38 (31.9%)	33 (27.5%)	71 (29.7%)	37 (31.1%)	33 (27.5%)	70 (29.3%)
Metastases to central nervous system	20 (16.8%)	23 (19.2%)	43 (18.0%)	23 (19.3%)	23 (19.2%)	46 (19.2%)
Glioblastoma	14 (11.8%)	12 (10.0%)	26 (10.9%)	13 (10.9%)	12 (10.0%)	25 (10.5%)
Acoustic neuroma	7 (5.9%)	13 (10.8%)	20 (8.4%)	8 (6.7%)	13 (10.8%)	21 (8.8%)
Glioma	3 (2.5%)	4 (3.3%)	7 (2.9%)	3 (2.5%)	4 (3.3%)	7 (2.9%)
Schwannoma	2 (1.7%)	4 (3.3%)	6 (2.5%)	2 (1.7%)	4 (3.3%)	6 (2.5%)
Oligodendroglioma	2 (1.7%)	3 (2.5%)	5 (2.1%)	2 (1.7%)	3 (2.5%)	5 (2.1%)
Brain neoplasm	2 (1.7%)	2 (1.7%)	4 (1.7%)	2 (1.7%)	2 (1.7%)	4 (1.7%)
Glioblastoma multiforme	2 (1.7%)	2 (1.7%)	4 (1.7%)	2 (1.7%)	2 (1.7%)	4 (1.7%)
Malignant glioma	1 (0.8%)	3 (2.5%)	4 (1.7%)	1 (0.8%)	3 (2.5%)	4 (1.7%)
Anaplastic oligodendroglioma	1 (0.8%)	2 (1.7%)	3 (1.3%)	1 (0.8%)	2 (1.7%)	3 (1.3%)
Pituitary tumour benign	2 (1.7%)	1 (0.8%)	3 (1.3%)	2 (1.7%)	1 (0.8%)	3 (1.3%)
Anaplastic astrocytoma	1 (0.8%)	1 (0.8%)	2 (0.8%)	2 (1.7%)	1 (0.8%)	3 (1.3%)
Astrocytoma, low grade	2 (1.7%)	0	2 (0.8%)	2 (1.7%)	0	2 (0.8%)
Craniopharyngioma	2 (1.7%)	0	2 (0.8%)	2 (1.7%)	0	2 (0.8%)
Ependymoma	2 (1.7%)	0	2 (0.8%)	1 (0.8%)	0	1 (0.4%)
Gliosarcoma	1 (0.8%)	1 (0.8%)	2 (0.8%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
Medulloblastoma	0	2 (1.7%)	2 (0.8%)	0	2 (1.7%)	2 (0.8%)
Metastases to spine	1 (0.8%)	1 (0.8%)	2 (0.8%)	0	1 (0.8%)	1 (0.4%)
Brain stem glioma	1 (0.8%)	0	1 (0.4%)	1 (0.8%)	0	1 (0.4%)
Brain teratoma	0	1 (0.8%)	1 (0.4%)	0	1 (0.8%)	1 (0.4%)
Ependymoma malignant	0	1 (0.8%)	1 (0.4%)	0	1 (0.8%)	1 (0.4%)
Glomus tumour	1 (0.8%)	0	1 (0.4%)	1 (0.8%)	0	1 (0.4%)
Haemangioblastoma	1 (0.8%)	0	1 (0.4%)	1 (0.8%)	0	1 (0.4%)
Haemangiopericytoma of meninges	0	1 (0.8%)	1 (0.4%)	0	1 (0.8%)	1 (0.4%)
Meningeal neoplasm	1 (0.8%)	0	1 (0.4%)	1 (0.8%)	0	1 (0.4%)
Metastases to meninges	1 (0.8%)	0	1 (0.4%)	1 (0.8%)	0	1 (0.4%)
Prolactin-producing pituitary tumour	0	1 (0.8%)	1 (0.4%)	0	1 (0.8%)	1 (0.4%)
Nervous system disorders	**10 (8.4%)**	**6 (5.0%)**	**16 (6.7%)**	**9 (7.6%)**	**6 (5.0%)**	**15 (6.3%)**
Central nervous system lesion	8 (6.7%)	3 (2.5%)	11 (4.6%)	7 (5.9%)	3 (2.5%)	10 (4.2%)
Brain oedema	1 (0.8%)	0	1 (0.4%)	1 (0.8%)	0	1 (0.4%)
Cerebral cyst	0	1 (0.8%)	1 (0.4%)	0	1 (0.8%)	1 (0.4%)
Colloid brain cyst	0	1 (0.8%)	1 (0.4%)	0	1 (0.8%)	1 (0.4%)
Intracranial mass	1 (0.8%)	0	1 (0.4%)	1 (0.8%)	0	1 (0.4%)
Spinal cord disorder	0	1 (0.8%)	1 (0.4%)	0	1 (0.8%)	1 (0.4%)
Infections and infestations	**1 (0.8%)**	**1 (0.8%)**	**2 (0.8%)**	**1 (0.8%)**	**1 (0.8%)**	**2 (0.8%)**
Neurocysticercosis	1 (0.8%)	1 (0.8%)	2 (0.8%)	1 (0.8%)	1 (0.8%)	2 (0.8%)
Injury, poisoning and procedural complications	**0**	**1 (0.8%)**	**1 (0.4%)**	**0**	**1 (0.8%)**	**1 (0.4%)**
Radiation necrosis	0	1 (0.8%)	1 (0.4%)	0	1 (0.8%)	1 (0.4%)
Investigations	**0**	**1 (0.8%)**	**1 (0.4%)**	**0**	**1 (0.8%)**	**1 (0.4%)**
Magnetic resonance imaging brain normal	0	1 (0.8%)	1 (0.4%)	0	1 (0.8%)	1 (0.4%)

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The number of patients in each group in each analysis set are presented in Table 26.

Table 26. CNS GDX-44-010- Analysis Data Sets – Screened Patients Set

	gadopiclenol / gadobutrol (N=128)	gadobutrol / gadopiclenol (N=128)	Total (N=260)
All Randomized Set	126 (98.4%)	125 (97.7%)	251 (96.5%)
Extended Full Analysis Set 1	124 (98.4%)	122 (97.6%)	246 (98.0%)
Extended Full Analysis Set 2	119 (94.4%)	122 (97.6%)	241 (96.0%)
Full Analysis Set 1	119 (94.4%)	120 (96.0%)	239 (95.2%)
Per Protocol Set 1	117 (98.3%)	120 (100%)	237 (99.2%)
Full Analysis Set 2	119 (94.4%)	120 (96.0%)	239 (95.2%)
Per Protocol Set 2	117 (98.3%)	119 (99.2%)	236 (98.7%)

Percentages for the extended FAS 1, extended FAS 2, FAS 1 and FAS 2 are based upon number of patients in the All Randomized Set.
Percentages for the Per Protocol Set are based on number of patients in the corresponding Full Analysis Set.

Note: Of the 6 randomised patients who discontinued before receiving the first contrast agent, 1 patient assigned to the gadopiclenol/gadobutrol group underwent the unenhanced part of the first MRI and was thus included in the All Randomised Set.

Table 27 and Table 28 below has been provided to better understand the number of patients and number of lesions analysed in each analysis dataset and for each off-site reader.

Table 27. Off-site readings - Number of patients and number of lesions (up to 3 most representative lesions per patient) by contrast agent and by MRI modality (Pre and Paired) for all efficacy datasets -

	Gadopiclenol (N=248)				Gadobutrol (N=245)			
	PRE		PAIRED		PRE		PAIRED	
	Patients	Lesions	Patients	Lesions	Patients	Lesions	Patients	Lesions
Randomized Set								
Reader 1	245	337	244	374	244	325	241	360
Reader 2	246	348	246	384	245	340	245	381
Reader 3	237	314	235	333	235	312	234	344
Extended FAS 1								
Reader 1	245	337	244	374				
Reader 2	246	348	246	384				
Reader 3	237	314	235	333				
FAS 1								
Reader 1	227	287	227	287				
Reader 2	229	279	229	279				
Reader 3	202	234	202	234				
PPS 1								
Reader 1	225	285	225	285				
Reader 2	227	277	227	277				
Reader 3	200	232	200	232				
Extended FAS 2								
Reader 1			239	367			237	355
Reader 2			241	378			241	376
Reader 3			230	328			230	339
FAS 2								
Reader 1			230	319			230	319
Reader 2			234	322			234	322
Reader 3			223	291			223	291
PPS 2								
Reader 1			227	315			227	315
Reader 2			231	319			231	319
Reader 3			220	288			220	288

Note: 248 patients underwent unenhanced MRI prior to administration of gadopiclenol, of which 1 patient did not subsequently receive gadopiclenol; 245 patients received gadobutrol.

Table 28. Off-Site Readings – Number of patients and number of lesions (up to 3 most representative lesions) seen by all 3 readers by contrast agent and by MRI modality (pre and paired) for all efficacy datasets

	Gadopiclenol (N=248)				Gadobutrol (N=245)			
	PRE		PAIRED		PRE		PAIRED	
	Patients	Lesions	Patients	Lesions	Patients	Lesions	Patients	Lesions
Extended FAS1	206	238	226	238				
FAS1	187	209	187	209				
PPS1	185	207	185	207				
Extended FAS2			222	282			220	281
FAS2			213	259			213	259
PPS2			211	257			211	257

- **Outcomes and estimation**

Primary criteria

Lesion visualisation

In the pivotal phase III study (GDX-44-010), the two primary objectives were achieved for all three blinded readers:

- **Primary objective 1: The superiority of the combined unenhanced/contrast-enhanced MRI (Paired) with gadopiclenol over unenhanced MRI (Pre-contrast) for lesion visualisation was demonstrated (Table 29).** The difference in mean of scores for each criterion was significantly different from zero with a type 1 error set at 0.025 in favor of Paired images compared to Pre-contrast images ($p<0.0001$).
- **Primary objective 2: The non-inferiority of gadopiclenol at 0.05 mmol/kg to gadobutrol at 0.1 mmol/kg for lesion visualisation was demonstrated (Table 30).** The difference in mean of scores for each criterion was close to 0 in all cases, with a lower limit of the 95% CI of the difference not lower than -0.06, that is largely above the non-inferiority margin of -0.35 ($p<0.0001$). As most 95% CI of the difference included the value "0", superiority of gadopiclenol at 0.05 mmol/kg over gadobutrol at 0.1 mmol/kg could not be concluded.

Table 29. CNS – GDX-44-010 Co-primary criteria 1 - Off-Site Readings - MRI with Gadopiclenol - PAIRED vs PRE – Mixed Model -FAS 1 (N=239)

FAS 1 (N=239)	n	LS Mean (SE)			95% CI difference	p-value
		Paired	Pre	Difference		
Border delineation						
Reader 1	227	3.90 (0.02)	2.08 (0.02)	1.82 (0.03)	[1.76 ; 1.88]	<0.0001
Reader 2	229	3.64 (0.04)	1.74 (0.04)	1.90 (0.05)	[1.81 ; 2.00]	<0.0001
Reader 3	202	3.97 (0.03)	2.61 (0.03)	1.36 (0.04)	[1.29 ; 1.44]	<0.0001
Internal morphology						
Reader 1	227	3.92 (0.03)	1.66 (0.03)	2.26 (0.03)	[2.20 ; 2.33]	<0.0001
Reader 2	229	3.65 (0.03)	1.88 (0.03)	1.77 (0.04)	[1.69 ; 1.85]	<0.0001
Reader 3	202	3.97 (0.04)	2.01 (0.04)	1.96 (0.05)	[1.85 ; 2.06]	<0.0001

FAS 1 (N=239)	n	LS Mean (SE)			95% CI difference	p-value
		Paired	Pre	Difference		
Degree of contrast enhancement						
Reader 1	227	3.77 (0.03)	1.00 (0.03)	2.77 (0.04)	[2.69 ; 2.85]	<0.0001
Reader 2	229	3.58 (0.03)	1.00 (0.03)	2.58 (0.05)	[2.49 ; 2.67]	<0.0001
Reader 3	202	3.90 (0.02)	1.00 (0.02)	2.90 (0.03)	[2.84 ; 2.95]	<0.0001

CI: Confidence Interval ; FAS: Full Analysis Set; LS: Least Squares ; SE: Standard Error. Only matching lesions are considered. The models include lesion visualisation factor as dependent variable, MRI modality (Pre and Paired MRI) as fixed factors, patient as random factor.

Table 30. CNS – GDX-44-010 Co-primary criteria 2 - Off-Site Readings – MRI with Gadopiclenol versus MRI with gadobutrol - Mixed Model – PPS 2 (N=236)

PPS 2 (N= 236)	n	LS Mean (SE)			95% CI difference	p-value
		Gadopiclenol	Gadobutrol	Difference		
Border delineation						
Reader 1	227	3.91 (0.02)	3.93 (0.02)	-0.02 (0.02)	[-0.06 ; 0.02]	<0.0001
Reader 2	231	3.64 (0.04)	3.60 (0.04)	0.03 (0.04)	[-0.04 ; 0.11]	<0.0001
Reader 3	220	3.97 (0.01)	3.95 (0.01)	0.02 (0.02)	[-0.01 ; 0.05]	<0.0001
Internal morphology						
Reader 1	227	3.93 (0.02)	3.93 (0.02)	-0.01 (0.02)	[-0.04 ; 0.03]	<0.0001
Reader 2	231	3.64 (0.04)	3.62 (0.04)	0.02 (0.03)	[-0.05 ; 0.09]	<0.0001
Reader 3	220	3.97 (0.02)	3.92 (0.02)	0.05 (0.02)	[0.01 ; 0.08]	<0.0001
Degree of contrast enhancement						
Reader 1	227	3.78 (0.04)	3.77 (0.04)	0.01 (0.03)	[-0.04 ; 0.07]	<0.0001
Reader 2	231	3.57 (0.04)	3.52 (0.04)	0.05 (0.04)	[-0.03 ; 0.12]	<0.0001
Reader 3	220	3.89 (0.03)	3.81 (0.03)	0.09 (0.03)	[0.03 ; 0.15]	<0.0001

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error; PPS: Per Protocol Set. Only matching lesions are considered. The models include lesion visualisation factor as dependent variable, contrast agent and period as fixed factors, patient as random factor. Non-inferiority margin: -0.35

A pooled analysis of the primary outcome criteria 2 over the three readers and for each lesion visualisation criterion is presented in the table below.

Table 31. Co-primary criteria 2 - off-site readings - global mixed model with readers as covariate - FAS 2 (N=239)

Comparison	n	LS Mean (SE) Gadopiclenol	LS Mean (SE) Gadobutrol	LS Mean Difference (SE)	95% CI	p-value
Border delineation	239	3.83 (0.02)	3.82 (0.02)	0.01 (0.02)	[-0.02 ; 0.05]	0.5025
Internal morphology	239	3.83 (0.02)	3.81 (0.02)	0.02 (0.02)	[-0.01 ; 0.05]	0.2006
Degree of contrast enhancement	239	3.73 (0.03)	3.68 (0.03)	0.05 (0.02)	[0.01 ; 0.09]	0.0172

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error.
Only matching lesions are considered.
The models include lesion visualization factor as dependent variable, contrast agent and reader as fixed factors, patient as random factor.
Source: Table 14.2.1.18
Listings 16.2.6.1, 16.2.6.2 and 16.2.6.3

These results of the primary analyses were confirmed in all supportive and sensitivity analyses. In addition, similar results were also obtained with on-site reading for the two primary objectives.

Additionally, similar results were obtained when non-matching lesions were included. The primary analyses 1 and 2 were repeated, this time also including the non-matching lesions, using the extended FAS 1 and extended FAS 2, respectively. For the primary criterion 1, the number of patients analysed was then 245, 246

and 244 for readers 1, 2 and 3, respectively, including an additional 18, 17 and 42 patients in the analysis, respectively. For the primary criterion 2, the number of patients analysed was 240 (+13), 241 (+10) and 234 (+14) for readers 1, 2 and 3, respectively.

The number of lesions seen with both contrast agents of with only one contrast agent are presented by reader in the table below.

Table 32. Overview of number of lesions observed with both contrast agents or with only one contrast agent

GDX-44-010	N lesions	Lesions seen with both contrast agents	Lesions seen only with gadopiclenol	Lesions seen only with gadobutrol
Reader 1	403	319 (79.2%)	48 (11.9%)	36 (8.9%)
Reader 2	432	322 (74.5%)	56 (13.0%)	54 (12.5%)
Reader 3	376	291 (77.4%)	37 (9.8%)	48 (12.8%)

The number of patients in which the number of lesions seen with each contrast agent differed is summarised by reader in the table below.

Table 33. Overview of number of patients by reader with the same or different number of lesions identified by the contrast agents

Body region	Reader	All patients or sequence	more lesions seen with gadobutrol	same number of lesions seen with both GBCAs	more lesions seen with gadopiclenol
GDX-44-010					
CNS	Reader 1	All patients	16 (6.64%)	195 (80.91%)	30 (12.45%)
		gadopiclenol-gadobutrol	8 (6.72%)	97 (81.51%)	14 (11.76%)
		gadobutrol - gadopiclenol	8 (6.56%)	98 (80.33%)	16 (13.11%)
	Reader 2	All patients	32 (13.28%)	175 (72.61%)	34 (14.11%)
		gadopiclenol-gadobutrol	15 (12.61%)	87 (73.11%)	17 (14.29%)
		gadobutrol - gadopiclenol	17 (13.93%)	88 (72.13%)	17 (13.93%)
	Reader 3	All patients	35 (14.52%)	179 (74.27%)	27 (11.2%)
		gadopiclenol-gadobutrol	17 (14.29%)	87 (73.11%)	15 (12.61%)
		gadobutrol - gadopiclenol	18 (14.75%)	92 (75.41%)	12 (9.84%)

Intra-reader variability was generally good, as well as inter-reader variability, showing consistent results between readers.

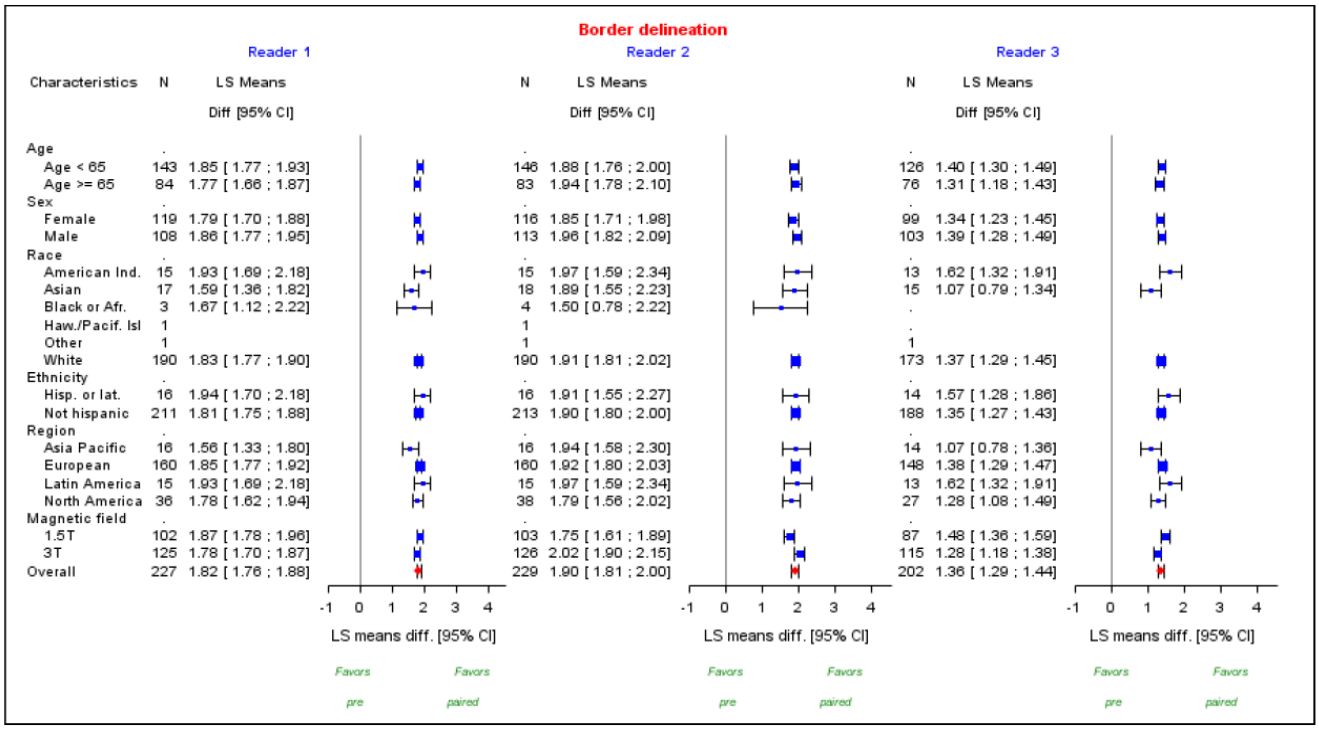
The analysis of the difference "Paired - Pre" for each of 3 co-primary criteria for MRI with gadobutrol showed similar results to those obtained with gadopiclenol, confirming the assay sensitivity.

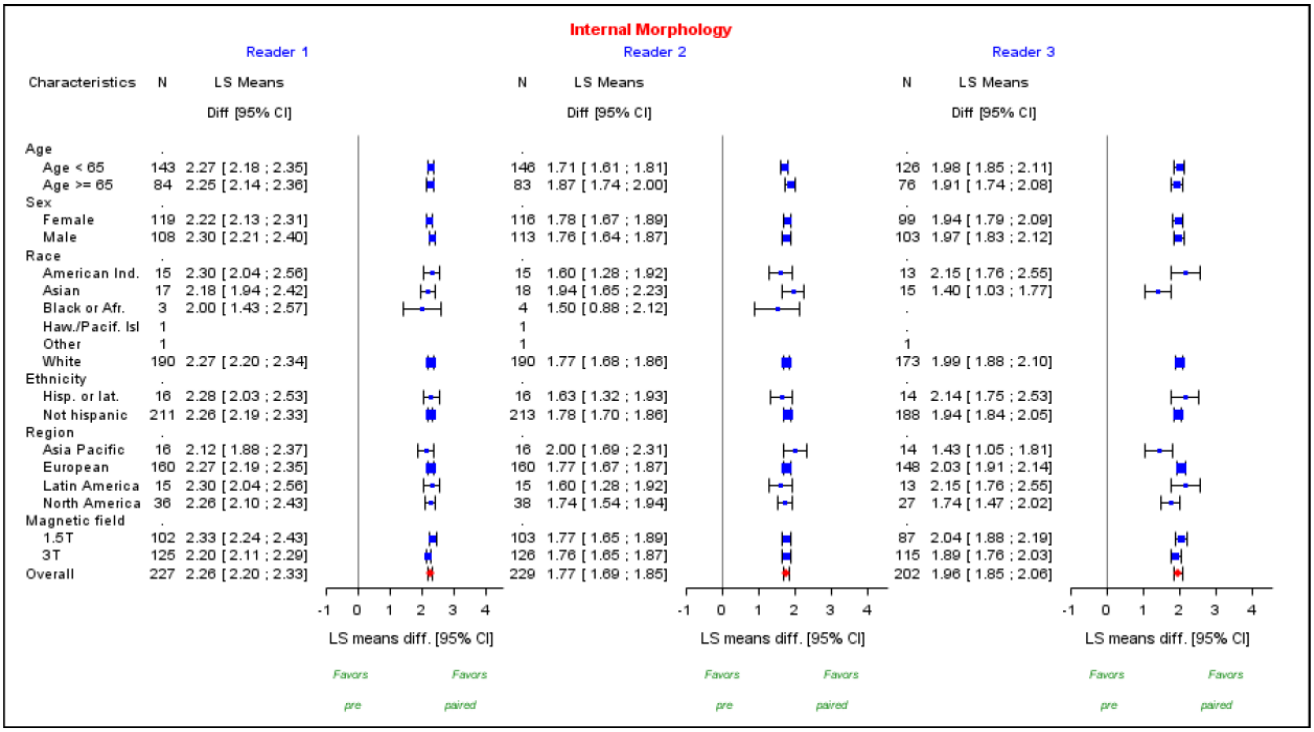
Subgroup analyses of the primary efficacy criteria

Lesion visualisation criteria, lesion to background ratio, percentage enhancement and impact on patient treatment plan have been analysed according to age class, sex, race, ethnicity, region, and magnetic field strength. No difference between subgroup modalities, and results were homogeneous within each

demographic parameter (age, sex, race, ethnicity, geographic region) were observed (Figure 3 and Figure 4 below). The results were also homogenous for MRI performed with magnetic field strength of 1.5T or 3T.

Figure 3. Lesion visualisation criteria - Off-site readings - Forest plot by demographic parameters and magnetic fields- FAS 1 (N=239)





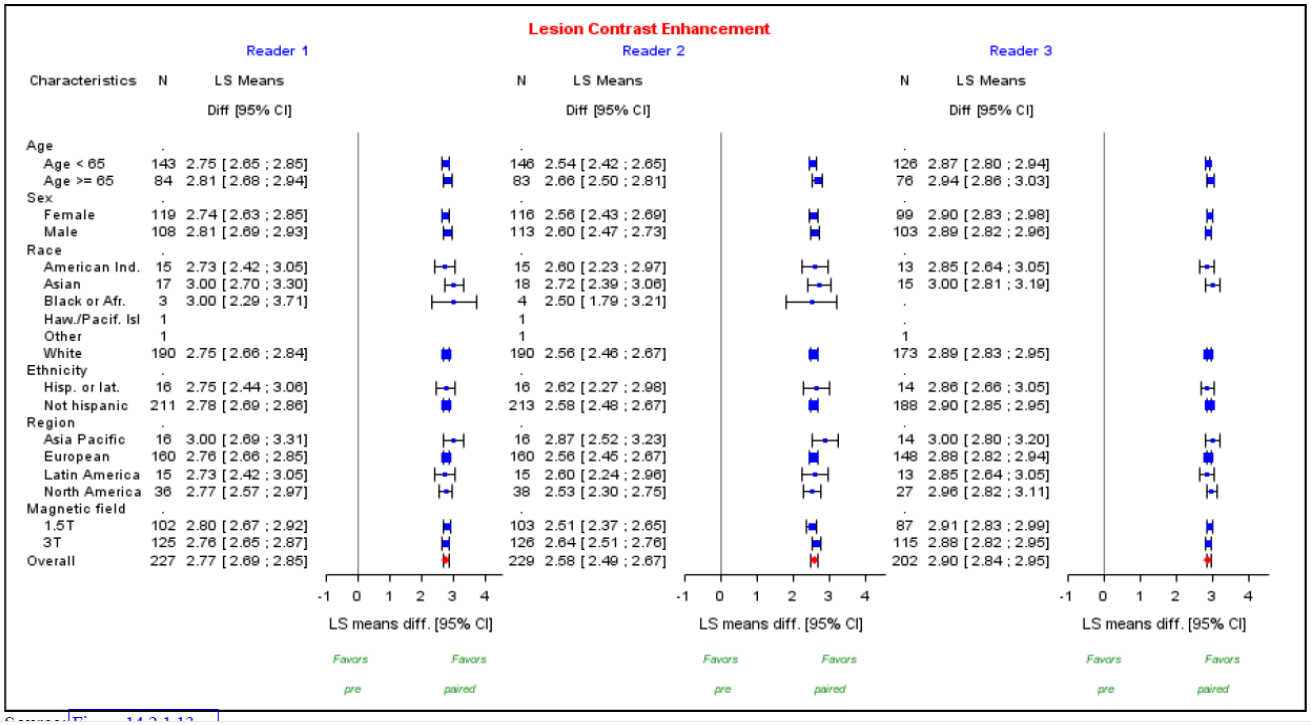
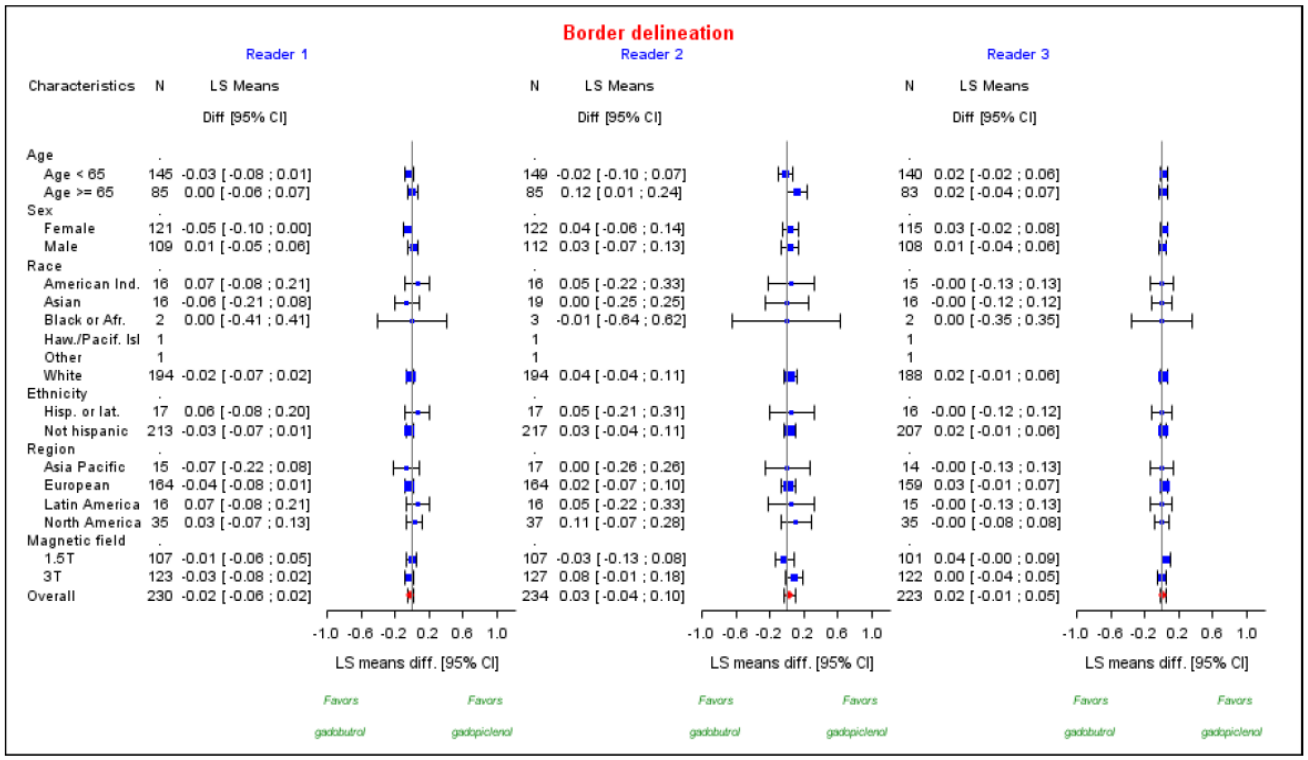
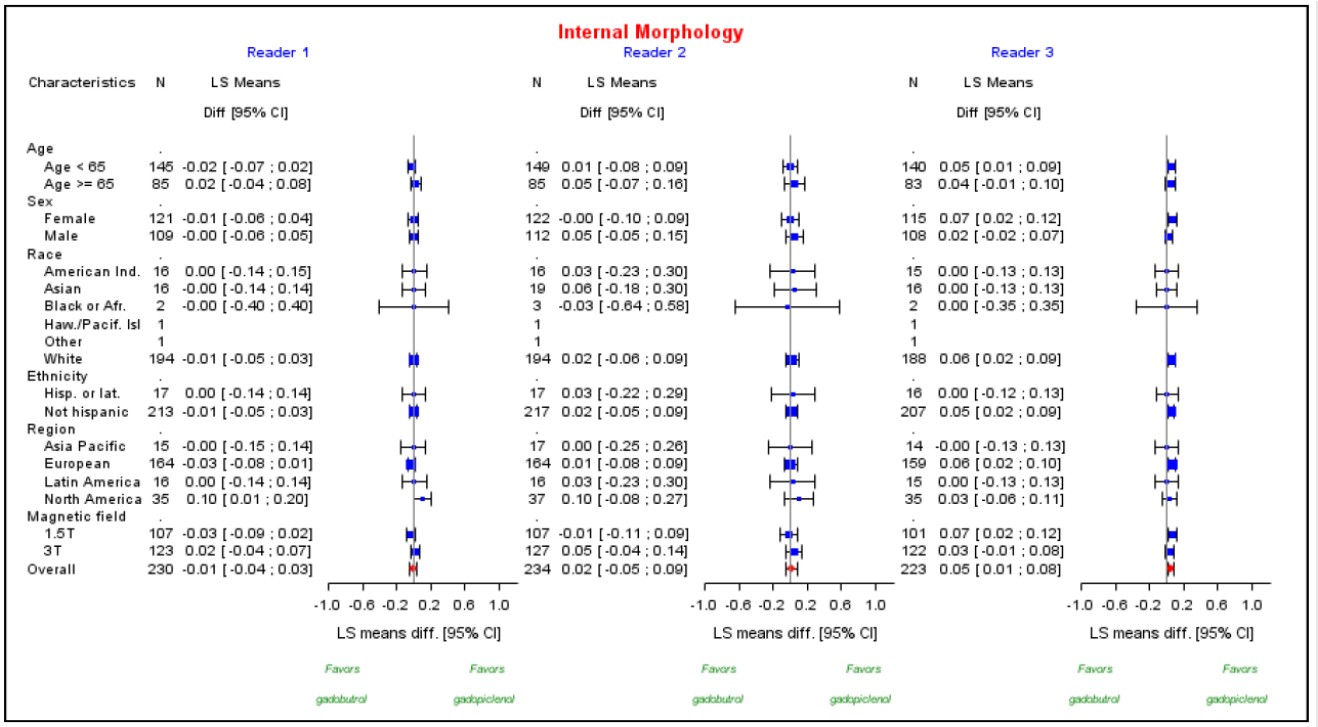
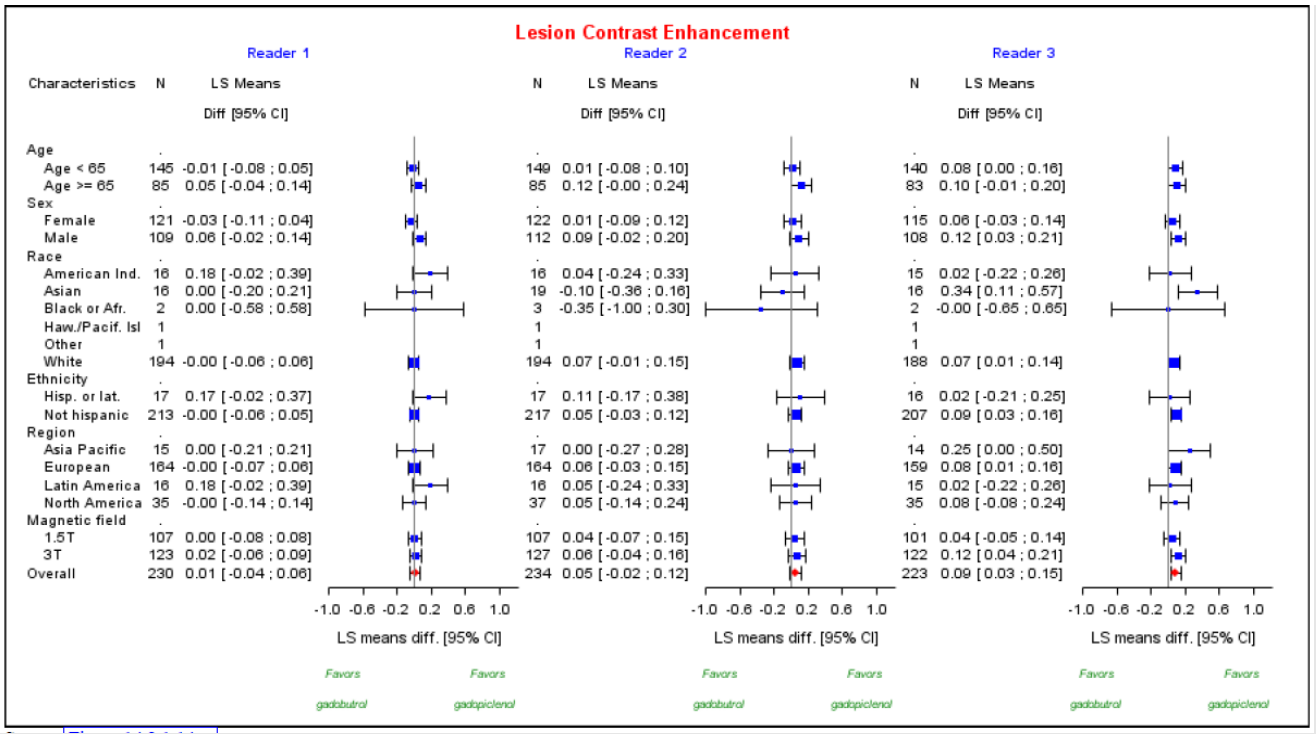


Figure 4. Lesion visualisation criteria - Off-Site Readings – Forest Plot by demographic parameters and magnetic field – FAS 2 (N= 239)







The results of a subgroup analysis of the primary endpoints for 95 patients who underwent surgery or radiation therapy is presented in Table 34 below.

Table 34. Lesion visualisation criteria by presence or not of surgery/radiation- Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol - Mixed Model - FAS 2 (N=239)

Comparison	n	LS Mean (SE) Gadopiclenol	LS Mean (SE) Gadobutrol	LS Mean Difference (SE)	95% CI	surgery/radiation *contrast agent interaction p-value
Border delineation						
surgery/radiation						
Reader 1	92	3.86 (0.03)	3.95 (0.03)	-0.08 (0.03)	[-0.14; -0.03]	0.0065
Reader 2	95	3.65 (0.06)	3.64 (0.06)	0.01 (0.06)	[-0.10; 0.12]	0.5851
Reader 3	90	3.99 (0.02)	3.97 (0.02)	0.02 (0.03)	[-0.03; 0.07]	0.9492
No surgery /radiation						
Reader 1	138	3.94 (0.02)	3.92 (0.02)	0.02 (0.02)	[-0.03; 0.07]	0.0065
Reader 2	139	3.64 (0.05)	3.59 (0.05)	0.05 (0.05)	[-0.04; 0.14]	0.5851
Reader 3	133	3.96 (0.02)	3.94 (0.02)	0.02 (0.02)	[-0.02; 0.06]	0.9492
Internal morphology						
surgery/radiation						
Reader 1	92	3.89 (0.03)	3.93 (0.03)	-0.04 (0.03)	[-0.10; 0.02]	0.1102
Reader 2	95	3.65 (0.06)	3.67 (0.06)	-0.01 (0.05)	[-0.12; 0.09]	0.4014
Reader 3	90	3.99 (0.02)	3.94 (0.02)	0.04 (0.03)	[-0.01; 0.10]	0.8676
No surgery /radiation						
Reader 1	138	3.95 (0.02)	3.93 (0.02)	0.02 (0.02)	[-0.03; 0.07]	0.1102
Reader 2	139	3.63 (0.05)	3.59 (0.05)	0.05 (0.04)	[-0.04; 0.13]	0.4014
Reader 3	133	3.96 (0.02)	3.91 (0.02)	0.05 (0.02)	[0.01; 0.09]	0.8676
Degree of contrast enhancement						
surgery/radiation						
Reader 1	92	3.84 (0.06)	3.85 (0.06)	-0.01 (0.04)	[-0.09; 0.08]	0.5527
Reader 2	95	3.64 (0.07)	3.61 (0.07)	0.03 (0.06)	[-0.08; 0.15]	0.7280
Reader 3	90	3.91 (0.05)	3.89 (0.05)	0.01 (0.05)	[-0.09; 0.11]	0.0448
No surgery /radiation						
Reader 1	138	3.75 (0.05)	3.72 (0.05)	0.02 (0.04)	[-0.04; 0.09]	0.5527
Reader 2	139	3.53 (0.06)	3.47 (0.06)	0.06 (0.05)	[-0.03; 0.16]	0.7280
Reader 3	133	3.89 (0.04)	3.75 (0.04)	0.14 (0.04)	[0.06; 0.22]	0.0448

CI: Confidence Interval; LS: Least Squares; SE: Standard Error.
Only matching lesions are considered.
The models include lesion visualisation factor as dependent variable, period, contrast agent and presence or not of surgery/radiation and interaction as fixed factors, patient as random factor.

Pooled data

Pooled data from GDX-44-010 and the subgroup of patients from GDX-44-004 who received gadopiclenol at 0.05 mmol/kg confirmed the non-inferiority of gadopiclenol versus the other pooled GBCAs (gadobutrol and gadobenate dimeglumine) (Table 35).

Table 35. CNS Pool - Lesion visualisation - Off-Site Readings – Mixed Model – FAS (N= 297)

	n	LS Mean (SE)			95% CI	p-value
		gadopiclenol	other GBCA#	Difference	Difference	
Border delineation						
Reader 1	287	3.65 (0.03)	3.68 (0.03)	-0.03 (0.02)	[-0.07 ; 0.01]	0.1707
Reader 2	281	2.84 (0.05)	2.84 (0.05)	-0.00 (0.05)	[-0.09 ; 0.09]	0.9811
Reader 3	274	3.86 (0.02)	3.89 (0.02)	-0.03 (0.02)	[-0.07 ; 0.01]	0.1919
Internal morphology						
Reader 1	287	3.64 (0.03)	3.64 (0.03)	-0.00 (0.02)	[-0.05 ; 0.04]	0.9371
Reader 2	281	2.72 (0.05)	2.75 (0.05)	-0.03 (0.04)	[-0.11 ; 0.06]	0.5436
Reader 3	274	3.86 (0.02)	3.87 (0.02)	-0.01 (0.02)	[-0.05 ; 0.04]	0.7914
Degree of contrast enhancement						
Reader 1	287	3.51 (0.05)	3.53 (0.05)	-0.01 (0.03)	[-0.08 ; 0.05]	0.6330
Reader 2	281	3.69 (0.05)	3.63 (0.05)	0.06 (0.04)	[-0.03 ; 0.14]	0.1808
Reader 3	274	3.79 (0.04)	3.74 (0.04)	0.04 (0.04)	[-0.03 ; 0.11]	0.2520

Secondary criteria

Improvement in lesion visualisation scores at patient-level

Improvement in lesion visualisation scores at patient-level was shown by Paired images with gadopiclenol scoring better than Pre-contrast images in more than 95% of the evaluations for all three readers and for all 3 criteria (border delineation, internal morphology and degree of contrast enhancement). Similar results were obtained with gadobutrol.

Lesion visualisation at lesion level

Lesion visualisation criteria at a lesion level for paired images with gadopiclenol compared with pre-contrast images showed similar results to those obtained at patient level. Assessment of lesion visualisation criteria by the off-site readers at lesion level for MRI with gadopiclenol vs MRI with gadobutrol is also similar to those obtained at patient level (Table 36). Lesion visualisation criteria by the off-site blinded readers at lesion level were also analysed according to lesion size (≤1 cm, >1 cm and ≤2 cm, >2 cm) (Table 37). No differences were observed for different lesion sizes.

Table 36. Lesion visualisation criteria at lesion level - Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol – Mixed Model – Extended FAS 2 (N=241)

Comparison	n	LS Mean (SE) Gadopiclenol	LS Mean (SE) Gadobutrol	LS Mean Difference (SE)	95% CI
Border delineation					
Reader 1	403	3.76 (0.03)	3.74 (0.03)	0.02 (0.02)	[-0.03 ; 0.06]
Reader 2	432	3.53 (0.04)	3.46 (0.04)	0.06 (0.03)	[-0.00 ; 0.13]
Reader 3	376	3.88 (0.03)	3.78 (0.03)	0.10 (0.03)	[0.04 ; 0.16]
Internal morphology					
Reader 1	403	3.92 (0.01)	3.93 (0.01)	-0.01 (0.02)	[-0.04 ; 0.02]
Reader 2	432	3.59 (0.03)	3.56 (0.03)	0.02 (0.03)	[-0.04 ; 0.09]
Reader 3	376	3.96 (0.01)	3.94 (0.01)	0.03 (0.02)	[-0.01 ; 0.06]
Degree of contrast enhancement					
Reader 1	403	3.92 (0.01)	3.93 (0.01)	-0.01 (0.02)	[-0.04 ; 0.02]
Reader 2	432	3.59 (0.03)	3.57 (0.03)	0.02 (0.03)	[-0.04 ; 0.08]
Reader 3	376	3.96 (0.01)	3.91 (0.01)	0.05 (0.02)	[0.02 ; 0.08]

n represents the number of lesions
CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error.
Matching and not matching lesions are considered.
The models include lesion visualization factor as dependent variable, contrast agent group and period as fixed factors, patient as random factor.
Source: Listings 16.2.6.1, 16.2.6.2 and 16.2.6.3

Table 37. Lesion visualisation criteria at lesion level - Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol – Lesion size analysis – Mixed Model – Extended FAS 2 (N=241)

	n	LS Mean (SE)			95% CI of difference	Lesion size*contrast Agent interaction p-value
		Gadopiclenol	Gadobutrol	Difference		
Border delineation						
≤1 cm						
Reader 1	95	3.89 (0.03)	3.91 (0.03)	-0.02 (0.04)	[-0.09 ; 0.05]	
Reader 2	105	3.27 (0.07)	3.28 (0.07)	-0.01 (0.08)	[-0.17 ; 0.15]	
Reader 3	62	3.90 (0.03)	3.80 (0.03)	0.10 (0.05)	[0.01 ; 0.19]	
>1 cm and ≤2 cm						
Reader 1	156	3.93 (0.02)	3.94 (0.02)	-0.01 (0.03)	[-0.06 ; 0.05]	0.9719
Reader 2	179	3.65 (0.05)	3.56 (0.05)	0.09 (0.06)	[-0.02 ; 0.20]	0.3734
Reader 3	148	3.97 (0.02)	3.94 (0.02)	0.04 (0.03)	[-0.02 ; 0.09]	0.1479
>2 cm						
Reader 1	184	3.92 (0.02)	3.93 (0.02)	-0.01 (0.02)	[-0.06 ; 0.03]	
Reader 2	202	3.70 (0.05)	3.71 (0.05)	-0.01 (0.05)	[-0.11 ; 0.08]	
Reader 3	207	3.97 (0.02)	3.97 (0.02)	0.00 (0.02)	[-0.04 ; 0.05]	
Internal morphology						
≤1 cm						
Reader 1	95	3.84 (0.03)	3.91 (0.03)	-0.07 (0.03)	[-0.13 ; 0.00]	
Reader 2	105	3.21 (0.06)	3.27 (0.07)	-0.06 (0.08)	[-0.22 ; 0.09]	
Reader 3	62	3.92 (0.04)	3.82 (0.04)	0.10 (0.05)	[0.01 ; 0.19]	
>1 cm and ≤2 cm						
Reader 1	156	3.94 (0.02)	3.92 (0.02)	0.02 (0.03)	[-0.03 ; 0.07]	0.1418
Reader 2	179	3.66 (0.05)	3.59 (0.05)	0.07 (0.06)	[-0.04 ; 0.18]	0.4038
Reader 3	148	3.97 (0.02)	3.88 (0.02)	0.09 (0.03)	[0.04 ; 0.15]	0.0210
>2 cm						
Reader 1	184	3.95 (0.02)	3.95 (0.02)	0.00 (0.02)	[-0.04 ; 0.05]	
Reader 2	202	3.72 (0.04)	3.70 (0.04)	0.02 (0.05)	[-0.07 ; 0.12]	
Reader 3	207	3.96 (0.02)	3.95 (0.02)	0.01 (0.02)	[-0.03 ; 0.05]	
Degree of contrast enhancement						
≤1 cm						
Reader 1	95	3.60 (0.06)	3.64 (0.06)	-0.04 (0.05)	[-0.15 ; 0.06]	
Reader 2	105	3.14 (0.07)	3.12 (0.08)	0.02 (0.09)	[-0.14 ; 0.19]	
Reader 3	62	3.85 (0.08)	3.73 (0.08)	0.11 (0.09)	[-0.07 ; 0.29]	
>1 cm and ≤2 cm						
Reader 1	156	3.82 (0.04)	3.77 (0.05)	0.05 (0.04)	[-0.02 ; 0.13]	0.3547
Reader 2	179	3.60 (0.06)	3.43 (0.05)	0.17 (0.06)	[0.05 ; 0.29]	0.0763
Reader 3	148	3.87 (0.05)	3.80 (0.05)	0.07 (0.05)	[-0.03 ; 0.18]	0.8294
>2 cm						
Reader 1	184	3.79 (0.04)	3.77 (0.04)	0.02 (0.03)	[-0.05 ; 0.08]	
Reader 2	202	3.65 (0.05)	3.66 (0.05)	-0.01 (0.05)	[-0.11 ; 0.09]	
Reader 3	207	3.90 (0.04)	3.78 (0.04)	0.11 (0.04)	[0.03 ; 0.20]	

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error
n represents the number of lesions
Non-matching and matching lesions are considered.
*The models include lesion visualization factor as dependent variable, contrast agent, lesion size, period and contrast agent*lesion size interaction as fixed factors, lesion as random factor.*
Center has been removed from the fixed factors for convergence issues.

Technical adequacy of images

There was some variability in the assessment of technical adequacy of Pre-contrast images between the 3 readers with the large majority of images (>95%) considered good by reader 1, poor by reader 2 and fair by reader 3. Regarding Paired images with gadopiclenol, all three readers considered the majority as being of good quality: 94.3%, 80.5% and 95.1% for readers 1, 2 and 3, respectively. Technical adequacy of paired images was similar with gadopiclenol and gadobutrol (95.1%, 80.4%, and 97.6% for gadobutrol for readers 1, 2, and 3 respectively).

Number, size and location of lesions

Most patients presented only one lesion identified, and the median largest diameter of the most representative lesion ranged from 18.8 to 23.8 mm with Pre-contrast images and 22.0 to 24.6 mm with Paired gadopiclenol images, depending on the blinded reader. The range of lesion size was 3 to 264 mm. There was no difference on lesion size measured on images with gadobutrol. For MRI with gadopiclenol, more lesions were identified with Paired images compared to Pre-contrast images for all three readers ($p<0.005$) (Table 38). The number of identified lesions was similar for both contrast agents, gadopiclenol and gadobutrol (Table 39).

Distribution of lesions according to location was similar between Pre-contrast and Paired images with gadopiclenol and between gadopiclenol and gadobutrol.

Table 38. Number of Lesions - Off-Site Readings - MRI with Gadopiclenol - PAIRED vs PRE – Descriptive Statistics – Extended FAS 1 (N=246)

	Gadopiclenol					
	Reader 1		Reader 2		Reader 3	
	Pre (N=246)	Paired (N=246)	Pre (N=246)	Paired (N=246)	Pre (N=246)	Paired (N=246)
Number of lesion(s)						
n	246	246	246	246	245	244
Mean (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	1.0	1.0	1.0	1.0	1.0	1.0
Min. ; Max.	0 ; 10	0 ; 10	1 ; 99	1 ; 99	0 ; 40	0 ; 35
Not assessable	0	0	0	0	1	2
In categories						
No lesion	1 (0.4%)	2 (0.8%)	0	0	8 (3.3%)	9 (3.7%)
1 lesion	182 (74.0%)	162 (65.9%)	177 (72.0%)	158 (64.2%)	186 (75.9%)	166 (68.0%)
2 lesions	34 (13.8%)	34 (13.8%)	36 (14.6%)	38 (15.4%)	25 (10.2%)	40 (16.4%)
3 lesions	15 (6.1%)	14 (5.7%)	17 (6.9%)	16 (6.5%)	9 (3.7%)	7 (2.9%)
More than 3 lesions	14 (5.7%)	34 (13.8%)	16 (6.5%)	34 (13.8%)	17 (6.9%)	22 (9.0%)
Not assessable	0	0	0	0	1	2

SD: Standard Deviation; Matching and not matching lesions are considered.

Table 39. Number of Lesions - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol – Descriptive Statistics – Extended FAS 2 (N=241)

	Reader 1		Reader 2		Reader 3	
	Gadopiclenol (N=241)	Gadobutrol (N=241)	Gadopiclenol (N=241)	Gadobutrol (N=241)	Gadopiclenol (N=241)	Gadobutrol (N=241)
Number of lesion(s)						
n	241	240	241	241	239	240
Mean (SD)	2.1 (2.3)	2.0 (2.2)	2.9 (7.8)	2.9 (8.1)	2.1 (3.9)	2.4 (5.0)
Median	1.0	1.0	1.0	1.0	1.0	1.0
Min. ; Max.	0 ; 10	0 ; 10	1 ; 99	1 ; 99	0 ; 35	0 ; 48
Not assessable	0	1	0	0	2	1
In categories						
No lesion	2 (0.8%)	3 (1.3%)	0	0	9 (3.8%)	10 (4.2%)
1 lesion	158 (65.6%)	160 (66.7%)	154 (63.9%)	156 (64.7%)	161 (67.4%)	161 (67.1%)
2 lesions	34 (14.1%)	36 (15.0%)	37 (15.4%)	35 (14.5%)	40 (16.7%)	29 (12.1%)
3 lesions	13 (5.4%)	13 (5.4%)	16 (6.6%)	13 (5.4%)	7 (2.9%)	12 (5.0%)
More than 3 lesions	34 (14.1%)	28 (11.7%)	34 (14.1%)	37 (15.4%)	22 (9.2%)	28 (11.7%)
Not assessable	0	1	0	0	2	1

Diagnostic confidence

The level of diagnostic confidence was improved with paired images compared to Pre-contrast images, with a level of "excellent" in 65.9% to 92.8% of the cases (depending on the blinded readers) with Paired images with gadopiclenol compared to less than 2% with pre-contrast image, where the levels of diagnostic confidence were most often moderate. There was a slightly higher percentage of an excellent level of diagnostic confidence with Paired images with gadopiclenol (66.0% to 93.0%) compared to gadobutrol (63.1% to 89.1%) for all 3 blinded readers. However, the median level of confidence was quite high with both contrast agents (5, which is the maximum) (Table 40). Regarding radiological diagnosis, the main difference between pre and paired images was for glial tumours, for which tumour grade could be determined in more cases with Paired images.

Table 40. Radiological Diagnosis and Level of Diagnostic Confidence - Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol – Extended FAS 2 (N=241)

	Reader 1		Reader 2		Reader 3	
	Gadopiclenol (N=239)*	Gadobutrol (N=237)*	Gadopiclenol (N=241)*	Gadobutrol (N=241)*	Gadopiclenol (N=230)*	Gadobutrol (N=230)*
Radiological diagnosis						
n	239	237	241	241	230	230
Not assessable	0	0	0	0	0	0
Glial tumor, low grade (I/II)	3 (1.3%)	4 (1.7%)	6 (2.5%)	5 (2.1%)	2 (0.9%)	3 (1.3%)
Glial tumor, high grade (III/IV)	66 (27.6%)	65 (27.4%)	52 (21.6%)	56 (23.2%)	61 (26.5%)	68 (29.6%)
Glial tumor, tumor grade cannot be determined	1 (0.4%)	2 (0.8%)	9 (3.7%)	13 (5.4%)	4 (1.7%)	2 (0.9%)
Meningioma	82 (34.3%)	83 (35.0%)	78 (32.4%)	77 (32.0%)	87 (37.8%)	88 (38.3%)
Schwannoma	28 (11.7%)	24 (10.1%)	20 (8.3%)	22 (9.1%)	28 (12.2%)	21 (9.1%)
Pituitary adenomas	5 (2.1%)	3 (1.3%)	9 (3.7%)	10 (4.1%)	4 (1.7%)	4 (1.7%)
Brain metastasis	47 (19.7%)	49 (20.7%)	52 (21.6%)	46 (19.1%)	38 (16.5%)	38 (16.5%)
Spine metastasis	0	0	1 (0.4%)	1 (0.4%)	0	0
Inflammatory disease	0	0	1 (0.4%)	0	0	0
Abscess	0	0	6 (2.5%)	2 (0.8%)	0	0
Stroke	0	0	1 (0.4%)	3 (1.2%)	0	0
Vascular malformation	1 (0.4%)	0	0	0	0	0
Other	6 (2.5%)	7 (3.0%)	6 (2.5%)	6 (2.5%)	6 (2.6%)	6 (2.6%)
Level of diagnostic confidence						
2 = Poor: uncertain	0	0	2 (0.8%)	4 (1.7%)	0	1 (0.4%)
3 = Moderate: moderately certain	5 (2.1%)	8 (3.4%)	22 (9.1%)	15 (6.2%)	2 (0.9%)	2 (0.9%)
4 = High: good certainty	73 (30.5%)	76 (32.1%)	58 (24.1%)	70 (29.0%)	14 (6.1%)	22 (9.6%)
5 = Excellent: very certain	161 (67.4%)	153 (64.6%)	159 (66.0%)	152 (63.1%)	214 (93.0%)	205 (89.1%)
Mean (SD)	4.7 (0.5)	4.6 (0.6)	4.6 (0.7)	4.5 (0.7)	4.9 (0.3)	4.9 (0.4)
Median	5.0	5.0	5.0	5.0	5.0	5.0
Min. ; Max.	3 ; 5	3 ; 5	2 ; 5	2 ; 5	3 ; 5	2 ; 5

*Only patients with at least one lesion are presented; no missing data. SD: Standard Deviation.

Impact of contrast-enhance MRI on subject treatment plan (on-site reading)

Based on unenhanced MRI, the proposed therapeutic management was most often biopsy or a treatment other than chemotherapy, surgery, or radiotherapy (multiple answers were possible). Based on Paired images, the proposed therapeutic management was more often chemotherapy, radiotherapy or surgery. The addition of contrast injection could change the treatment plan in 23.3% of the patients for gadopiclenol and 23.7% for gadobutrol. There was no difference between both contrast agents for the change on treatment plan (Table 41).

Table 41. Patient Treatment Plan Evaluation - On-Site Reading – MRI with Gadopiclenol vs MRI with Gadobutrol – Extended FAS 2 (N=241)

	Gadopiclenol (N=241)	Gadobutrol (N=241)
Could the treatment plan be changed?		
n	240	241
Yes	56 (23.3%)	57 (23.7%)
No	184 (76.7%)	184 (76.3%)
Missing data	1	0
If Yes, therapeutic management proposed:		
based on unenhanced MRI		
n	56	57
Surgery	7 (12.5%)	7 (12.3%)
Biopsy	16 (28.6%)	16 (28.1%)
Chemotherapy	2 (3.6%)	2 (3.5%)
Radiotherapy	1 (1.8%)	1 (1.8%)
Other treatment	37 (66.1%)	38 (66.7%)
based on combined unenhanced and enhanced MRI		
n	56	57
Surgery	19 (33.9%)	17 (29.8%)
Biopsy	7 (12.5%)	6 (10.5%)
Chemotherapy	27 (48.2%)	28 (49.1%)
Radiotherapy	25 (44.6%)	26 (45.6%)
Other treatment	12 (21.4%)	11 (19.3%)

When analyzing the data according to tumour classification based on unenhanced MRI, the treatment plan could be changed for 28% of 81 patients with malignant diagnosis and about 12% of 111 patients with non-malignant diagnosis (Table 42). There was no difference between both contrast agents for the change on the treatment plan.

Table 42. Patient Treatment Plan Evaluation by tumour classification before contrast agent administration - On-Site Reading - MRI with Gadopiclenol vs MRI with Gadobutrol – Extended FAS 2 (N= 241)

	Malignant		Non-Malignant		Not Assessable	
	Gadopiclenol (N=81)	Gadobutrol (N=81)	Gadopiclenol (N=110)	Gadobutrol (N=111)	Gadopiclenol (N=22)	Gadobutrol (N=22)
Could the treatment plan be changed?						
n	81	81	110	111	22	22
Yes	23 (28.4%)	23 (28.4%)	13 (11.8%)	14 (12.6%)	14 (63.6%)	14 (63.6%)
No	58 (71.6%)	58 (71.6%)	97 (88.2%)	97 (87.4%)	8 (36.4%)	8 (36.4%)
If Yes, therapeutic management proposed: based on unenhanced MRI						
n	23	23	13	14	14	14
Surgery	2 (8.7%)	2 (8.7%)	3 (23.1%)	3 (21.4%)	1 (7.1%)	1 (7.1%)
Biopsy	6 (26.1%)	6 (26.1%)	6 (46.2%)	6 (42.9%)	4 (28.6%)	4 (28.6%)
Chemotherapy	1 (4.3%)	1 (4.3%)	0	0	1 (7.1%)	1 (7.1%)
Radiotherapy	0	0	1 (7.7%)	1 (7.1%)	0	0
Other treatment	15 (65.2%)	15 (65.2%)	6 (46.2%)	7 (50.0%)	10 (71.4%)	10 (71.4%)
based on combined unenhanced and enhanced MRI						
n	23	23	13	14	14	14
Surgery	7 (30.4%)	6 (26.1%)	7 (53.8%)	7 (50.0%)	4 (28.6%)	3 (21.4%)
Biopsy	3 (13.0%)	3 (13.0%)	2 (15.4%)	2 (14.3%)	2 (14.3%)	1 (7.1%)
Chemotherapy	14 (60.9%)	14 (60.9%)	3 (23.1%)	3 (21.4%)	8 (57.1%)	9 (64.3%)
Radiotherapy	15 (65.2%)	15 (65.2%)	5 (38.5%)	5 (35.7%)	4 (28.6%)	5 (35.7%)
Other treatment	0	0	5 (38.5%)	5 (35.7%)	4 (28.6%)	3 (21.4%)

Tumor Classification Not assessable includes the following diagnosis: "Not assessable" and "Glial tumor, tumor grade cannot be determined"

Quantitative parameters (contrast to noise ratio, percentage of lesion enhancement and lesion to background ratio)

Lesion to brain ratio (LBR) and percentage of enhancement were significantly higher with gadopiclenol compared to gadobutrol for all three readers, with 95% CI of the difference not including 0 (p<0.0001). For CNR, the difference was statistically significant for two readers (Table 43).

Table 43. CNS - GDX-44-010 - Percentage of enhancement, Contrast to Noise Ratio, Lesion to Background Ratio - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol - Mixed Model – FAS 2 (N= 239)

	n	LS Mean (SE)			95% CI difference	p-value
		Gadopiclenol	Gadobutrol	Difference		
Percentage of enhancement*						
Reader 1	230	195.01 (7.90)	158.61 (7.90)	36.41 (4.46)	[27.63 ; 45.18]	<0.0001
Reader 2	233	221.52 (9.31)	184.72 (9.31)	36.80 (6.71)	[23.58 ; 50.01]	<0.0001
Reader 3	223	196.55 (8.55)	153.69 (8.55)	42.85 (5.22)	[32.57 ; 53.14]	<0.0001
Contrast to Noise Ratio**						
Reader 1	228	178.32 (12.67)	153.07 (12.67)	25.26 (12.92)	[-0.21 ; 50.72]	0.0519
Reader 2	233	114.60 (7.19)	96.27 (7.19)	18.33 (7.71)	[3.14 ; 33.52]	0.0182
Reader 3	223	60.50 (2.86)	47.04 (2.86)	13.46 (2.41)	[8.70 ; 18.22]	<0.0001
Lesion to Background Ratio**						
Reader 1	228	2.03 (0.04)	1.83 (0.04)	0.20 (0.02)	[0.16 ; 0.24]	<0.0001
Reader 2	233	2.18 (0.04)	1.97 (0.04)	0.21 (0.03)	[0.16 ; 0.26]	<0.0001

	n	LS Mean (SE)			95% CI difference	p-value
		Gadopiclenol	Gadobutrol	Difference		
Reader 3	223	2.03 (0.04)	1.79 (0.04)	0.24 (0.02)	[0.19 ; 0.28]	<0.0001

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error; Only matching lesions are considered.
*The models include Percentage of enhancement as dependent variable, contrast agent group and period as fixed factors, patient as random factor.
** The models include Contrast to Noise Ratio (or Lesion to Background Ratio) as dependent variable, contrast agent group, period and the unenhanced value (Pre) as fixed factors, patient as random factor.

Overall diagnostic preference

The overall diagnostic preference was assessed in a global matched-pairs fashion (Paired images from MRI with gadopiclenol and MRI with gadobutrol for each patient) by three additional blinded readers are presented in Table 44. The most frequent reasons for preference were superior contrast enhancement and better delineation of normal structure and lesion. They also considered that the internal structure of the lesions was better visualised.

Table 44. CNS - GDX-44-010 - Overall Diagnostic Preference - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol

Dose of gadopiclenol	Reader	N	gadopiclenol preferred	No preference	gadobutrol preferred	p-value (a)
0.5 mmol/kg	4	241	108 (44.8%)	98 (40.7%)	35 (14.5%)	<0.0001
	5	241	131 (54.4%)	52 (21.6%)	58 (24.1%)	<0.0001
	6	241	138 (57.3%)	56 (23.2%)	47 (19.5%)	<0.0001

(a) Wilcoxon signed-rank test.

- **Ancillary analyses**

Expert concordance assessment

An additional image evaluation has been conducted to assess concordance in lesion detectability obtained with 0.05 mmol/kg gadopiclenol and 0.1 mmol/kg of comparator gadobutrol in MRI.

Methodology

This assessment was performed by a total of three experienced neuroradiologists ("Blinded Readers") reading MR images of CNS (MR images of brain and spine from study GDX-44-010) and Head and Neck (MR images from study GDX-44-011), who were fully blinded to all patient clinical information and to the contrast agent used in each MR exam, and independently and separately reviewed all the investigational MRI images in a fully randomised order to assess the number of lesions and locate them in each MR exam from original study GDX-44-010 (CNS) and from study GDX-44-011 (head & neck) obtained with 0.05 mmol/kg gadopiclenol and 0.1 mmol/kg gadobutrol. Screen shots were obtained documenting the lesions that were marked and numbered on the images by each reader.

The following assessments were performed by each reader independently for each MRI exam based on the randomised order for presentation of exams:

- Technical adequacy (are the images interpretable?): Yes/No

If the whole MR exam was judged as technically inadequate, then the evaluation was stopped for that MR exam.

If the whole MR exam was judged as technically adequate, then the following was assessed:

- Lesions detected: yes/no? If yes, the table with lesion number/location was completed.

- For each detected lesion, the individual lesion location was defined based on the codes provided

Each detected lesion was marked together with its corresponding lesion number on the images and screenshots were obtained.

One additional independent experienced neuroradiologist (Concordance Reader) tracked all lesions detected on Exam 1 (Visit 2) and Exam 2 (Visit 4) across the evaluations of the blinded readers by assigning one unique reference number for each matched lesion. All patients were presented to the Concordance Reader even if the patient had no lesions identified by one or two Blinded Readers.

In case of discordant lesions, i.e., lesions seen on one exam but not in the other, respective Panels (Concordance Reader and each individual Blinded Reader) assessed the nature of the lesion (radiology diagnosis based on image interpretation in routine practice) and potential clinical impact of this non-concordance in detection of lesions. The patient profiles consisting of all the available clinical information (e.g., medical history and results of previous imaging studies) were provided to the Panels.

All the selected blinded and concordance readers had an extensive and significant experience in the assessment and interpretation of MRI examinations of the CNS. None of the readers was involved in the initial evaluation of the MR images from study GDX-44-010, or in the images analysis provided in March 2023 to EMA.

All the individual patient studies for which both paired images (unenhanced and contrast enhanced MRI) for gadopiclenol and gadobutrol MRIs were available and without major protocol deviations (Per Protocol Set of the original studies for the primary evaluation) were included in this assessment.

Additionally, 10% of the patient studies (both Exam 1 and Exam 2) were randomised and included twice in the read queue in a blinded manner. The first read of these patients was the basis of concordance/discordance analysis, while second read was the basis of intra-reader variability assessment.

Results

Concordance in lesion detection was analysed for 235 patients with assessable and comparable images.

Lesion level

A perfect agreement in lesion detectability between gadopiclenol at 0.05 mmol/kg and gadobutrol at 0.1 mmol/kg was observed for 88.0% to 89.8% of the lesions detected with gadobutrol (depending on the reader)(Table 45).

In patients with a single lesion detected with gadobutrol, this lesion was also detected with gadopiclenol in all cases except 2 (98.7% to 100% of the cases). The large majority of patients (95%) had no more than 10 lesions and among these patients, the rate of common lesions detected with gadopiclenol and gadobutrol was 92.5% to 94.6% (Table 46).

Table 45. Summary for CNS of concordance in lesions detected with each GBCA

	N lesions detected with gadobutrol	Lesions seen with both contrast agents (matching lesions)	Lesions seen only with gadobutrol	Lesions seen only with gadopiclenol
GDX-44-010 (CNS)				
Reader 1	590	**529 (89.7%)**	61	60
Reader 2	633	**557 (88.0%)**	76	78
Reader 3	880	**790 (89.8%)**	90	54

Table 46. GDX-44-010 (CNS) - Number of identical lesions ("common lesions") detected per patient using gadobutrol as standard of care, as per blinded unpaired assessments followed by concordance lesion tracking

Number of lesions detected per patient on gadobutrol MRI	Reader 1			Reader 2			Reader 3		
	N patients	No. of Lesions Detected		N patients	No. of Lesions Detected		N patients	No. of Lesions Detected	
		on gadobutrol MRIs	on both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)
001	156	156	154 (98.7%)	140	140	140 (100%)	135	135	134 (99.3%)
002	32	64	63 (98.4%)	44	88	85 (96.6%)	39	78	76 (97.4%)
003	13	39	35 (89.7%)	15	45	43 (95.6%)	23	69	67 (97.1%)
004	4	16	15 (93.8%)	9	36	28 (77.8%)	9	36	32 (88.9%)
005	4	20	16 (80%)	4	20	17 (85%)	2	10	10 (100%)
006	3	18	14 (77.8%)	2	12	6 (50%)	4	24	23 (95.8%)
007	4	28	23 (82.1%)	2	14	12 (85.7%)	3	21	18 (85.7%)
008	3	24	18 (75%)	1	8	5 (62.5%)		.	
009		.		1	9	9 (100%)	2	18	15 (83.3%)
010	1	10	9 (90%)		.		2	20	14 (70%)
Total for patients with ≤10 lesions	***220***	***375***	***347 (92.5%)***	***218***	***372***	***345 (92.7%)***	***219***	***411***	***389 (94.6%)***
011	1	11	8 (72.7%)		.		1	11	11 (100%)
012	1	12	7 (58.3%)		.		3	36	30 (83.3%)
013		.			.		1	13	13 (100%)
014		.		2	28	24 (85.7%)		.	
015		.		1	15	11 (73.3%)		.	
017		.			.		1	17	15 (88.2%)
019	1	19	17 (89.5%)		.			.	
020		.			.		1	20	18 (90%)
022		.			.		1	22	22 (100%)
024	1	24	21 (87.5%)		.			.	
025		.		1	25	22 (88%)	1	25	20 (80%)
026	1	26	22 (84.6%)		.			.	
028		.		1	28	20 (71.4%)		.	
032		.			.		1	32	26 (81.3%)
033	1	33	28 (84.8%)		.			.	
034		.		1	34	23 (67.6%)		.	
035	1	35	33 (94.3%)		.			.	
038		.		1	38	36 (94.7%)		.	
039		.		1	39	30 (76.9%)		.	
047		.			.		1	47	44 (93.6%)
054		.		1	54	46 (85.2%)		.	
055	1	55	46 (83.6%)		.			.	
061		.			.		1	61	48 (78.7%)
085		.			.		1	85	74 (87.1%)
100		.			.		1	100	80 (80%)

Number of lesions detected per patient on gadobutrol MRI	Reader 1			Reader 2			Reader 3		
	N patients	No. of Lesions Detected		N patients	No. of Lesions Detected		N patients	No. of Lesions Detected	
		on gadobutrol MRIs	on both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)
Total	***228***	***590***	***529 (89.7%)***	***227***	***633***	***557 (88.0%)***	***233***	***880***	***790 (89.8%)***

Patient level

At patient level, a perfect agreement in lesion detectability was obtained for 84.3% to 86.0% of the patients (Table 47).

Depending on the reader, among the 235 assessed patients, 190 to 197 (80.9% to 83.8%) had only common lesions detected with both GBCAs (perfect match), 31 to 36 (13.2% to 15.3%) had common lesions and additional lesions individually seen with one of the GBCAs and 1 or 2 (0.4% to 0.9%) had no common lesions (Table 48). Furthermore, no lesions were detected consistently with both GBCAs for 2 to 8 patients (0.9% to 3.4%), depending on the reader.

There was a similar number of additional lesions seen uniquely with gadobutrol or seen uniquely with gadopiclenol. When a patient presented with both lesions detected only with gadobutrol and lesions detected only with gadopiclenol, it was generally in a clinical situation when the number of lesions does not have potential clinical impact on patient management and treatment decision.

Table 47. Summary for CNS of the number of patients with perfect and imperfect agreement between contrast agents in the set of lesions observed

		N patients	**# patients in which more lesions detected by gadobutrol**	**# patients in which more lesions detected by gadopiclenol**	**# patients in which each GBCA detected the same number and set of lesions**	**# patients in which each GBCA detected the same number but a different set of lesions**
CNS (GDX-44-010)	**Reader 1**	235	13 (5.5%)	10 (4.3%)	202 (86.0%)	10 (4.3%)
	Reader 2	235	7 (3.0%)	15 (6.4%)	198 (84.3%)	15 (6.4%)
	Reader 3	235	16 (6.8%)	16 (6.8%)	199 (84.7%)	4 (1.7%)

Table 48. GDX-44-010 (CNS) - Lesion detection at patient level, blinded unpaired assessment followed by concordance lesion tracking

				Reader 1 (N=235*)	Reader 2 (N=235*)	Reader 3 (N=235*)
	Patients with lesions detected on:					
	Both MRIs (common lesions)	Gadobutrol MRI only	Gadopiclenol MRI only			
Perfect matches (no lesions or only common lesions)	No lesions detected			**7 (3%)**	**8 (3.4%)**	**2 (0.9%)**
	Yes	None	None	**195 (83%)**	**190 (80.9%)**	**197 (83.8%)**
Common lesions +additional lesions seen with only one GBCA	Yes	Yes	None	7 (3%)	5 (2.1%)	9 (3.8%)
	Yes	None	Yes	5 (2.1%)	11 (4.7%)	12 (5.1%)
	Yes	Yes	Yes	19 (8.1%)	20 (8.5%)	14 (6%)
No common lesions	None	Yes	None	1 (0.4%)	1 (0.4%)	0
	None	None	Yes	0	0	0
	None	Yes	Yes	1 (0.4%)	0	1 (0.4%)

Discordant lesions

Between 10% and 12% of the lesions detected with gadobutrol (61 to 90 lesions, depending on the reader) were not detected with gadopiclenol (Table 49). It is worth noting that 43 out of the 90 discordant lesions reported for Reader 3 are from only 3 patients with 61 to 100 lesions detected with gadobutrol, therefore in a clinical situation when numbers do not matter any longer as far as potential implications on patient management are concerned (Table 45). This is also highlighted in Table 51, with a higher number of discordant lesions reported in the 5% of patients who had more than 10 lesions detected with gadobutrol (Table 50).

The lesions only detected with gadobutrol were mostly secondary malignant lesions (48/61, 55/76, 47/90 for Reader 1, 2 and 3, respectively). Only 3/61 or 2/76 were considered as "not a true lesion" by Reader 1 and Reader 2, more (17/90) by Reader 3 who counted more lesions overall.

The lesions detected only with gadopiclenol (54 to 78) were also mostly secondary malignant lesions (47/60, 46/78, 34/54 for Reader 1, 2 and 3, respectively), while 10% to 14% were considered as not true lesions (6/60, 11/78 and 6/54 for Reader 1, 2 and 3, respectively).

The readers attributed the reason for discordance to themselves in the large majority of cases (73% to 89 % of all discordant lesions).

Table 49. GDX-44-010 (CNS) - Assessment of discordance in lesion detection following concordance lesion tracking

	Lesions detected with gadobutrol			Lesions detected with gadopiclenol		
Reader	**Reader 1**	**Reader 2**	**Reader 3**	**Reader 1**	**Reader 2**	**Reader 3**
N lesions detected with the GBCA	**590**	**633**	**880**	**589**	**635**	**844**
Lesion not detected with the other GBCA	**61 (10.3%)**	**76 (12%)**	**90 (10.2%)**	**60 (10.2%)**	**78 (12.3%)**	**54 (6.4%)**
Nature of the lesion						
Not a true lesion	3	2	17	6	11	6
Non-malignant	8	14	24	5	18	13
Malignant - primary	1	5	2	2	3	1
Malignant - secondary	48	55	47	47	46	34
Malignant - unknown	1	0	0	0	0	0
Discordance potentially due to:						
Reader	45	68	79	44	65	45
Contrast agent	11	0	0	10	3	0
Other reasons	5	8	11	6	10	9

Table 50. GDX-44-010 (CNS) - Assessment of discordance in lesion detection following concordance lesion tracking according to number of lesions per patient

	Patients with ≤10 lesions			Patients with > 10 lesions		
Reader	**Reader 1**	**Reader 2**	**Reader 3**	**Reader 1**	**Reader 2**	**Reader 3**
N lesions detected with gadobutrol	**376**	**372**	**401**	**214**	**261**	**479**
Lesion detected on **gadobutrol MR** images but not detected on gadopiclenol MR images	30 (8%)	27 (7.3%)	20 (5%)	31 (14.5%)	49 (18.8%)	70 (14.6%)
Not a true lesion	3 (0.8%)		2 (0.5%)		2 (0.8%)	15 (3.1%)
Non-malignant	3 (0.8%)	2 (0.5%)	6 (1.5%)	5 (2.3%)	12 (4.6%)	18 (3.8%)
Malignant	24 (6.4%)	25 (6.7%)	12 (3%)	26 (12.1%)	35 (13.4%)	37 (7.7%)
Primary	1 (0.3%)	3 (0.8%)	2 (0.5%)		2 (0.8%)	
Secondary	22 (5.9%)	22 (5.9%)	10 (2.5%)	26 (12.1%)	33 (12.6%)	37 (7.7%)
Unknown	1 (0.3%)					
Discordance potentially due to						
Reader	25 (6.6%)	24 (6.5%)	15 (3.7%)	20 (9.3%)	44 (16.9%)	64 (13.4%)
Contrast Agent	1 (0.3%)	-	-	10 (4.7%)	-	-
Other reasons	4 (1.1%)	3 (0.8%)	5 (1.2%)	1 (0.5%)	5 (1.9%)	6 (1.3%)
N lesions detected with gadopiclenol	**369**	**373**	**402**	**220**	**262**	**442**
Lesion detected on **gadopiclenol MR** images but not detected on gadobutrol MR images	23 (6.2%)	28 (7.5%)	21 (5.2%)	37 (16.8%)	50 (19.1%)	33 (7.5%)
Not a true lesion	3 (0.8%)	5 (1.3%)	4 (1%)	3 (1.4%)	6 (2.3%)	2 (0.5%)
Non-malignant	1 (0.3%)	5 (1.3%)	7 (1.7%)	4 (1.8%)	13 (5%)	6 (1.4%)
Malignant	19 (5.1%)	18 (4.8%)	10 (2.5%)	30 (13.6%)	31 (11.8%)	25 (5.7%)
Primary	2 (0.5%)	1 (0.3%)	1 (0.2%)		2 (0.8%)	
Secondary	17 (4.6%)	17 (4.6%)	9 (2.2%)	30 (13.6%)	29 (11.1%)	25 (5.7%)
Discordance potentially due to						
Reader	16 (4.3%)	26 (7%)	15 (3.7%)	28 (12.7%)	39 (14.9%)	30 (6.8%)
Contrast agent	5 (1.4%)	-	-	5 (2.3%)	3 (1.1%)	--
Other reasons	2 (0.5%)	2 (0.5%)	6 (1.5%)	4 (1.8%)	8 (3.1%)	3 (0.7%)

Clinical impact

Among the 60 patients with discordant lesions for at least one reader, no potential clinical impact was identified for 40 patients. The main reason was that the discordant lesions were identified/not identified in patients with multiple brain metastases, when additional identified lesions do not have impact on patient management any longer (e.g., if already a whole brain radiation therapy would be the treatment of choice for the patient) (Table 51).

The discordance in lesion detection between gadopiclenol and gadobutrol could have potentially led to changes in patient management for 20 patients: due to lesions only seen with gadobutrol for 6 patients, lesions only seen with gadopiclenol for 7 patients and both cases (lesions only seen with gadobutrol and lesions only seen with gadopiclenol in the same patient) for 7 patients (Table 52). The clinical impact was indicated as "possible target for stereotactic radiosurgery (SRS)" for 16 patients with brain metastatic disease, which was the patient population with the largest number of discordances, or a modification in the indication to different techniques of radiotherapy in other patients. For 17 patients, the cause of discordance was only attributed to the reader. In two cases, the lesion was not detected because it was covered by artifacts or not covered by the exam. The contrast agent was the potential cause of discordance for 2 patients: in one patient, the lesion was only seen with gadopiclenol and in the other patient 2 lesions were seen only with gadopiclenol and one only with gadobutrol. Therefore, only one discordance due to a lesion seen with gadobutrol but not with gadopiclenol could have had a potential clinical impact on patient management.

Table 51. GDX-44-010 (CNS) - Assessment of potential clinical impact at patient level

	Reader 1 (N=235)	Reader 2 (N=235)	Reader 3 (N=235)
Patients with lesions detected uniquely on gadobutrol MR images	**8 (3.4%)**	**6 (2.6%)**	**9 (3.8%)**
Potential impact on patient management	4 (1.7%)	4 (1.7%)	2 (0.9%)
No potential impact on patient management	4 (1.7%)	2 (0.9%)	7 (3%)
• Potentially non-malignant lesion to be left untouched	1	-	1
• Potentially non-malignant lesion to be at best followed-up	1	1	1
• Potentially not true lesion	1	-	-
• Potentially malignant lesion in a clinical situation when numbers do not matter any longer	1	-	3
• Other	-	1	2
Patients with lesions detected uniquely on gadopiclenol MR images	**5 (2.1%)**	**11 (4.7%)**	**12 (5.1%)**
Potential impact on patient management	4 (1.7%)	5 (2.1%)	3 (1.3%)
No potential impact on patient management	1 (0.4%)	6 (2.6%)	9 (3.8%)
• Potentially non-malignant lesion to be left untouched	-	1	
• Potentially non-malignant lesion to be at best followed-up	-	1	2
• Potentially not true lesion	1	3	3
• Potentially malignant lesion in a clinical situation when numbers do not matter any longer	-	-	1
• Other	-	1	3
Patients with one or more lesion/s detected uniquely on gadopiclenol MR images, and one or more lesion/s detected uniquely on gadobutrol MR images	**20 (8.5%)**	**20 (8.5%)**	**15 (6.4%)**
Potential impact on patient management just for gadobutrol MRI	1 (0.4%)	1 (0.4%)	-
Potential impact on patient management for both gadobutrol and gadopiclenol MRI	3 (1.3%)	3 (1.3%)	-
No potential impact on patient management	16 (6.8%)	16 (6.8%)	15 (6.4%)
• Potentially non-malignant lesion to be left untouched	-	1	1
• Potentially non-malignant lesion to be at best followed-up	2	1	2
• Potentially not true lesion	-	1	-
• Potentially malignant lesion in a clinical situation when numbers do not matter any longer	10	8	9
• Other	4	5	3

Table 52. GDX-44-010 (CNS) - Patients with discordant lesions that could have a potential impact on patient management

Patient	Reader	Discordant Lesion/s Detected with	Rationale for clinical impact	Discordance potentially due to
1	Reader 3	uniquely gadopiclenol	possible target for SRS	Reader
2	Reader 2	uniquely gadopiclenol	possible target for SRS	Reader
	Reader 3	uniquely gadopiclenol	possible target for SRS	Reader
3	Reader 2	uniquely gadobutrol	possible target for SRS	Reader

Patient	Reader	Discordant Lesion/s Detected with	Rationale for clinical impact	Discordance potentially due to
4	Reader 1	gadopiclenol and gadobutrol (clinical impact for both)	Both lesions poorly visualised on v2 and V4	Reader
	Reader 2	uniquely gadobutrol	possible target for SRS	Reader
	Reader 3	uniquely gadobutrol	possible target of SRS	Reader
5	Reader 1	uniquely gadobutrol	possible target for SRS	Artifacts cover the lesion in V2
	Reader 2	uniquely gadopiclenol	possible target for SRS	Reader
	Reader 3	uniquely gadopiclenol	possible target of SRS	Reader
6	Reader 1	gadopiclenol and gadobutrol (clinical impact for both)	Modify the indication to different techniques of radiotherapy.	*Lesions detected only with gadopiclenol:* LES002 Contrast agent LES007 Reader LES008 Contrast agent *Lesions detected only with gadobutrol:* LES005 partial volume on V2 LES006 Reader **LES007 Contrast agent**
	Reader 2	uniquely gadobutrol	Modify the indication to different techniques of radiotherapy.	Reader
7	Reader 1	uniquely gadobutrol	possible target for SRS	Reader
8	Reader 1	uniquely gadobutrol	possible target for SRS	Reader
9	Reader 2	gadopiclenol and gadobutrol (clinical impact for both)	Modify the indication to different techniques of radiotherapy.	Reader
10	Reader 3	uniquely gadobutrol	possible target of SRS	Reader
11	Reader 2	uniquely gadobutrol	Modify the indication to treatment.	Reader
12	Reader 1	uniquely gadopiclenol	possible target for SRS	Reader
	Reader 2	uniquely gadopiclenol	possible target for SRS	Reader
13	Reader 1	uniquely gadopiclenol	possible target for SRS	Contrast agent
14	Reader 1	uniquely gadopiclenol	possible target for SRS	Reader
15	Reader 2	uniquely gadopiclenol	Modify the indication to treatment.	lesion not covered by the exam in v2
16	Reader 1	gadopiclenol and gadobutrol (clinical impact only for lesion detected with gadopiclenol)	Lesion 011 poorly visualised on v2 (MRI with gadobutrol)	Reader (lesion detected only with gadobutrol) Contrast agent (lesion detected only with gadopiclenol)
	Reader 2	gadopiclenol and gadobutrol (clinical impact for both)	possible target for SRS	Reader
17	Reader 2	gadopiclenol and gadobutrol (clinical impact for both)	possible target for SRS	Reader

Patient	Reader	Discordant Lesion/s Detected with	Rationale for clinical impact	Discordance potentially due to
18	Reader 1	uniquely gadobutrol	possible target for SRS	Reader
19	Reader 1	gadopiclenol and gadobutrol (clinical impact for both)	possible target for SRS	Reader
	Reader 2	gadopiclenol and gadobutrol (clinical impact only for lesion detected with gadobutrol)	possible target for SRS	Reader
20	Reader 1	uniquely gadopiclenol	possible target for SRS	Reader; Partial volume at v2
	Reader 2	uniquely gadopiclenol	possible target for therapy	Reader

Intra-reader and inter-reader variability

The intra-reader agreement was assessed on 10% of the images. The intra-reader agreement was excellent for Reader 2 (92.1% with both GBCAs) and Reader 3 (100% with gadopiclenol and 96.1% with gadobutrol) and slightly lower for Reader 1 (85.7% with gadopiclenol and 89.1% with gadobutrol)

The inter-reader agreement was assessed on all images following the concordance lesion tracking. The inter-reader agreement was similar for lesions seen with gadobutrol or lesions seen with gadopiclenol. Overall, at least 2 out of 3 readers agree for 74.8% of the lesions with gadopiclenol and 75.4% of the lesions with gadobutrol.

- ***Study GDX-44-011- Efficacy and Safety of Gadopiclenol for Body Magnetic Resonance Imaging (MRI) (the PROMISE Study)***

Methods

GDX-44-011 was a prospective, multi-centre, randomised, double-blind, controlled and cross-over Phase III study to evaluate the safety and efficacy of gadopiclenol at 0.05 mmol/kg compared with gadobutrol at 0.1 mmol/kg for body MRI in 304 adult patients.

The pivotal Phase III study (GDX-44-011) had the same design than the Phase III study conducted for CNS imaging (GDX-44-010) as described in above.

- **Study Participants**

The main inclusion criteria were female of male adult patients presented with known or suspected enhancing abnormality(ies) and/or lesion(s) in at least one body region among head & neck, thorax (including breast), abdomen (including liver, pancreas and kidneys), pelvis (including uterus, ovary and prostate) and musculoskeletal (including extremities) based on a previous imaging procedure performed within 12 months. If the patient was treated (either with radiation, surgery, biopsy or other relevant treatments) between previous imaging evaluation and trial MRI, there should still be a high suspicion of the remaining lesion(s) on the basis of available clinical information. If the patient was treated (either with radiation, surgery, biopsy or other relevant treatments) between previous imaging evaluation and trial MRI, there should still be a high suspicion of enhancing abnormality(ies) and/or lesion(s) on the basis of available clinical information. Additionally, eligible subjects where patients scheduled for a CNS contrast-enhanced MRI examination for clinical reasons and agreed to have a second contrast-enhanced MRI examination for the purpose of the trial.

Following recommendations for use of GBCAs, patients with severe renal impairment (eGFR < 30 mL/min/1.73 m² and patients with known sensitivity to gadolinium were excluded. Additionally, patients with

known or suspected lesion(s) referred for contrast-enhanced MRI of CNS or of heart or for MR Angiography and patients with NYHA class III/IV, were excluded from the study.

- **Treatments**

The study design was identical to the one of GDX-44-010 described above.

However, as different body regions were included in the study, readers with different expertise were involved, resulting in 18 independent blinded readers (3 readers for primary evaluation and 3 readers for global matched-pairs assessment for overall diagnostic preference per body region of head & neck, thorax, and musculoskeletal)

Imaging procedure

MR equipment: The procedure was performed using an MRI scanner that could perform the required pulse sequences. MRI units with 1.5T or 3T magnetic field were used, regardless of the manufacturer. The following information had to be recorded in the clinical eCRF: the manufacturer and field strength of the MRI device.

For a single patient, the same MR equipment had to be used for the two MRI examinations required by the protocol

MRI sequences: The same parameter setting for the same sequence had to be used for unenhanced images and for contrast-enhanced images in each patient. The required sequences and parameters for MRI with gadopiclenol and gadobutrol had to be as similar as possible. Depending on scanned organs/regions, different scanning protocols were used. Core sequences for the majority of organs required per protocol are listed below. Details on the required sequence and parameters were provided in the Imaging Manual.

- Breast MRI

  Morphological Pre-contrast images (unenhanced MRI): 2D axial T1-weighted sequence and 2D axial T2-weighted sequence.

  Dynamic post contrast images (contrast-enhanced MRI): 3D axial T1 fat saturation weighted sequence without injection (mask) and after injection minimum 3 repetitions <2min.

- Liver MRI

  Dynamic contrast-enhanced T1-weighted imaging with 3D fat-saturated acquisitions (pre-contrast, late arterial phase, portal venous phase, and delayed phase). Fat and iron sensitive in-phase and opposed-phase and T2-weighted imaging with fat saturation were required.

- Prostate MRI

  Contrast-enhanced T1-weighted imaging was obtained dynamically through the prostate. In addition, T2 weighted imaging was obtained.

- Female Pelvis MRI

  Contrast-enhanced T1-weighted imaging was obtained. In addition, T2 weighted and T2 weighted fat-suppressed imaging were obtained.

- Musculoskeletal MRI

  Contrast-enhanced T1-weighted imaging was obtained. When post-contrast, non-fat suppressed T1-weighted imaging were required.

- **Objectives**

The study objectives/endpoints were identical to the one of GDX-44-010 described above.

- **Sample size**

Two coprimary objectives are used in the pivotal study GDX-44-011. The sample size for each of the objectives was determined as follows:

Number of patients for the primary objective 1:

The success hypothesis used in the sample calculation is based upon the Gutierrez publication (below) where the minimal observed mean of the difference was 0.41 with a SD ranging from 0.5 to 0.8 as displayed below (Table 53).

Table 53. Mean (SD) of the difference between combined unenhanced and gadobutrol-enhanced imaging vs imaging unenhanced imaging (N=336)

Reader	Border delineation	Internal Morphology	Degree of Contrast Enhancement
1	0.67 (0.66)	0.62 (0.47)	1.26 (0.61)
2	0.72 (0.78)	0.82 (0.61)	1.59 (0.77)
3	0.43 (0.50)	0.41 (0.52)	1.06 (0.51)

Considering that in the current trial the scale used is not exactly the same (4-point scale instead of 3-point scale for one parameter) and to account a possible greater heterogeneity, the expected difference is set to 0.35 and the expected standard deviation is set to 1.5.

Hence, expecting that for each of the 3 co-primary criteria, the difference in mean scores will be 0.35

(["Paired" – "Pre"] within patient) with 1.5 standard deviation, a sample of 200 patients in the gadopiclenol group will have 90% power when using a single group superiority t-test with a 0.025 one-sided significance level.

As a 20% drop-out rate is expected, sample size increases to 250 patients. During the course of the study, the rate of non-valid primary criteria 1 was assessed and was eventually greater than expected (from 20% to 33%) leading to an increase of the sample size from 250 to 300 to maintain statistical power.

Number of patients for the primary objective 2:

- Sample size hypothesis:

The standard deviation on lesion visualisation criteria for gadopiclenol is estimated on the basis of the Guerbet Phase IIb GDX-44-004 clinical trial results on lesion visualisation criteria presented in the Table 54 below**.**

Table 54. Mean (SD) of the combined unenhanced and gadopiclenol-enhanced imaging (N=61)

Reader	Border delineation	Internal Morphology	Degree of Contrast Enhancement
1	3.37 (0.55)	3.34 (0.64)	3.23 (0.80)
2	1.97 (0.74)	1.71 (0.75)	3.76 (0.58)
3	3.72 (0.49)	3.72 (0.49)	3.68 (0.50)

Considering that the results for gadobutrol would be similar (meaning that the standard deviation of the difference is expected ranging from $\sqrt{2}*0.50=0.7$ to $\sqrt{2}*0.80=1.15$) and taking into account a possible greater heterogeneity of patient population to be included in the study, the expected standard deviation of the difference between gadopiclenol and gadobutrol is estimated to 1.75.

For this 2x2 cross-over design, the statistical analysis is based on the observed Student's t-based two-sided 95% confidence interval (95%CI) of the gadopiclenol-gadobutrol difference for each co-primary criterion.

An enrolment of 200 patients is deemed necessary for the lower limit of the 95% CI to exceed the noninferiority margin set to 0.35, assuming 80% power, and for each co-primary criterion, the expected difference in mean scores is 0 with an expected standard deviation of 1.75.

If one assumed a patient drop-out rate of 20%, a minimum enrolment of 250 patients with anomalies / lesions of various body organs is planned.

Therefore, a total number of 250 patients will allow sufficient power to meet both objectives. During the course of the study, the rate of non-valid primary criteria 1 and 2 was assessed and was eventually greater than expected (from 20% to 33%), leading to an increase of the sample size from 250 to 300 to maintain statistical power.

- **Randomisation and Blinding (masking)**

At visit 2, the patients were randomly assigned to one series of 2 MRIs (gadopiclenol-gadobutrol or gadobutrol-gadopiclenol) in a 1:1 ratio. The randomisation to determine the order of injection at visit 2 and visit 4 was done via Interactive Web Response System (IWRS) and performed in blocks to prevent unequal treatment allocation.

The trial design and the injection of the IMPs required identifying two separate teams in each trial site. One managed the blinded data and another one was unblinded and was in charge of the IMPs preparation and administration. The unblinded staff had to document in a separate patient's file all the unblinded information related to the IMPs and had to complete the dedicated restricted field in clinical eCRF pages.

During the course of the trial, the two teams did not exchange any information regarding the IMPs (nature of IMP injected, order of administration). The unblinded documentation was stored, shielded from the view of the blinded staff.

The investigator and the patient remained blinded to IMPs allocation (nature of the IMPs and order of the IMP injection). A designated unblinded site staff member was in charge of preparation and administration of the IMPs.

The blinded centralised image evaluations (off-site read) were performed by 3 independent blinded radiologists and the global matched-pairs assessment was performed by 3 additional independent blinded radiologists. Therefore 18 readers were involved for the evaluations: Head and Neck (6 readers), Thorax/Abdomen/Pelvis (6 readers) and Musculoskeletal (6 readers). An imaging electronic Case Report Form (eCRF) was used to ensure that the images were properly aligned and to ensure that all necessary data for the trial purpose were documented by the independent blinded readers.

- **Statistical methods**

The pivotal Phase III Body study had the same endpoints as the Phase III CNS study (GDX 44 010), analysed with the same statistical methods as described in Section 3.3.1.7

However, as different body regions were included in the study, readers with different expertise were needed for the reading of study images. The primary evaluation of the blinded images was performed by 3 independent blinded radiologists (reader 1, reader 2, reader 3) per body region. Three other independent radiologists (reader 4, reader 5, reader 6) per body region were involved in the off-site reading of images assessed side by side (global matched-pairs fashion) for overall diagnostic preference. Hence, according to the different anatomic locations, 18 independent blinded readers were selected and qualified for the entire study images reads:

- 6 readers for Head and Neck (H&N)
- 6 readers for Thorax (including breast), Abdomen (including liver, pancreas and kidneys) or Pelvis (including uterus, ovary and prostate)
- 6 readers for Musculoskeletal (including extremities) (MSK)

Therefore, for the primary evaluation, Reader 1 was the pooling of reader 1 for H&N, reader 1 for Thorax/Abdomen/ Pelvis and reader 1 for MSK. The same applied for reader 2 and reader 3.

Results

- **Participant flow**

Among the 324 patients screened for the GDX-44-011 study, 304 (93.8%) were randomised of which 152 in each arm. Out of them, 151 (99.3%) underwent the first MRI with gadopiclenol, and 149 (98.0%) underwent the first MRI with gadobutrol, and 294 patients underwent the safety follow-up visit (V3). At V4, 277 patients (91.1%) underwent the second MRI and received gadobutrol (n=141) or gadopiclenol (n=136). Finally, 275 patients performed the safety follow-up (V5) and completed the study, of which 275 (90.5%) completed the study. Overall, a total of 29 patients prematurely discontinued the study (Table 55).

Table 55. Body GDX-44-011 - Reasons for Premature Discontinuation – Randomised Patients

	gadopiclenol / gadobutrol (N=152)	gadobutrol / gadopiclenol (N=152)	Total (N=304)
Premature discontinuation from the trial	**11 (7.2%)**	**18 (11.8%)**	**29 (9.5%)**
Premature discontinuation from the trial before receiving the first contrast agent	**1 (0.7%)**	**3 (2.2%)**	**4 (1.4%)**
Reasons of premature discontinuation			
n	1	3	4
Discovery of an Unexpected, Significant or Unacceptable Risk to the Patient Enrolled in the Trial	0	1 (33.3%)	1 (25.0%)
Other reason	1 (100%)	2 (66.7%)	3 (75.0%)
Premature discontinuation from the trial before receiving the second contrast agent *	**10 (6.6%)**	**13 (8.6%)**	**23 (7.6%)**
Reasons of premature discontinuation			
n	10	13	23
Withdrawal of patient's consent	3 (30.0%)	4 (30.8%)	7 (30.4%)
Withdrawal of patient's consent due to COVID-19 pandemic	1 (10.0%)	1 (7.7%)	2 (8.7%)
COVID-19	1 (10.0%)	0	1 (4.3%)
Adverse event other than COVID-19	1 (10.0%)	1 (7.7%)	2 (8.7%)
COVID-19 pandemic preventing patient from following protocol schedule	0	2 (15.4%)	2 (8.7%)
Other reason	4 (40.0%)	5 (38.5%)	9 (39.1%)
Premature discontinuation from the trial after receiving the second contrast agent	**0**	**2 (1.3%)**	**2 (0.7%)**
Reasons of premature discontinuation			
n	0	2	2
Withdrawal of patient's consent due to COVID-19 pandemic	0	2 (100%)	2 (100%)

%: (n row / n randomized) * 100, except for reasons of premature discontinuation where percentages are computed on number of patients prematurely discontinued from the trial.
* Between two planned contrast agent administrations.

Table 56. Overall disposition – Screened patients set (N=324)

	gadopiclenol / gadobutrol (N=152)	gadobutrol / gadopiclenol (N=152)	Total (N=324)
Visit 1: screening			324 (100%)
Screened patients			324 (100%)
Visit 2			308 (95.1%)
Randomized patients	152 (100%)	152 (100%)	304 (93.8%)
Patients receiving the first contrast agent administration*	151 (99.3%)	149 (98.0%)	300 (98.7%)
Visit 3 (Safety visit)	148 (97.4%)	145 (95.4%)	294 (96.7%)
Visit 4	141 (92.8%)	137 (90.1%)	278 (91.4%)
Patients receiving the second contrast agent administration[2]	141 (92.8%)	136 (89.5%)	277 (91.1%)
Visit 5 (Safety visit)	141 (92.8%)	134 (88.2%)	275 (90.5%)
Patients who completed the trial	141 (92.8%)	134 (88.2%)	275 (90.5%)

Percentage of total randomized patients calculated on the number of screened patients. Other percentages are calculated on the number of randomized patients.
* 1 patient received gadopiclenol instead of gadobutrol at the first administration.
1 patient received the first contrast agent but was not randomized; therefore, this patient is not counted in this table.

The 304 randomised patients underwent MRI for imaging of different body regions: abdomen for 108 patients, head & neck for 25, musculoskeletal for 23, pelvis for 65 and thorax for 79 (Table 57). The body region was not indicated for 4 randomised patients who discontinued before the first MRI and did not receive any contrast agent.

Table 57. Patient overall disposition by Body Region – Randomised Patients (N=304)

	gadopiclenol / gadobutrol (N=152)	gadobutrol / gadopiclenol (N=152)	Total (N=304)
Head & Neck			
Randomized patients	**13**	**12**	**25**
Patients receiving the first contrast agent administration	13 (100%)	12 (100%)	25 (100%)
Patients receiving the second contrast agent administration	13 (100%)	11 (91.7%)	24 (96.0%)
Patients who completed the trial	13 (100%)	11 (91.7%)	24 (96.0%)
Abdomen (including liver, pancreas and kidney)			
Randomized patients	**52**	**56**	**108**
Patients receiving the first contrast agent administration*	52 (100%)	56 (100%)	108 (100%)
Patients receiving the second contrast agent administration	47 (90.4%)	50 (89.3%)	97 (89.8%)
Patients who completed the trial	47 (90.4%)	49 (87.5%)	96 (88.9%)
Pelvis (including uterus, ovary and prostate)			
Randomized patients	**30**	**35**	**65**
Patients receiving the first contrast agent administration	30 (100%)	35 (100%)	65 (100%)
Patients receiving the second contrast agent administration	27 (90.0%)	32 (91.4%)	59 (90.8%)
Patients who completed the trial	27 (90.0%)	32 (91.4%)	59 (90.8%)
Thorax (including breast)			
Randomized patients	**44**	**35**	**79**
Patients receiving the first contrast agent administration	44 (100%)	35 (100%)	79 (100%)
Patients receiving the second contrast agent administration	43 (97.7%)	33 (94.3%)	76 (96.2%)
Patients who completed the trial	43 (97.7%)	32 (91.4%)	75 (94.9%)
Musculoskeletal (including extremities)			
Randomized patients	**12**	**11**	**23**
Patients receiving the first contrast agent administration	12 (100%)	11 (100%)	23 (100%)
Patients receiving the second contrast agent administration	11 (91.7%)	10 (90.9%)	21 (91.3%)
Patients who completed the trial	11 (91.7%)	10 (90.9%)	21 (91.3%)

Information on body region is missing for 4 randomized patients who did not receive the contrast agent and did not undergo MRI (premature discontinuation from the trial before receiving the first contrast agent).
**1 patient received Gadopiclenol instead of Gadobutrol at the first administration*

Major protocol deviations

Among randomised patients, major protocol deviations were reported for 50 patients (16.4%), some impacting both primary criteria, and some specific for one of the two primary criteria, explaining the different datasets used for efficacy analyses (Table 58). The most frequent major protocol deviation was "MRI examination not performed".

Table 58. Body GDX-44-011 - Major Protocol Deviations – Randomised patients

	gadopiclenol / gadobutrol (N=152)		gadobutrol / gadopiclenol (N=152)		Randomized (N=304)	
	n (%) patients	n events	n (%) patients	n events	n (%) patients	n events
At least one major protocol deviation (all deviations)	22 (14.5%)	26	28 (18.4%)	39	50 (16.4%)	65
At least one major protocol deviation related to both criteria 1 and criteria 2	3 (2.0%)	3	23 (15.1%)	25	26 (8.6%)	28
- Non-inclusion criteria #1 met	0	0	5 (3.3%)	5	5 (1.6%)	5
- Patient did not receive the IMP allocated by randomization	0	0	1 (0.7%)	1	1 (0.3%)	1
- Gadopiclenol volume actually administered is different from the theoretical one of more than 20%	2 (1.3%)	2	3 (2.0%)	3	5 (1.6%)	5
- MRI examination with gadopiclenol not performed*	1 (0.7%)	1	13 (8.6%)	13	14 (4.6%)	14
- MRI examination with gadopiclenol not performed due to COVID-19 pandemic	0	0	3 (2.0%)	3	3 (1.0%)	3
At least one major protocol deviation related to criteria 1	6 (3.9%)	6	4 (2.6%)	4	10 (3.3%)	10
- Not matching lesion: among patients with gadopiclenol MRI examination available, those with no matching enhancing lesions on Paired and Pre contrast images for all off-site readers	6 (3.9%)	6	4 (2.6%)	4	10 (3.3%)	10
At least one major protocol deviation related to criteria 2	17 (11.2%)	17	9 (5.9%)	10	26 (8.6%)	27
- Not matching lesion: among patients with both MRI examinations available, those with no matching enhancing lesions at both examination for all off-site readers	1 (0.7%)	1	3 (2.0%)	3	4 (1.3%)	4
- Imaging protocol not respected with major impact on co-primary criteria for gadobutrol administration	0	0	1 (0.7%)	1	1 (0.3%)	1
- The gadobutrol volume actually administered is different from the theoretical one more than 20%	4 (2.6%)	4	2 (1.3%)	2	6 (2.0%)	6
- Temperature excursion for gadobutrol with risk of freezing	1 (0.7%)	1	0	0	1 (0.3%)	1
- Extravasation during gadobutrol administration	0	0	1 (0.7%)	1	1 (0.3%)	1
- MRI examination with gadobutrol not performed*	9 (5.9%)	9	3 (2.0%)	3	12 (3.9%)	12
- MRI examination with gadobutrol not performed due to COVID-19 pandemic	2 (1.3%)	2	0	0	2 (0.7%)	2

One patient may have more than one deviation.
*for other reason than Covid-19 pandemic.

Impact of COVID-19 pandemic

There was a low impact on the recruitment because some sites with high recruitment rate were kept open, taking into consideration all safety measures and respecting national recommendations. The trial was completed with the planned sample size despite the disruption that occurred, and the objectives were achieved. The study is considered with minimal disruption:

- A protocol amendment has been issued to increase the sample size as the anticipated rate of non-evaluable patients was estimated to be higher than initially planned. Seven patients withdrew from the study due to Covid-19 pandemic, which slightly increased the total number of non-evaluable patients, however this amendment cannot be considered as due to the COVID-19 pandemic.

- No modifications of trial visits or trial procedures were necessary.
- No changes in vendors or other third parties.
- No change in statistical analysis. As the final number of patients was obtained and the number of protocol deviations was limited, statistical power was adequate and the trial was able to meet its objectives. There was no impact on statistical hypothesis.

  Quality Tolerance Limits were assessed as originally planned for the trial and were not exceeded.

- **Recruitment**

This study was conducted at 33 centres in 11 countries (Bulgaria (1 centre); Germany (4 centres); Spain (1 centre); France (3 centres); Hungary (2 centres); Ukraine (2 centres); Italy (1 centre); Republic of Korea (5 centres); Poland (5 centres); United States of America (7 centres); Mexico (2 centres).

Out of the 278 randomised patients of the FAS 1, 159 (57.2%) were from Europe.

The study period was from 27 August 2019 – 09 December 2020.

- **Conduct of the study**

The protocol version v1.0 dated 14 January 2019, was amended twice.

A first amendment (protocol v2.0) was prepared in early June 2020 but never submitted.

The protocol v3.0, including global amendment 2 dated 30 June 2020, implemented the following change:

- The anticipated actual rate of non-evaluable patients (drop-out rate and non-valid primary criteria rate) was estimated to be higher than initially planned: the revised hypothesis for the non-evaluable patient rate was about 33% instead of 20%. This increase in drop-out rate was due in part to the Covid-19 pandemic impact on enrollment of patients and/or compliance with the protocol, but also to the variety and complexity of organs in this study. Therefore, to secure the target 200 evaluable patients needed for sufficient statistical power to meet both primary study objectives, the sample size had to be increased from 250 to 300 enrolled patients.
- The protocol was also amended specifically for France (version 1.0_FRA1.0 dated 17 May 2019 and version No. 3.0 FRA 1.0 [including global amendment 2] dated 30 June 2020) upon the request of French Competent Authorities (ANSM). This amendment 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: Patient with known liver failure or liver transplantation.

- **Baseline data**

The demographics and baseline characteristics were similar between randomisation groups and are summarised in Table 59 below.

Table 59. Body GDX-44-011 – Demographic Data – Full Analysis Sets

	FAS 1 (N= 278)			FAS 2 (N= 273)		
	gadopiclenol / gadobutrol (N=145)	gadobutrol / gadopiclenol (N=133)	Total (N=278)	gadopiclenol / gadobutrol (N=140)	gadobutrol / gadopiclenol (N=133)	Total (N=273)
Age (years)						
n	145	133	278	140	133	273
Mean (SD)	57.5 (12.9)	56.9 (13.1)	57.2 (13.0)	57.1 (12.6)	57.0 (13.1)	57.0 (12.8)
Median	58.0	57.0	58.0	58.0	57.0	58.0
Min. ; Max.	25 ; 82	21 ; 86	21 ; 86	25 ; 80	21 ; 86	21 ; 86
Age by category						
<65 years	95 (65.5%)	89 (66.9%)	184 (66.2%)	94 (67.1%)	89 (66.9%)	183 (67.0%)
≥ 65 years	50 (34.5%)	44 (33.1%)	94 (33.8%)	46 (32.9%)	44 (33.1%)	90 (33.0%)
Sex						
n	145	133	278	140	133	273
Male	63 (43.4%)	51 (38.3%)	114 (41.0%)	59 (42.1%)	52 (39.1%)	111 (40.7%)
Female	82 (56.6%)	82 (61.7%)	164 (59.0%)	81 (57.9%)	81 (60.9%)	162 (59.3%)
If Female: Childbearing potential						
n	82	82	164	81	81	162
Woman of childbearing potential using effective contraception	19 (23.2%)	31 (37.8%)	50 (30.5%)	22 (27.2%)	31 (38.3%)	53 (32.7%)
Post-menopausal (with minimum 12 months of amenorrhea)	37 (45.1%)	35 (42.7%)	72 (43.9%)	33 (40.7%)	34 (42.0%)	67 (41.4%)
Surgically sterilized	26 (31.7%)	16 (19.5%)	42 (25.6%)	26 (32.1%)	16 (19.8%)	42 (25.9%)
Weight at Visit 2 (kg)						
n	145	133	278	140	133	273
Mean (SD)	75.3 (17.1)	75.5 (17.1)	75.4 (17.1)	74.6 (17.3)	75.3 (17.2)	74.9 (17.2)
Median	74.0	74.0	74.0	72.0	74.0	73.0
Min. ; Max.	40 ; 133	45 ; 124	40 ; 133	40 ; 133	45 ; 124	40 ; 133
Weight at Visit 4 (kg)						
n	135	133	268	140	133	273
Mean (SD)	75.3 (17.4)	75.5 (17.2)	75.4 (17.3)	74.7 (17.4)	75.2 (17.2)	75.0 (17.3)
Median	73.0	74.0	73.5	72.0	74.0	73.0
Min. ; Max.	40 ; 133	45 ; 124	40 ; 133	40 ; 133	45 ; 124	40 ; 133
Visit not performed	10	0	10			
Height (cm)						
n	145	133	278	140	133	273
Mean (SD)	165.7 (9.6)	167.0 (9.0)	166.3 (9.3)	165.5 (9.5)	166.9 (9.0)	166.2 (9.3)
Median	165.0	167.0	165.0	164.5	167.0	165.0
Min. ; Max.	144 ; 190	143 ; 190	143 ; 190	144 ; 190	143 ; 190	143 ; 190

	FAS 1 (N= 278)			FAS 2 (N= 273)		
	gadopiclenol / gadobutrol (N=145)	gadobutrol / gadopiclenol (N=133)	Total (N=278)	gadopiclenol / gadobutrol (N=140)	gadobutrol / gadopiclenol (N=133)	Total (N=273)
BMI at Visit 2 (kg/m²)						
n	145	133	278	140	133	273
Mean (SD)	27.38 (5.65)	27.07 (5.83)	27.23 (5.73)	27.16 (5.69)	27.02 (5.86)	27.09 (5.76)
Median	26.35	26.30	26.33	26.15	26.30	26.18
Min. ; Max.	14.9 ; 47.8	14.4 ; 45.0	14.4 ; 47.8	14.9 ; 47.8	14.4 ; 45.0	14.4 ; 47.8
BMI at Visit 4 (kg/m²)						
n	135	133	268	140	133	273
Mean (SD)	27.38 (5.76)	27.07 (5.87)	27.22 (5.81)	27.22 (5.72)	27.01 (5.91)	27.11 (5.80)
Median	26.50	26.08	26.33	26.33	26.08	26.18
Min. ; Max.	14.9 ; 47.4	14.4 ; 45.0	14.4 ; 47.4	14.9 ; 47.4	14.4 ; 45.0	14.4 ; 47.4
Visit not performed	10	0	10			
Ethnicity						
n	145	133	278	140	133	273
Not Hispanic Or Latino	114 (78.6%)	113 (85.0%)	227 (81.7%)	110 (78.6%)	113 (85.0%)	223 (81.7%)
Hispanic Or Latino	31 (21.4%)	20 (15.0%)	51 (18.3%)	30 (21.4%)	20 (15.0%)	50 (18.3%)
Race (multiple choices)						
n	145	133	278	140	133	273
White	102 (70.3%)	94 (70.7%)	196 (70.5%)	97 (69.3%)	94 (70.7%)	191 (70.0%)
Asian	22 (15.2%)	22 (16.5%)	44 (15.8%)	24 (17.1%)	22 (16.5%)	46 (16.8%)
Black Or African American	2 (1.4%)	4 (3.0%)	6 (2.2%)	2 (1.4%)	4 (3.0%)	6 (2.2%)
Native Hawaiian Or Other Pacific Islander	0	0	0	1 (0.7%)	0	1 (0.4%)
American Indian Or Alaska Native	18 (12.4%)	12 (9.0%)	30 (10.8%)	17 (12.1%)	12 (9.0%)	29 (10.6%)
Other	1 (0.7%)	1 (0.8%)	2 (0.7%)	1 (0.7%)	1 (0.8%)	2 (0.7%)
Geographical Region						
n	145	133	278	140	133	273
North America	27 (18.6%)	18 (13.5%)	45 (16.2%)	28 (20.0%)	18 (13.5%)	46 (16.8%)
Latin America	18 (12.4%)	12 (9.0%)	30 (10.8%)	17 (12.1%)	12 (9.0%)	29 (10.6%)
Asia Pacific	22 (15.2%)	22 (16.5%)	44 (15.8%)	23 (16.4%)	22 (16.5%)	45 (16.5%)
European countries	78 (53.8%)	81 (60.9%)	159 (57.2%)	72 (51.4%)	81 (60.9%)	153 (56.0%)

SD: Standard Deviation, BMI: Body Mass Index
%: (n row / n non missing) * 100.
For the item "Race", a patient may have more than one answer. Hence, sum of percentages may be above 100% for this item

Demographics by body region

The demographic characteristics are summarised by body region in Table 60 below.

Table 60. Demographic Data by body region – FAS 1 (N= 278) and FAS 2 (N=273)

	H&N		Abdomen		Pelvis		Thorax		MSK	
	FAS 1 (N=21)	FAS 2 (N= 22)	FAS 1 (N=101)	FAS 2 (N= 95)	FAS 1 (N=61)	FAS 2 (N= 59)	FAS 1 (N=73)	FAS 2 (N= 76)	FAS 1 (N=22)	FAS 2 (N= 21)
Age (years)										
Mean (SD)	57.1 (10.8)	57.5 (10.4)	61.1 (11.9)	61.3 (11.7)	57.5 (14.7)	57.0 (14.5)	51.1 (11.4)	50.9 (11.3)	58.9 (12.5)	59.2 (12.7)
Median	58.0	58.5	62.0	61.0	57.0	56.0	51.0	51.0	63.0	65.0
Min. ; Max.	35 ; 77	35 ; 77	25 ; 86	25 ; 86	28 ; 82	28 ; 80	21 ; 79	21 ; 79	30 ; 78	30 ; 78
Age by category										
<65 years	14 (66.7%)	15 (68.2%)	58 (57.4%)	55 (57.9%)	36 (59.0%)	35 (59.3%)	65 (89.0%)	68 (89.5%)	11 (50.0%)	10 (47.6%)
≥ 65 years	7 (33.3%)	7 (31.8%)	43 (42.6%)	40 (42.1%)	25 (41.0%)	24 (40.7%)	8 (11.0%)	8 (10.5%)	11 (50.0%)	11 (52.4%)
Sex										
Male	15 (71.4%)	15 (68.2%)	63 (62.4%)	60 (63.2%)	19 (31.1%)	20 (33.9%)	3 (4.1%)	3 (3.9%)	14 (63.6%)	13 (61.9%)
Female	6 (28.6%)	7 (31.8%)	38 (37.6%)	35 (36.8%)	42 (68.9%)	39 (66.1%)	70 (95.9%)	73 (96.1%)	8 (36.4%)	8 (38.1%)
If Female: Childbearing potential										
n	6	7	38	35	42	39	70	73	8	8
Woman of childbearing potential using effective contraception	2 (33.3%)	2 (28.6%)	5 (13.2%)	4 (11.4%)	17 (40.5%)	17 (43.6%)	25 (35.7%)	29 (39.7%)	1 (12.5%)	1 (12.5%)
Post-menopausal (with minimum 12 months of amenorrhea)	3 (50.0%)	3 (42.9%)	26 (68.4%)	24 (68.6%)	19 (45.2%)	16 (41.0%)	17 (24.3%)	17 (23.3%)	7 (87.5%)	7 (87.5%)
Surgically sterilized	1 (16.7%)	2 (28.6%)	7 (18.4%)	7 (20.0%)	6 (14.3%)	6 (15.4%)	28 (40.0%)	27 (37.0%)		
Weight at Visit 2 (kg)										
Mean (SD)	77.0 (14.1)	75.1 (15.3)	74.9 (17.8)	74.4 (17.8)	74.4 (16.1)	74.7 (16.1)	76.1 (18.3)	75.2 (18.4)	76.6 (16.0)	76.4 (16.4)
Median	78.0	77.0	72.0	72.0	72.0	74.0	73.0	71.0	78.0	78.0
Min. ; Max.	53 ; 103	51 ; 103	40 ; 133	40 ; 133	45 ; 123	45 ; 123	45 ; 118	45 ; 118	53 ; 103	53 ; 103
Weight at Visit 4 (kg)										
Mean (SD)	77.0 (14.2)	75.0 (15.2)	74.4 (17.8)	74.3 (17.9)	74.8 (16.3)	74.8 (16.2)	76.3 (18.6)	75.4 (18.5)	76.7 (16.4)	76.7 (16.4)
Median	76.0	76.0	72.0	72.0	72.5	73.0	72.0	72.0	78.0	78.0
Min. ; Max.	53 ; 103	53 ; 103	40 ; 133	40 ; 133	45 ; 123	45 ; 123	45 ; 119	45 ; 119	53 ; 103	53 ; 103
Missing data	0	0	5	0	3	0	1	0	1	0

	H&N		Abdomen		Pelvis		Thorax		MSK	
	FAS 1 (N=21)	FAS 2 (N= 22)	FAS 1 (N=101)	FAS 2 (N= 95)	FAS 1 (N=61)	FAS 2 (N= 59)	FAS 1 (N=73)	FAS 2 (N= 76)	FAS 1 (N=22)	FAS 2 (N= 21)
Height (cm)										
Mean (SD)	172.5 (9.6)	171.7 (9.8)	167.8 (9.3)	167.6 (9.4)	165.6 (8.9)	166.1 (8.6)	161.8 (6.9)	161.7 (6.9)	170.9 (11.1)	170.6 (11.3)
Median	172.0	172.0	170.0	170.0	165.0	166.0	160.0	160.0	173.0	172.0
Min. ; Max.	160 ; 190	155 ; 190	143 ; 187	143 ; 187	148 ; 180	148 ; 180	147 ; 183	147 ; 183	151 ; 190	151 ; 190
BMI at Visit 2 (kg/m²)										
Mean (SD)	25.76 (3.80)	25.37 (4.13)	26.46 (5.19)	26.33 (5.15)	27.13 (5.30)	27.09 (5.30)	29.10 (6.95)	28.78 (6.96)	26.25 (5.20)	26.27 (5.32)
Median	25.01	25.16	25.95	25.82	26.31	26.31	28.65	27.73	25.47	25.47
Min. ; Max.	20.4 ; 33.1	17.6 ; 33.1	14.9 ; 42.5	14.9 ; 42.5	14.4 ; 41.2	14.4 ; 41.2	17.3 ; 47.8	17.3 ; 47.8	18.3 ; 36.7	18.3 ; 36.7
BMI at Visit 4 (kg/m²)										
Mean (SD)	25.75 (3.81)	25.33 (4.15)	26.36 (5.21)	26.29 (5.20)	27.07 (5.38)	27.12 (5.35)	29.18 (7.03)	28.86 (6.99)	26.36 (5.28)	26.36 (5.28)
Median	25.01	24.70	25.84	25.82	26.44	26.56	28.51	27.81	25.47	25.47
Min. ; Max.	20.1 ; 32.7	17.3 ; 32.7	14.9 ; 42.5	14.9 ; 42.5	14.4 ; 41.2	14.4 ; 41.2	17.6 ; 47.4	17.6 ; 47.4	18.9 ; 36.7	18.9 ; 36.7
Missing data	0	0	5	0	3	0	1	0	1	0
Ethnicity										
Not Hispanic Or Latino	16 (76.2%)	17 (77.3%)	98 (97.0%)	93 (97.9%)	52 (85.2%)	50 (84.7%)	41 (56.2%)	44 (57.9%)	20 (90.9%)	19 (90.5%)
Hispanic Or Latino	5 (23.8%)	5 (22.7%)	3 (3.0%)	2 (2.1%)	9 (14.8%)	9 (15.3%)	32 (43.8%)	32 (42.1%)	2 (9.1%)	2 (9.5%)
Race (multiple choices)										
White	13 (61.9%)	14 (63.6%)	70 (69.3%)	65 (68.4%)	46 (75.4%)	44 (74.6%)	48 (65.8%)	50 (65.8%)	19 (86.4%)	18 (85.7%)
Asian	3 (14.3%)	3 (13.6%)	27 (26.7%)	27 (28.4%)	6 (9.8%)	6 (10.2%)	6 (8.2%)	8 (10.5%)	2 (9.1%)	2 (9.5%)
Black or African. American	0	0	1 (1.0%)	1 (1.1%)	0	0	5 (6.8%)	5 (6.6%)	0	0
Native Hawaiian or other PI	0	0	0	0	0	0	0	1 (1.3%)	0	0
American Indian or Alaska native	5 (23.8%)	5 (22.7%)	3 (3.0%)	2 (2.1%)	9 (14.8%)	9 (15.3%)	12 (16.4%)	12 (15.8%)	1 (4.5%)	1 (4.8%)
Other	0	0	0	0	0	0	2 (2.7%)	2 (2.6%)	0	0
Geographical Region										
North America	0	0	0	0	0	0	45 (61.6%)	46 (60.5%)	0	0
Latin America	5 (23.8%)	5 (22.7%)	3 (3.0%)	2 (2.1%)	9 (14.8%)	9 (15.3%)	12 (16.4%)	12 (15.8%)	1 (4.5%)	1 (4.8%)
Asia Pacific	3 (14.3%)	3 (13.6%)	27 (26.7%)	27 (28.4%)	6 (9.8%)	6 (10.2%)	6 (8.2%)	7 (9.2%)	2 (9.1%)	2 (9.5%)
European countries	13 (61.9%)	14 (63.6%)	71 (70.3%)	66 (69.5%)	46 (75.4%)	44 (74.6%)	10 (13.7%)	11 (14.5%)	19 (86.4%)	18 (85.7%)

H&N: Head & Neck; Abdomen: including liver, pancreas and kidney; Pelvis: including uterus, ovary and prostate; Thorax: including breast; MSK: Musculoskeletal, including extremities.
No missing data, unless otherwise mentioned

Study disease

In both FAS 1 (Table below) and FAS 2, about 66% of the patients presented with neoplasms (benign, malignant and unspecified (including cysts and polyps), the most frequent being metastasis to liver (9.4% - 9.5%) and breast cancer (8.6% - 9.2%). The other most frequent diseases according to preferred terms were breast mass (8.8% - 9.0%) and hepatic lesions (4.0% - 4.7%).

Table 61. Trial Disease Diagnosis According to Primary SOC and PT - FAS 1 (N= 278)

	gadopiclenol / gadobutrol (N=145)	gadobutrol / gadopiclenol (N=133)	Total (N=278)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	95 (65.5%)	88 (66.2%)	183 (65.8%)
Metastases to liver	13 (9.0%)	13 (9.8%)	26 (9.4%)
Breast cancer	14 (9.7%)	10 (7.5%)	24 (8.6%)
Hepatocellular carcinoma	4 (2.8%)	4 (3.0%)	8 (2.9%)
Pancreatic neoplasm	4 (2.8%)	3 (2.3%)	7 (2.5%)
Uterine leiomyoma	3 (2.1%)	3 (2.3%)	6 (2.2%)
Breast neoplasm	1 (0.7%)	4 (3.0%)	5 (1.8%)
Hepatic neoplasm	4 (2.8%)	1 (0.8%)	5 (1.8%)
Colon neoplasm	2 (1.4%)	2 (1.5%)	4 (1.4%)
Cervix carcinoma	0	3 (2.3%)	3 (1.1%)
Hepatic cancer	2 (1.4%)	1 (0.8%)	3 (1.1%)
Invasive ductal breast carcinoma	2 (1.4%)	1 (0.8%)	3 (1.1%)
Ovarian cancer	2 (1.4%)	1 (0.8%)	3 (1.1%)
Pancreatic carcinoma	0	3 (2.3%)	3 (1.1%)
Prostate cancer	3 (2.1%)	0	3 (1.1%)
Rectal neoplasm	1 (0.7%)	2 (1.5%)	3 (1.1%)
Adrenal neoplasm	1 (0.7%)	1 (0.8%)	2 (0.7%)
Bladder cancer	0	2 (1.5%)	2 (0.7%)
Cervix neoplasm	2 (1.4%)	0	2 (0.7%)
Endometrial cancer	1 (0.7%)	1 (0.8%)	2 (0.7%)
Intraductal papilloma of breast	0	2 (1.5%)	2 (0.7%)
Joint neoplasm	1 (0.7%)	1 (0.8%)	2 (0.7%)
Metastases to bone	2 (1.4%)	0	2 (0.7%)
Metastases to pelvis	0	2 (1.5%)	2 (0.7%)
Ovarian neoplasm	0	2 (1.5%)	2 (0.7%)
Pharyngeal cancer	0	2 (1.5%)	2 (0.7%)
Renal cell carcinoma	1 (0.7%)	1 (0.8%)	2 (0.7%)
Renal neoplasm	1 (0.7%)	1 (0.8%)	2 (0.7%)
Tongue neoplasm	1 (0.7%)	1 (0.8%)	2 (0.7%)
Abdominal neoplasm	1 (0.7%)	0	1 (0.4%)
Adrenal adenoma	0	1 (0.8%)	1 (0.4%)
Anal neoplasm	0	1 (0.8%)	1 (0.4%)
Bone neoplasm	1 (0.7%)	0	1 (0.4%)
Breast cancer metastatic	1 (0.7%)	0	1 (0.4%)
Cholangiocarcinoma	0	1 (0.8%)	1 (0.4%)
Colon cancer	0	1 (0.8%)	1 (0.4%)
Fallopian tube cancer	1 (0.7%)	0	1 (0.4%)
Female reproductive neoplasm	1 (0.7%)	0	1 (0.4%)
Fibroadenoma of breast	1 (0.7%)	0	1 (0.4%)
Gastric neoplasm	1 (0.7%)	0	1 (0.4%)
Haemangioma of liver	0	1 (0.8%)	1 (0.4%)
Head and neck cancer	1 (0.7%)	0	1 (0.4%)
Intraductal papillary mucinous neoplasm	0	1 (0.8%)	1 (0.4%)
Intraductal papillary-mucinous carcinoma of pancreas	0	1 (0.8%)	1 (0.4%)
Intraductal proliferative breast lesion	1 (0.7%)	0	1 (0.4%)
Laryngeal cancer	1 (0.7%)	0	1 (0.4%)
Laryngeal neoplasm	1 (0.7%)	0	1 (0.4%)
Leiomyosarcoma	0	1 (0.8%)	1 (0.4%)
Liposarcoma	0	1 (0.8%)	1 (0.4%)
Lung cancer metastatic	1 (0.7%)	0	1 (0.4%)

Malignant melanoma	1 (0.7%)	0	1 (0.4%)
Mediastinum neoplasm	0	1 (0.8%)	1 (0.4%)
Meningioma	0	1 (0.8%)	1 (0.4%)
Metastases to central nervous system	0	1 (0.8%)	1 (0.4%)
Metastases to pancreas	0	1 (0.8%)	1 (0.4%)
Metastases to peritoneum	1 (0.7%)	0	1 (0.4%)
Metastases to soft tissue	0	1 (0.8%)	1 (0.4%)
Metastases to spine	1 (0.7%)	0	1 (0.4%)
Metastases to vagina	1 (0.7%)	0	1 (0.4%)
Metastasis	1 (0.7%)	0	1 (0.4%)
Mixed hepatocellular cholangiocarcinoma	1 (0.7%)	0	1 (0.4%)
Neoplasm prostate	1 (0.7%)	0	1 (0.4%)
Neoplasm skin	0	1 (0.8%)	1 (0.4%)
Oesophageal adenocarcinoma	0	1 (0.8%)	1 (0.4%)
Osteosarcoma recurrent	0	1 (0.8%)	1 (0.4%)
Ovarian cancer metastatic	1 (0.7%)	0	1 (0.4%)
Ovarian epithelial cancer	1 (0.7%)	0	1 (0.4%)
Ovarian germ cell teratoma benign	1 (0.7%)	0	1 (0.4%)
Papillary cystadenoma lymphomatosum	1 (0.7%)	0	1 (0.4%)
Pelvic neoplasm	0	1 (0.8%)	1 (0.4%)
Pharyngeal neoplasm	1 (0.7%)	0	1 (0.4%)
Prostate cancer recurrent	1 (0.7%)	0	1 (0.4%)
Rectal cancer	0	1 (0.8%)	1 (0.4%)
Renal cancer metastatic	1 (0.7%)	0	1 (0.4%)
Salivary gland neoplasm	0	1 (0.8%)	1 (0.4%)
Sarcoma of skin	1 (0.7%)	0	1 (0.4%)
Sarcoma	0	1 (0.8%)	1 (0.4%)
Soft tissue neoplasm	1 (0.7%)	0	1 (0.4%)
Uterine cancer	1 (0.7%)	0	1 (0.4%)
Uterine neoplasm	1 (0.7%)	0	1 (0.4%)
Reproductive system and breast disorders	22 (15.2%)	20 (15.0%)	42 (15.1%)
Breast mass	15 (10.3%)	10 (7.5%)	25 (9.0%)
Benign prostatic hyperplasia	3 (2.1%)	3 (2.3%)	6 (2.2%)
Ovarian cyst	0	4 (3.0%)	4 (1.4%)
Breast hyperplasia	2 (1.4%)	0	2 (0.7%)
Breast calcifications	0	1 (0.8%)	1 (0.4%)
Breast fibrosis	1 (0.7%)	0	1 (0.4%)
Endometrial hyperplasia	0	1 (0.8%)	1 (0.4%)
Gynaecomastia	0	1 (0.8%)	1 (0.4%)
Metrorrhagia	1 (0.7%)	0	1 (0.4%)
Hepatobiliary disorders	11 (7.6%)	8 (6.0%)	19 (6.8%)
Hepatic lesion	6 (4.1%)	7 (5.3%)	13 (4.7%)
Hepatic mass	3 (2.1%)	0	3 (1.1%)
Hepatitis	1 (0.7%)	0	1 (0.4%)
Liver disorder	0	1 (0.8%)	1 (0.4%)
Liver injury	1 (0.7%)	0	1 (0.4%)
Musculoskeletal and connective tissue disorders	5 (3.4%)	4 (3.0%)	9 (3.2%)
Haemophilic arthropathy	2 (1.4%)	0	2 (0.7%)
Vertebral lesion	1 (0.7%)	1 (0.8%)	2 (0.7%)
Arthropathy	0	1 (0.8%)	1 (0.4%)

Mandibular mass	1 (0.7%)	0	1 (0.4%)
Neck mass	0	1 (0.8%)	1 (0.4%)
Osteosclerosis	1 (0.7%)	0	1 (0.4%)
Tendon disorder	0	1 (0.8%)	1 (0.4%)
Gastrointestinal disorders	1 (0.7%)	5 (3.8%)	6 (2.2%)
Pancreatic mass	0	3 (2.3%)	3 (1.1%)
Pancreatic cyst	1 (0.7%)	1 (0.8%)	2 (0.7%)
Peritoneal lesion	0	1 (0.8%)	1 (0.4%)
Blood and lymphatic system disorders	1 (0.7%)	2 (1.5%)	3 (1.1%)
Lymphadenopathy	1 (0.7%)	1 (0.8%)	2 (0.7%)
Splenic lesion	0	1 (0.8%)	1 (0.4%)
Investigations	2 (1.4%)	1 (0.8%)	3 (1.1%)
Bone density decreased	1 (0.7%)	0	1 (0.4%)
Breast scan abnormal	0	1 (0.8%)	1 (0.4%)
Ultrasound breast abnormal	1 (0.7%)	0	1 (0.4%)
Renal and urinary disorders	3 (2.1%)	0	3 (1.1%)
Renal mass	2 (1.4%)	0	2 (0.7%)
Renal cyst	1 (0.7%)	0	1 (0.4%)
Congenital, familial and genetic disorders	0	2 (1.5%)	2 (0.7%)
Brca1 gene mutation	0	1 (0.8%)	1 (0.4%)
Factor VIII deficiency	0	1 (0.8%)	1 (0.4%)
Endocrine disorders	2 (1.4%)	0	2 (0.7%)
Goitre	1 (0.7%)	0	1 (0.4%)
Thyroid mass	1 (0.7%)	0	1 (0.4%)
General disorders and administration site conditions	2 (1.4%)	0	2 (0.7%)
Granuloma	1 (0.7%)	0	1 (0.4%)
Inflammation	1 (0.7%)	0	1 (0.4%)
Infections and infestations	1 (0.7%)	1 (0.8%)	2 (0.7%)
Cellulitis	0	1 (0.8%)	1 (0.4%)
Osteomyelitis	1 (0.7%)	0	1 (0.4%)
Nervous system disorders	0	1 (0.8%)	1 (0.4%)
Multiple sclerosis	0	1 (0.8%)	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	0	1 (0.8%)	1 (0.4%)
Mediastinal disorder	0	1 (0.8%)	1 (0.4%)

- **Numbers analysed**

The number of patients in each group in each analysis set are presented in Table 62.

Table 62. Analysis Data Sets: Full Analysis and Per Protocol Sets – Screened patients Set (N=324)

	gadopiclenol / gadobutrol (N=152)	gadobutrol / gadopiclenol (N=152)	Total (N=324)
All Randomized Set	151 (99.3%)	149 (98.0%)	300 (92.6%)
Extended Full Analysis Set 1	150 (99.3%)	136 (91.3%)	286 (95.3%)
Extended Full Analysis Set 2	140 (92.7%)	136 (91.3%)	276 (92.0%)
Full Analysis Set 1	145 (96.0%)	133 (89.3%)	278 (92.7%)
Per Protocol Set 1	143 (98.6%)	128 (96.2%)	271 (97.5%)
Full Analysis Set 2	140 (92.7%)	133 (89.3%)	273 (91.0%)
Per Protocol Set 2	135 (96.4%)	125 (94.0%)	260 (95.2%)

Percentages for the extended FAS 1, extended FAS 2, FAS 1 and FAS 2 are based upon number of patients in the All Randomized Set.
Percentages for the Per Protocol Set are based on number of patients in the corresponding Full Analysis Set.

Table 63 below has been provided to better understand the number of patients and number of lesions analysed in each analysis dataset and for each off-site reader.

Table 63. Off-Site Readings – Number of patients and number of lesions (up to 3 most representative lesions per patient) by contrast agent and by MRI modality (Pre and Paired) for all efficacy datasets

	Gadopiclenol (N=287)				Gadobutrol (N=290)			
	PRE		PAIRED		PRE		PAIRED	
	Patients	Lesions	Patients	Lesions	Patients	Lesions	Patients	Lesions
Randomized Set								
Reader 1	282	570	281	533	284	585	283	530
Reader 2	275	449	270	421	274	447	277	435
Reader 3	283	569	284	513	285	569	287	512
Extended FAS 1								
Reader 1	282	570	281	533				
Reader 2	275	449	270	421				
Reader 3	283	569	284	513				
FAS 1								
Reader 1	251	375	251	375				
Reader 2	230	315	230	315				
Reader 3	262	401	262	401				
PPS 1								
Reader 1	245	368	245	368				
Reader 2	226	311	226	311				
Reader 3	256	394	256	394				
Extended FAS 2								
Reader 1			271	518			270	511
Reader 2			261	406			265	419
Reader 3			274	496			274	489
FAS 2								
Reader 1			250	388			250	388
Reader 2			231	312			231	312
Reader 3			254	382			254	382
PPS 2								
Reader 1			240	376			240	376
Reader 2			223	303			223	303
Reader 3			243	370			243	370

- **Outcomes and estimation**

Primary criteria

Lesion visualisation

In the pivotal phase III study (GDX-44-011), the two primary objectives were achieved for all three blinded readers:

- **Primary objective 1: The superiority of the combined unenhanced/contrast-enhanced MRI (Paired) with gadopiclenol over unenhanced MRI (Pre-contrast) for lesion visualisation was demonstrated (Table 64).** The difference in mean of scores each lesion visualisation criterion was significantly different from zero with a type 1 error set at 0.025 in favor of Paired images compared to Pre-contrast images ($p<0.0001$).
- **Primary objective 2: The non-inferiority of gadopiclenol at 0.05 mmol/kg to gadobutrol at 0.1 mmol/kg for lesion visualisation was demonstrated (Table 65).** The lower limit of the

95% CI of the difference was not lower than -0.10, that is largely above the non-inferiority margin of -0.35 (p<0.0001).

Table 64. Body GDX-44-011 Co-primary criteria 1 - Off-Site Readings - MRI with Gadopiclenol - PAIRED vs PRE – Mixed Model – FAS 1 (N= 278)

FAS 1 (N=278)	n	LS Mean (SE)			95% CI difference	p-value
		Paired	Pre	Difference		
Border delineation						
Reader 1	251	3.79 (0.03)	2.26 (0.03)	1.53 (0.04)	[1.46 ; 1.60]	<0.0001
Reader 2	230	3.48 (0.06)	3.01 (0.06)	0.47 (0.06)	[0.36 ; 0.58]	<0.0001
Reader 3	262	3.49 (0.03)	1.78 (0.03)	1.71 (0.04)	[1.65 ; 1.78]	<0.0001
Internal morphology						
Reader 1	251	3.80 (0.02)	1.99 (0.02)	1.81 (0.03)	[1.76 ; 1.87]	<0.0001
Reader 2	230	3.75 (0.05)	3.22 (0.05)	0.53 (0.06)	[0.42 ; 0.64]	<0.0001
Reader 3	262	3.72 (0.03)	1.69 (0.03)	2.03 (0.04)	[1.95 ; 2.11]	<0.0001
Degree of contrast enhancement						
Reader 1	251	3.64 (0.03)	1.00 (0.03)	2.64 (0.04)	[2.56 ; 2.72]	<0.0001
Reader 2	230	2.82 (0.05)	1.00 (0.05)	1.82 (0.07)	[1.68 ; 1.96]	<0.0001
Reader 3	262	3.33 (0.03)	1.00 (0.03)	2.33 (0.04)	[2.26 ; 2.41]	<0.0001

CI: Confidence Interval; LS: Least Squares ; SE: Standard Error. Only matching lesions are considered.

The models include lesion visualisation factor as dependent variable, MRI modality (Pre and Paired MRI) as fixed factors, patient as random factor.

Table 65. Body – GDX-44-011 Co-primary criteria 2 - Off-Site Readings – MRI with Gadopiclenol versus MRI with gadobutrol - Mixed Model – PPS 2 (N= 260)

PPS 2 (N= 260)	n	LS Mean (SE)			95% CI difference	p-value
		Gadopiclenol	Gadobutrol	Difference		
Border delineation						
Reader 1	240	3.82 (0.02)	3.81 (0.02)	0.00 (0.03)	[-0.05 ; 0.05]	<0.0001
Reader 2	223	3.56 (0.05)	3.53 (0.05)	0.02 (0.04)	[-0.05 ; 0.10]	<0.0001
Reader 3	243	3.53 (0.03)	3.57 (0.03)	-0.04 (0.03)	[-0.10 ; 0.01]	<0.0001
Internal morphology						
Reader 1	240	3.83 (0.02)	3.83 (0.02)	-0.00 (0.03)	[-0.06 ; 0.05]	<0.0001
Reader 2	223	3.75 (0.04)	3.75 (0.04)	-0.00 (0.04)	[-0.07 ; 0.07]	<0.0001
Reader 3	243	3.74 (0.03)	3.77 (0.03)	-0.03 (0.02)	[-0.08 ; 0.02]	<0.0001
Degree of contrast enhancement						
Reader 1	240	3.69 (0.04)	3.68 (0.04)	0.01 (0.04)	[-0.06 ; 0.09]	<0.0001
Reader 2	223	2.88 (0.07)	2.86 (0.07)	0.03 (0.05)	[-0.07 ; 0.12]	<0.0001
Reader 3	243	3.35 (0.04)	3.37 (0.04)	-0.02 (0.03)	[-0.08 ; 0.04]	<0.0001

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error. Only matching lesions are considered.
The models include lesion visualisation factor as dependent variable, contrast agent and period as fixed factors, patient as random factor.

A pooled analysis of the primary outcome criteria 2 over the three readers and for each lesion visualisation criterion is presented in the Table 66 below.

Table 66. Co-primary criteria 2 - off-site readings - global mixed model with readers as covariate - FAS 2 (N=273)

	n	LS Mean (SE) Gadopiclenol	LS Mean (SE) Gadobutrol	LS Mean Difference (SE)	95% CI	p-value
Border delineation	273	3.60 (0.03)	3.60 (0.03)	-0.00 (0.02)	[-0.05 ; 0.04]	0.8987
Internal morphology	273	3.75 (0.02)	3.76 (0.02)	-0.01 (0.02)	[-0.05 ; 0.03]	0.6822
Degree of contrast enhancement	273	3.30 (0.04)	3.29 (0.04)	0.01 (0.03)	[-0.05 ; 0.07]	0.8546

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error.
Only matching lesions are considered.
*The models include lesion visualization factor as dependent variable, reader, period, contrast agent and reader*contrast agent interaction as fixed factors, patient as random factor.*
Source: Table 14.2.1.26
Listings 16.2.6.1, 16.2.6.2 and 16.2.6.3

According to the applicant, these results of the primary analyses were confirmed in all supportive and sensitivity analyses. Similar results were also obtained with on-site reading for the two primary objectives.

Additionally, similar results were obtained when non-matching lesions were included. The primary analyses 1 and 2 were repeated, this time also including the non-matching lesions, using the extended FAS 1 and extended FAS 2, respectively. For the primary criterion 1, the number of patients analysed included an additional 32, 49 and 24 patients for reader 1, 2 and 3, respectively. For the primary criterion 2, the number of patients analysed included an additional 32, 48 and 33 patients for reader 1, 2 and 3, respectively.

The numbers of lesions seen with both contrast agents of with only one contrast agent are presented by reader in the Table 67 below.

Table 67. Overview of numbers of lesion observed with both contrast agents or with only one contrast agent

GDX-44-011	N lesions	Lesions seen with both contrast agents	Lesions seen only with gadopiclenol	Lesions seen only with gadobutrol
Reader 1	641	388 (60.5%)	130 (20.3%)	123 (19.2%)
Reader 2	513	312 (60.8%)	94 (18.3%)	107 (20.9%)
Reader 3	603	382 (63.4%)	114 (18.9%)	107 (17.7%)

The number of patients in which the number of lesions seen with each contrast agent differed is summarised by reader in the Table 68 below.

Table 68. Overview of number of patients by reader with the same or different number of lesions identified by the contrast agents

Body region	Reader	All patients or sequence	more lesions seen with gadobutrol	same number of lesions seen with both GBCAs	more lesions seen with gadopiclenol
Musculo-skeletal	Reader 1	All patients	-	20 (95.24%)	1 (4.76%)
		gadopiclenol-gadobutrol	-	10 (90.91%)	1 (9.09%)
		gadobutrol - gadopiclenol	-	10 (100%)	-
	Reader 2	All patients	1 (4.76%)	19 (90.48%)	1 (4.76%)
		gadopiclenol-gadobutrol	-	10 (90.91%)	1 (9.09%)
		gadobutrol - gadopiclenol	1 (10.00%)	9 (90.00%)	
	Reader 3	All patients	1 (4.76%)	20 (95.24%)	-
		gadopiclenol-gadobutrol	1 (9.09%)	10 (90.91%)	-
		gadobutrol - gadopiclenol	-	10 (100%)	-
Pelvis	Reader 1	All patients	10 (16.95%)	40 (67.80%)	9 (15.25%)
		gadopiclenol-gadobutrol	3 (11.11%)	19 (70.37%)	5 (18.52%)
		gadobutrol - gadopiclenol	7 (21.88%)	21 (65.63%)	4 (12.50%)
	Reader 2	All patients	17 (28.81%)	26 (44.07%)	16 (27.12%)
		gadopiclenol-gadobutrol	8 (29.63%)	11 (40.74%)	8 (29.63%)
		gadobutrol - gadopiclenol	9 (28.13%)	15 (46.88%)	8 (25.00%)
	Reader 3	All patients	7 (11.86%)	37 (62.71%)	15 (25.42%)
		gadopiclenol-gadobutrol	4 (14.81%)	15 (55.56%)	8 (29.63%)
		gadobutrol - gadopiclenol	3 (9.38%)	22 (68.75%)	7 (21.88%)
Thorax	Reader 1	All patients	18 (23.68%)	36 (47.37%)	22 (28.95%)
		gadopiclenol-gadobutrol	14 (32.56%)	19 (44.19%)	10 (23.26%)
		gadobutrol - gadopiclenol	4 (12.12%)	17 (51.52%)	12 (36.36%)
	Reader 2	All patients	12 (15.79%)	56 (73.68%)	8 (10.53%)
		gadopiclenol-gadobutrol	6 (13.95%)	29 (67.44%)	8 (18.60%)
		gadobutrol - gadopiclenol	6 (18.18%)	27 (81.82%)	-
	Reader 3	All patients	12 (15.79%)	49 (64.47%)	15 (19.74%)
		gadopiclenol-gadobutrol	7 (16.28%)	23 (53.49%)	13 (30.23%)
		gadobutrol - gadopiclenol	5 (15.15%)	26 (78.79%)	2 (6.06%)

GDX-44-011					
Abdomen	Reader 1	All patients	16 (16.67%)	57 (59.38%)	23 (23.96%)
		gadopiclenol-gadobutrol	10 (21.74%)	26 (56.52%)	10 (21.74%)
		gadobutrol - gadopiclenol	6 (12.00%)	31 (62.00%)	13 (26.00%)
	Reader 2	All patients	21 (21.88%)	58 (60.42%)	17 (17.71%)
		gadopiclenol-gadobutrol	10 (21.74%)	27 (58.7%)	9 (19.57%)
		gadobutrol - gadopiclenol	11 (22.00%)	31 (62.00%)	8 (16.00%)
	Reader 3	All patients	22 (22.92%)	58 (60.42%)	16 (16.67%)
		gadopiclenol-gadobutrol	13 (28.26%)	25 (54.35%)	8 (17.39%)
		gadobutrol - gadopiclenol	9 (18.00%)	33 (66.00%)	8 (16.00%)
Head & Neck	Reader 1	All patients	3 (12.50%)	16 (66.67%)	5 (20.83%)
		gadopiclenol-gadobutrol	2 (15.38%)	8 (61.54%)	3 (23.08%)
		gadobutrol - gadopiclenol	1 (9.09%)	8 (72.73%)	2 (18.18%)
	Reader 2	All patients	3 (12.50%)	18 (75%)	3 (12.50%)
		gadopiclenol-gadobutrol	2 (15.38%)	10 (76.92%)	1 (7.69%)
		gadobutrol - gadopiclenol	1 (9.09%)	8 (72.73%)	2 (18.18%)
	Reader 3	All patients	5 (20.83%)	13 (54.17%)	6 (25.00%)
		gadopiclenol-gadobutrol	3 (23.08%)	7 (53.85%)	3 (23.08%)
		gadobutrol - gadopiclenol	2 (18.18%)	6 (54.55%)	3 (27.27%)

Analysis of intra-readers' and inter-readers' variability showed generally good reproducibility of readings.

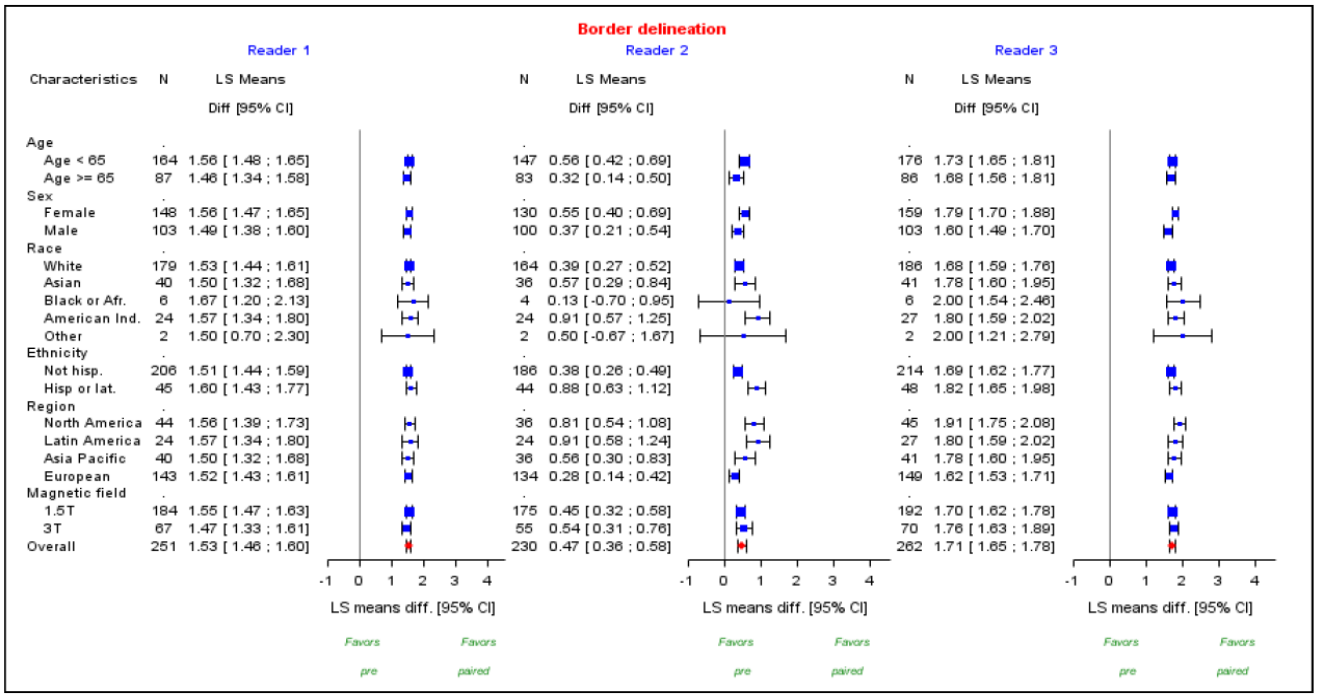
The analysis of the difference "Paired - Pre" for each of 3 co-primary criteria for MRI with gadobutrol showed similar results to those obtained with gadopiclenol, confirming the assay sensitivity.

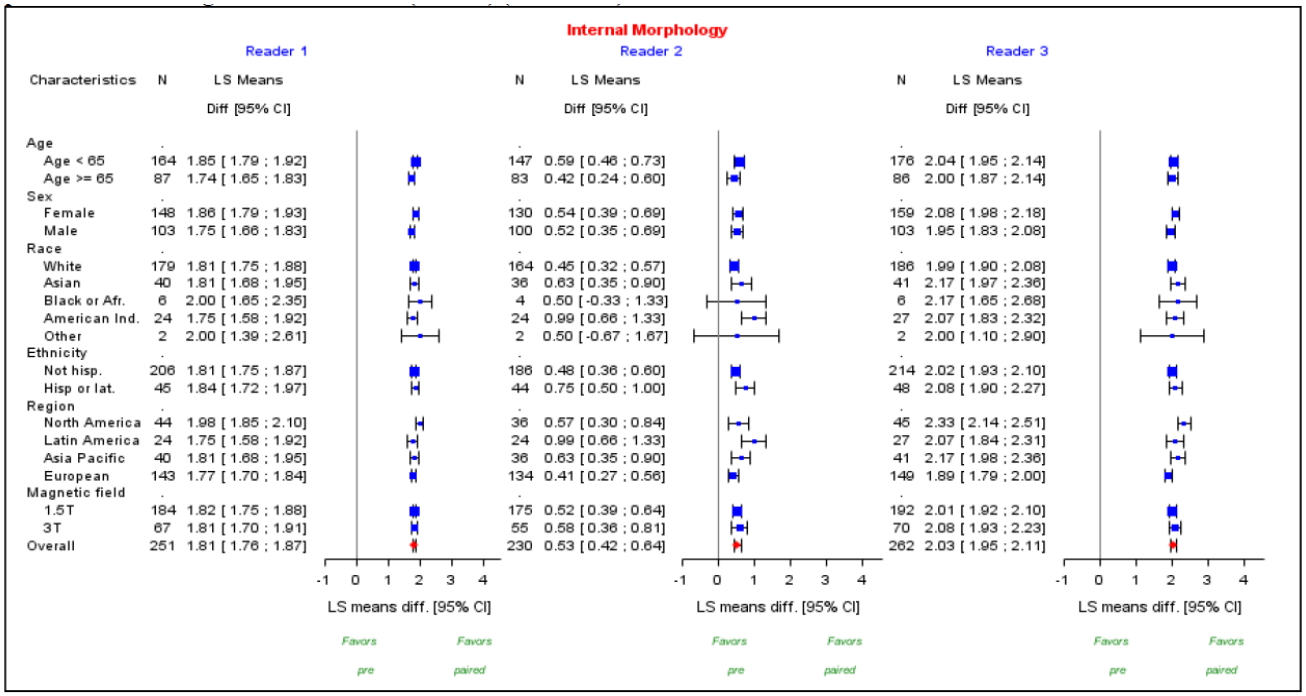
Subgroup analyses of the primary efficacy criteria

Lesion visualisation criteria by demographic parameters and magnetic field strength

The mixed models did not show any heterogeneity in lesion visualisation assessment between body regions, organs, classes of age, sex, race, ethnicity, geographic region. The results were also similar for MRI performed with magnetic field strength of 1.5T or 3T (Figure 5 and Figure 6 below).

Figure 5. Lesion visualisation criteria - Off-Site Readings - MRI with Gadopiclenol - PAIRED vs PRE - Forest Plot by demographic parameters and magnetic field - FAS 1 (N=278)





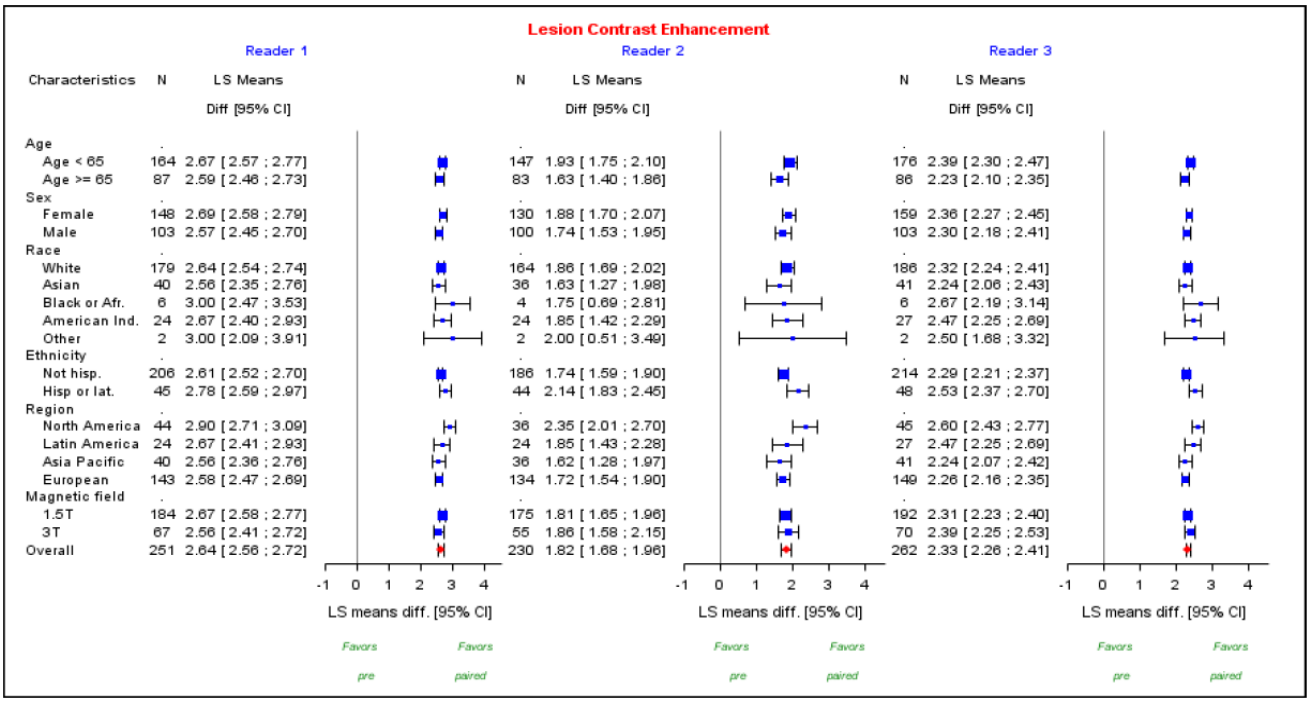
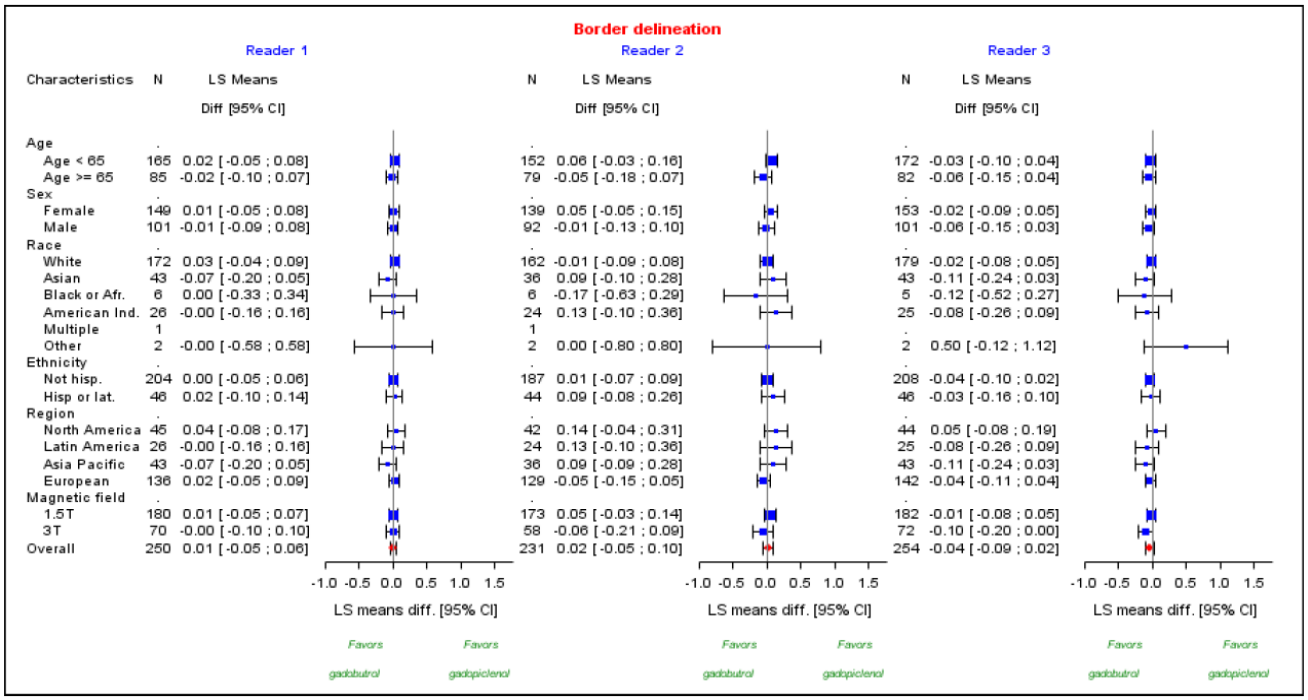
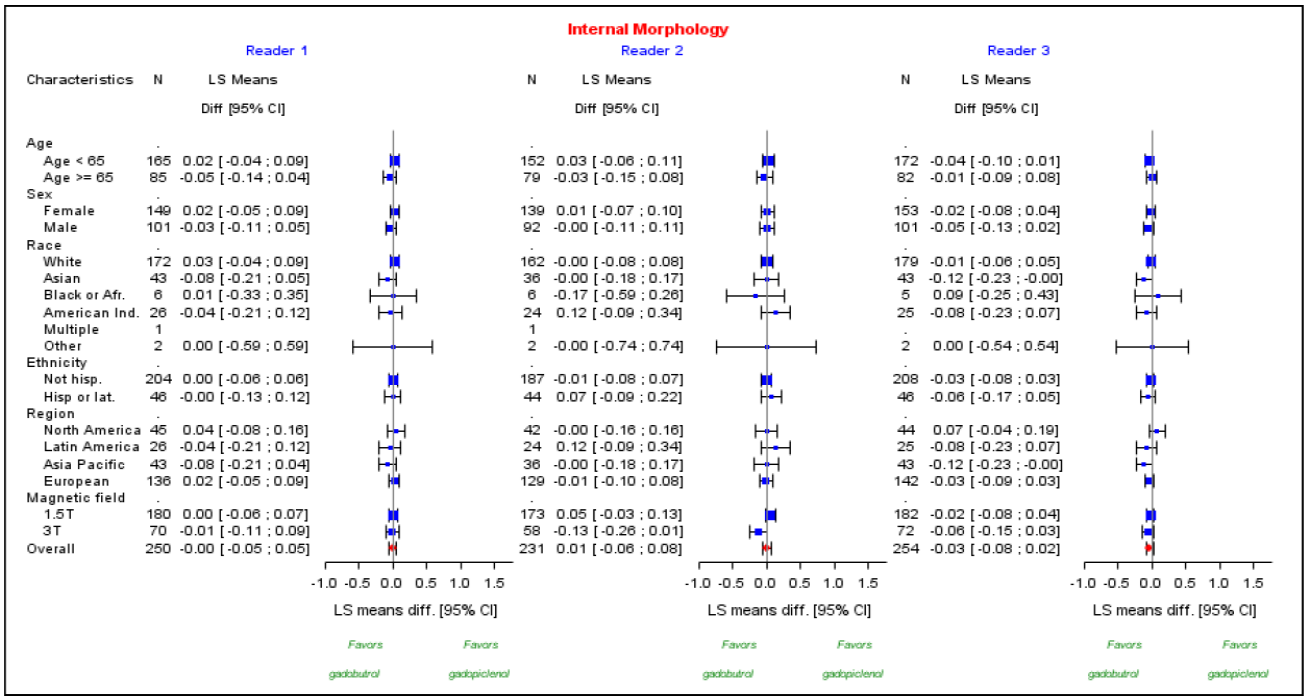
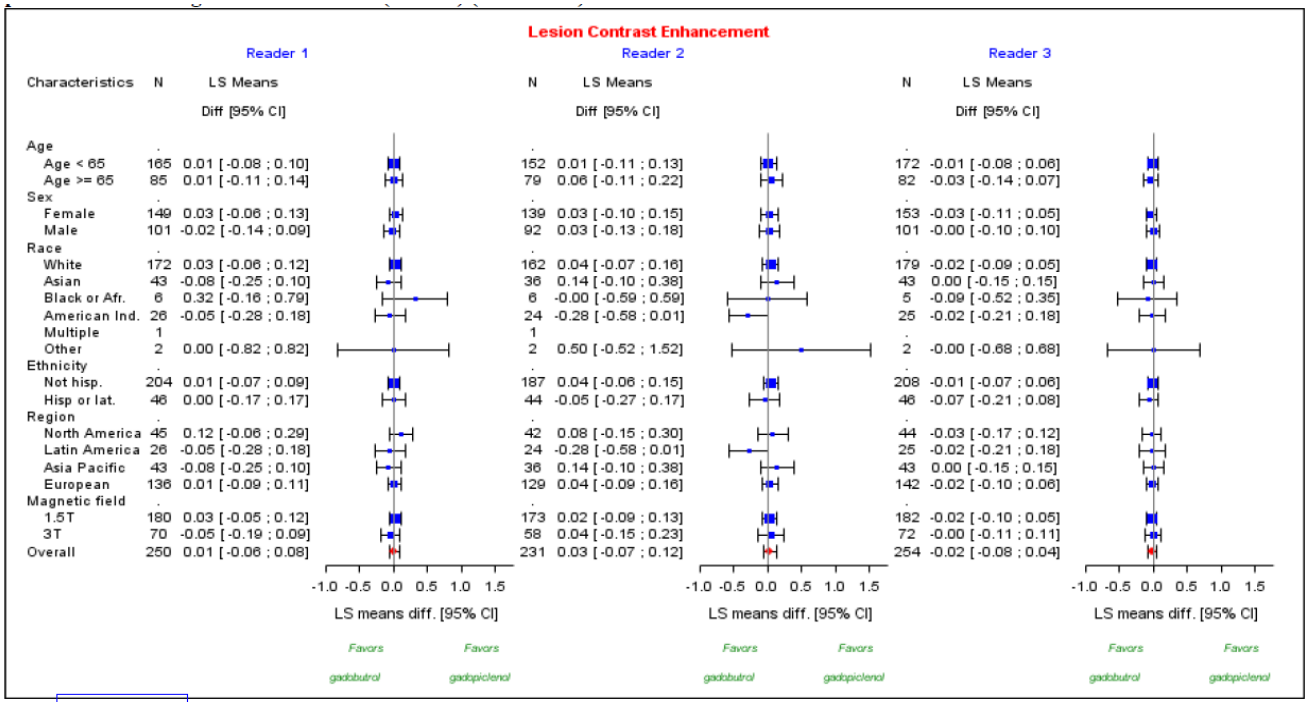


Figure 6. Lesion visualisation criteria - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol - Forest Plot by demographic parameters and magnetic field - FAS 2 (N=273)





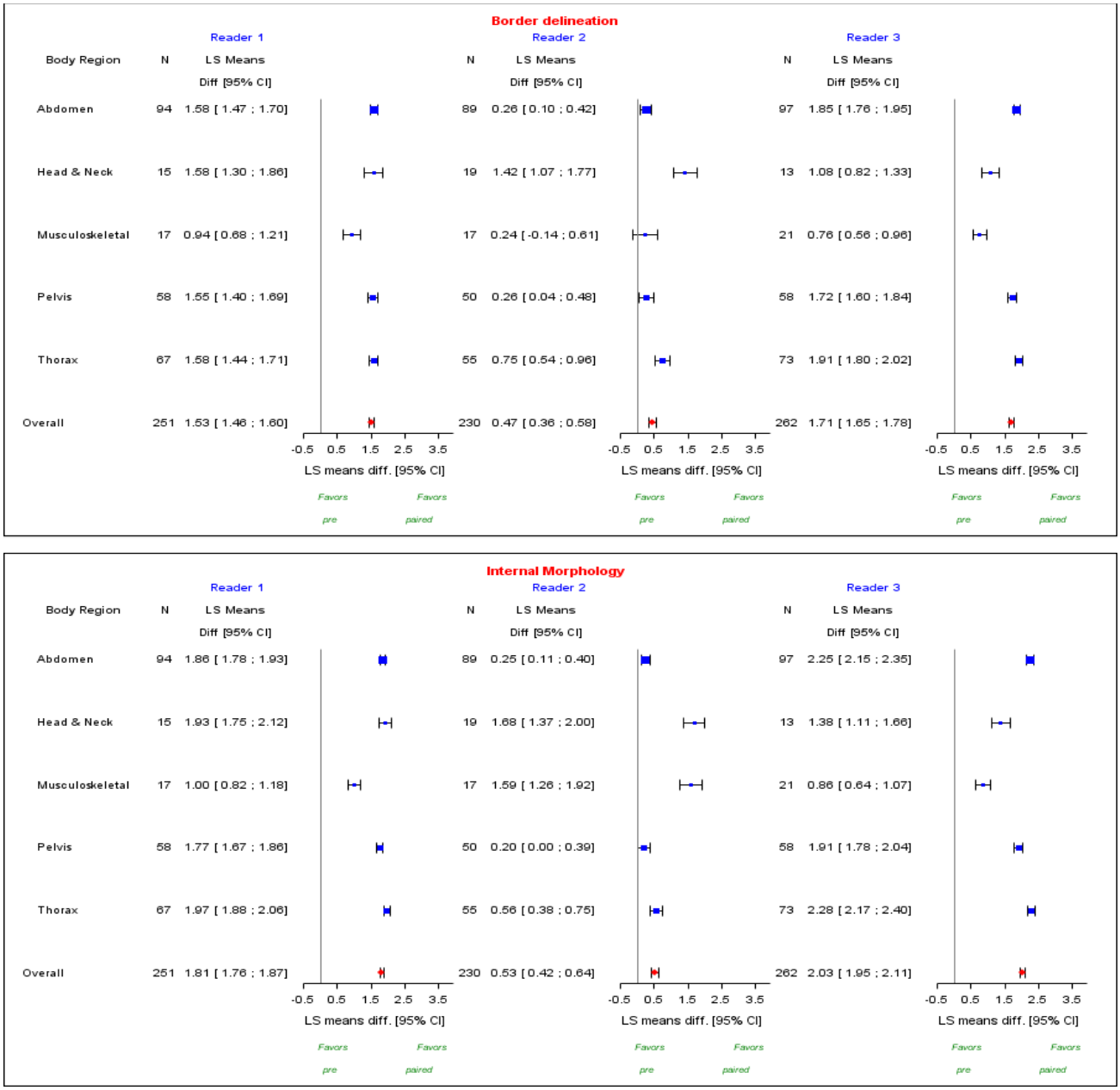


Lesion visualisation criteria by body region

The mixed models showed mostly homogeneous results between body regions. Paired images were superior to Pre-contrast images in all body regions for border delineation, internal morphology and contrast enhancement. The difference was statistically significant in all evaluations except for border delineation assessed by Reader 2 in Musculoskeletal examination (on 17 patients) (Figure 7). Regarding the comparison of MRI with gadopiclenol and MRI with gadobutrol, the 95% CI of the difference was above the non-inferiority

margin (-0.35) except for contrast enhancement in MSK for Reader 1 (on 16 patients) and Reader 3 (on 18 patients) and internal morphology in Head & Neck for Reader 2 (on 18 patients) (Figure 7 below).

Figure 7. Body GDX-44-011 - Lesion visualisation criteria - Off-Site Readings – MRI with Gadopiclenol – PAIRED vs PRE - Forest Plot by body region – FAS 1 (N= 278)



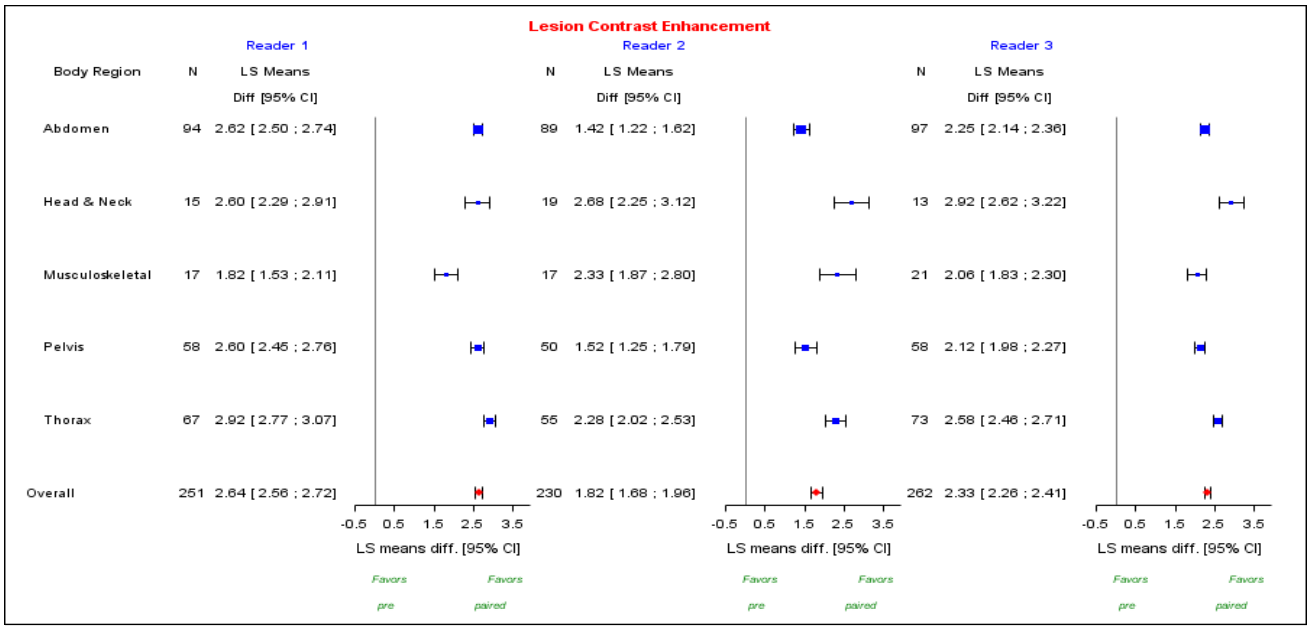
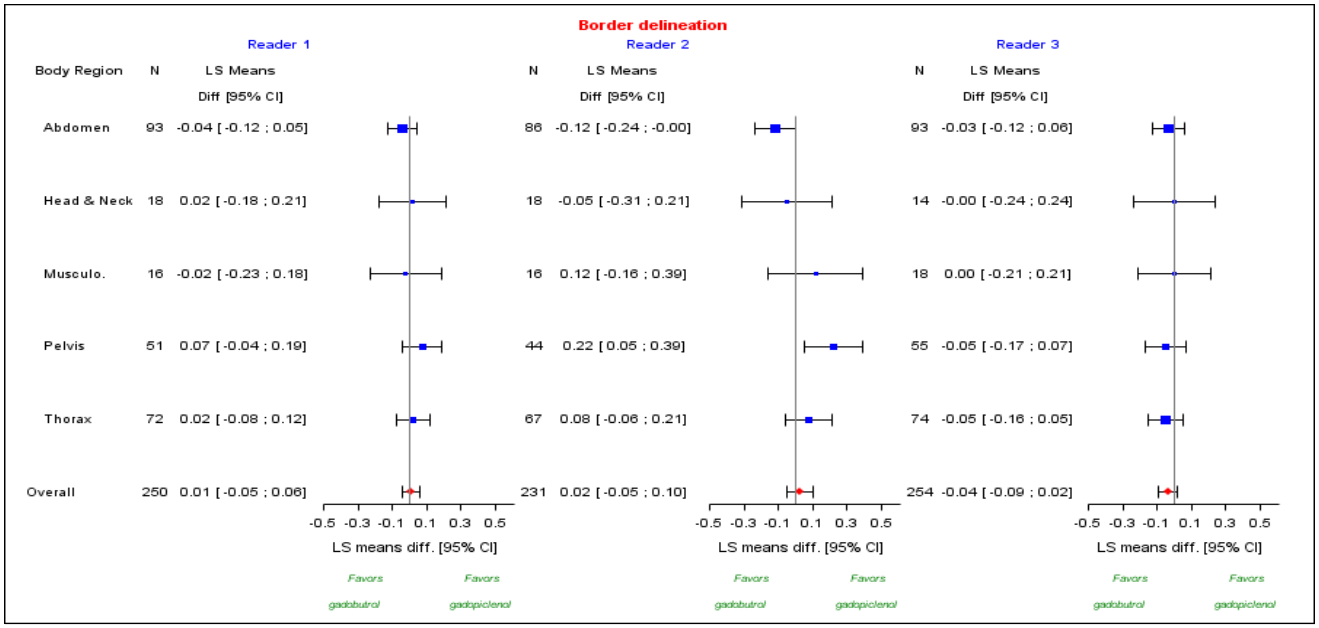
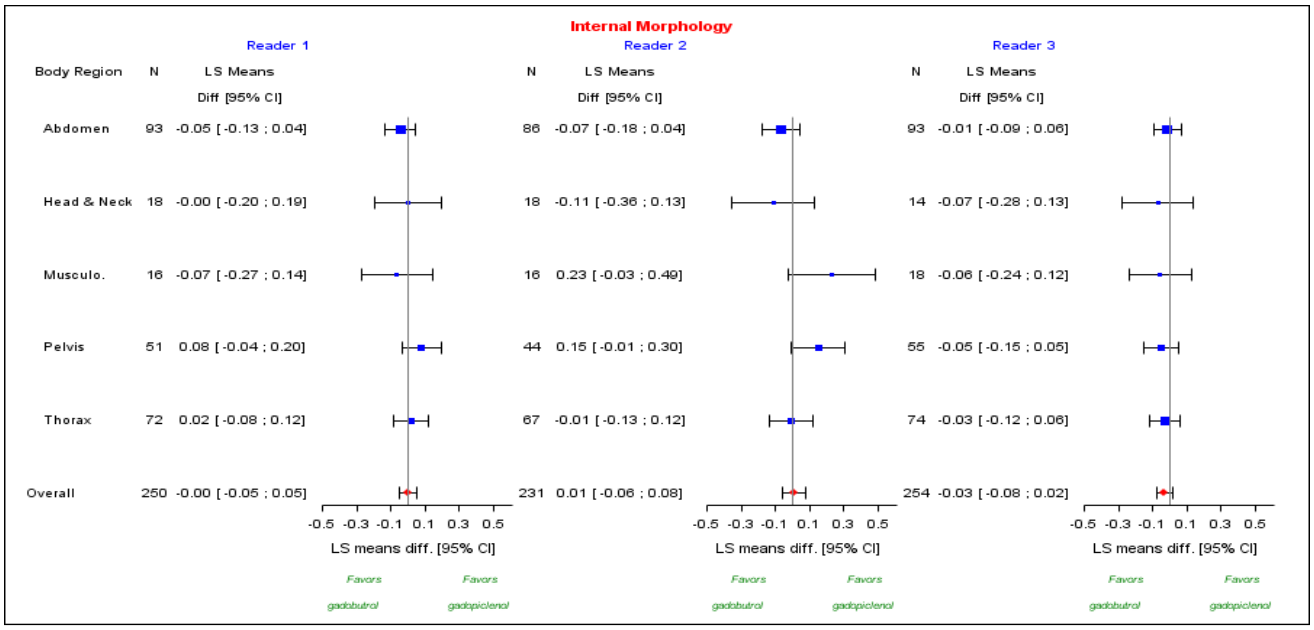
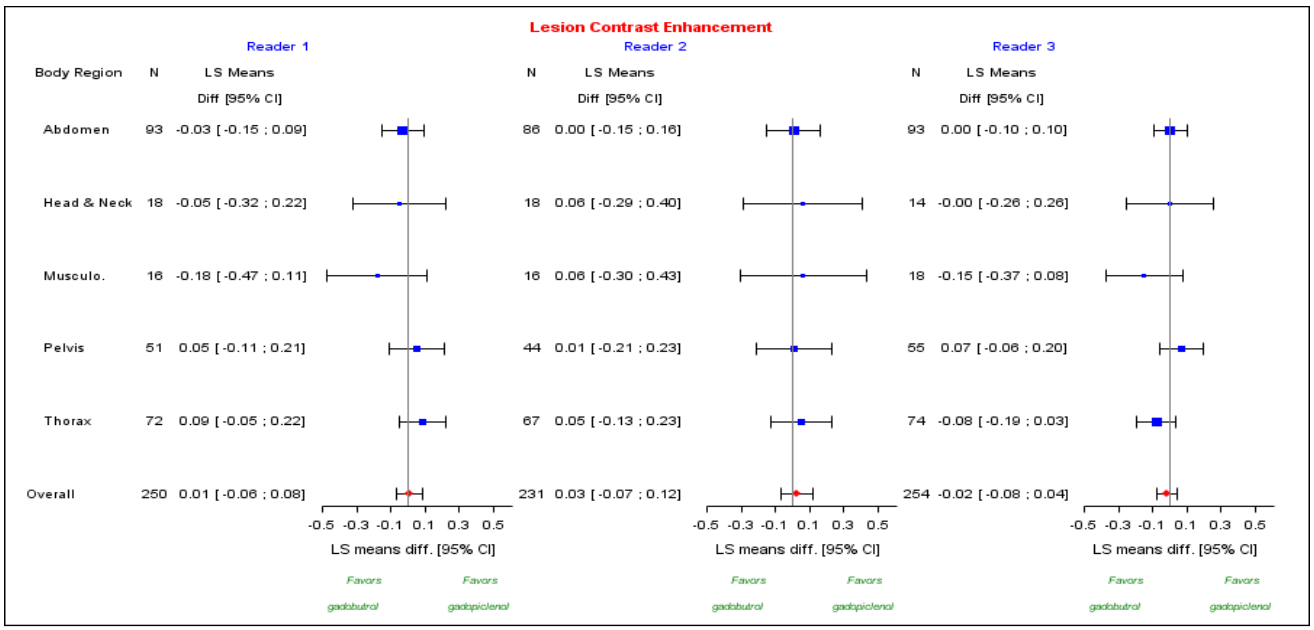


Figure 8. Body GDX-44-011 - Lesion visualisation criteria - Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol - Forest Plot by body region – FAS 2 (N= 273)



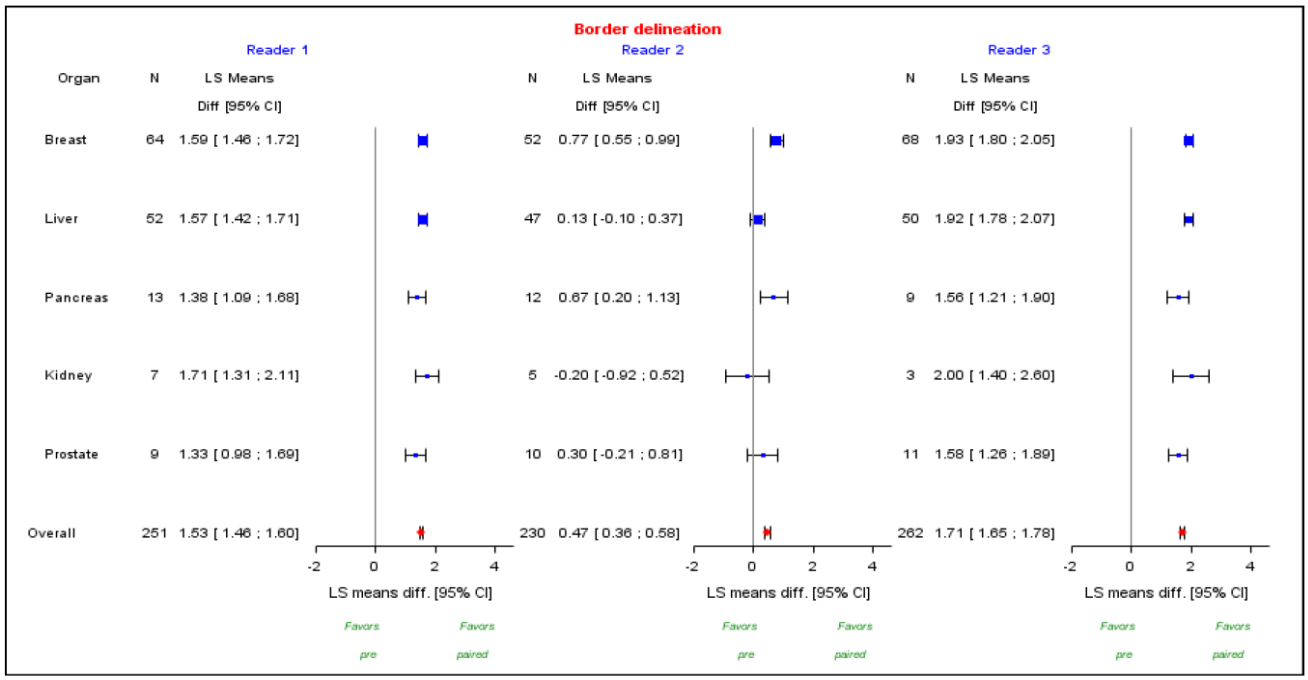


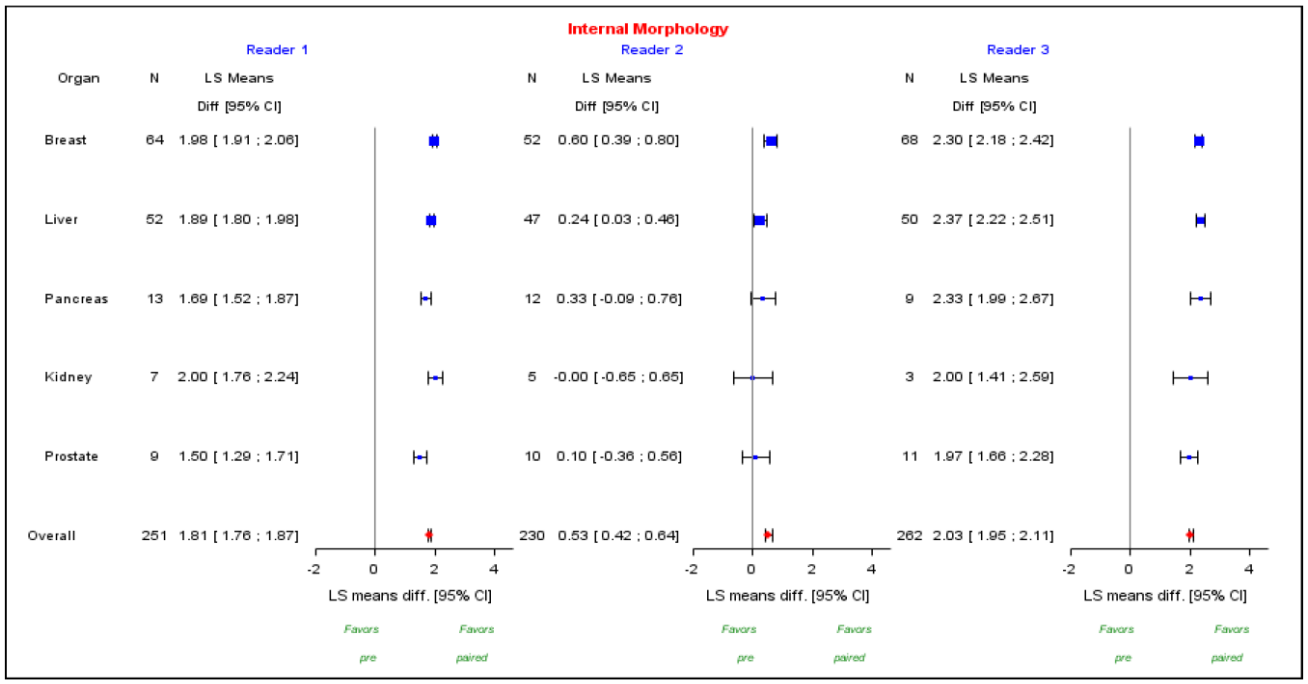


Lesion visualisation criteria by organ

Lesion visualisation criteria by organ (breast, liver, kidney, pancreas, prostate) are presented in the figures below.

Figure 9. Lesion visualisation criteria - Off-Site Readings – MRI with Gadopiclenol– PAIRED vs PRE- Forest Plot by organ – FAS 1 (N=278)





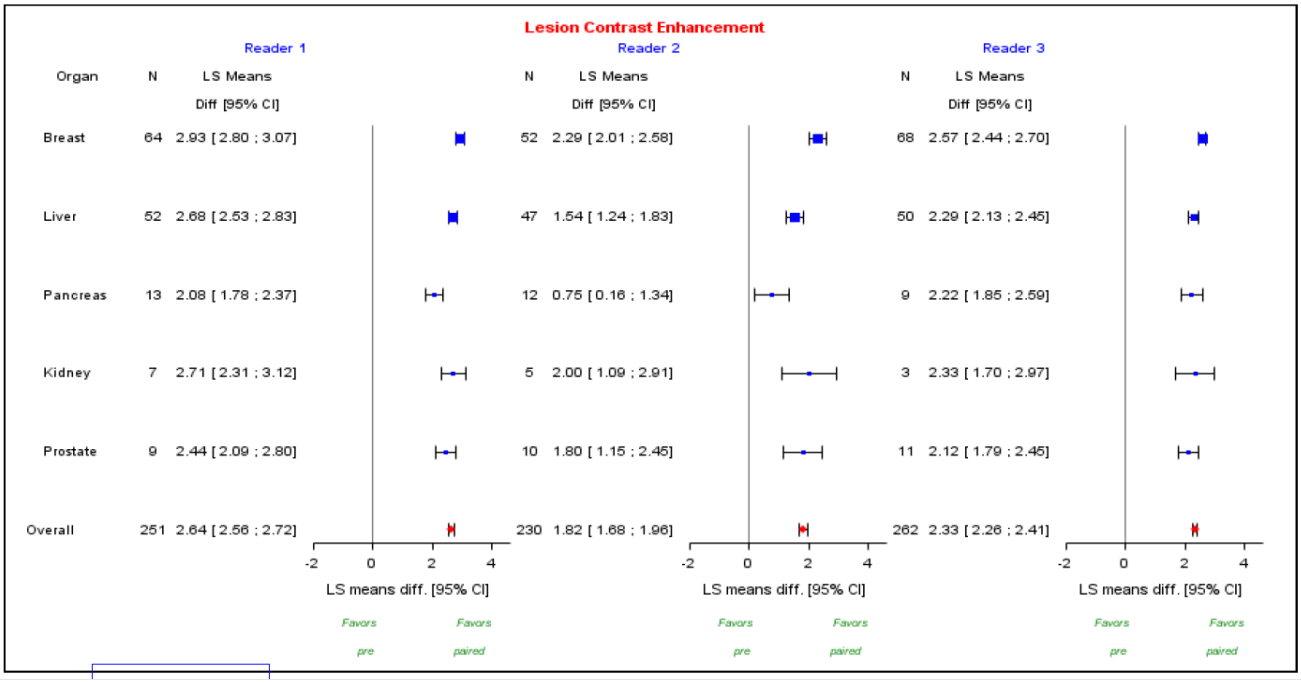
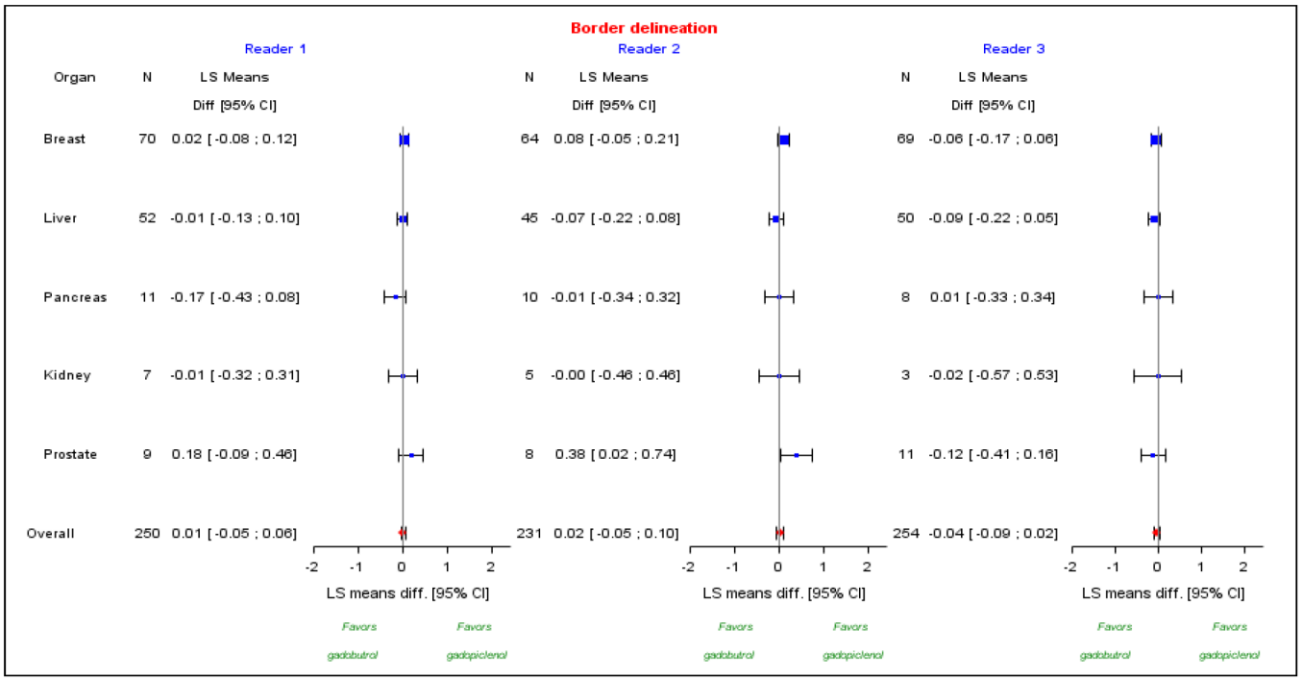
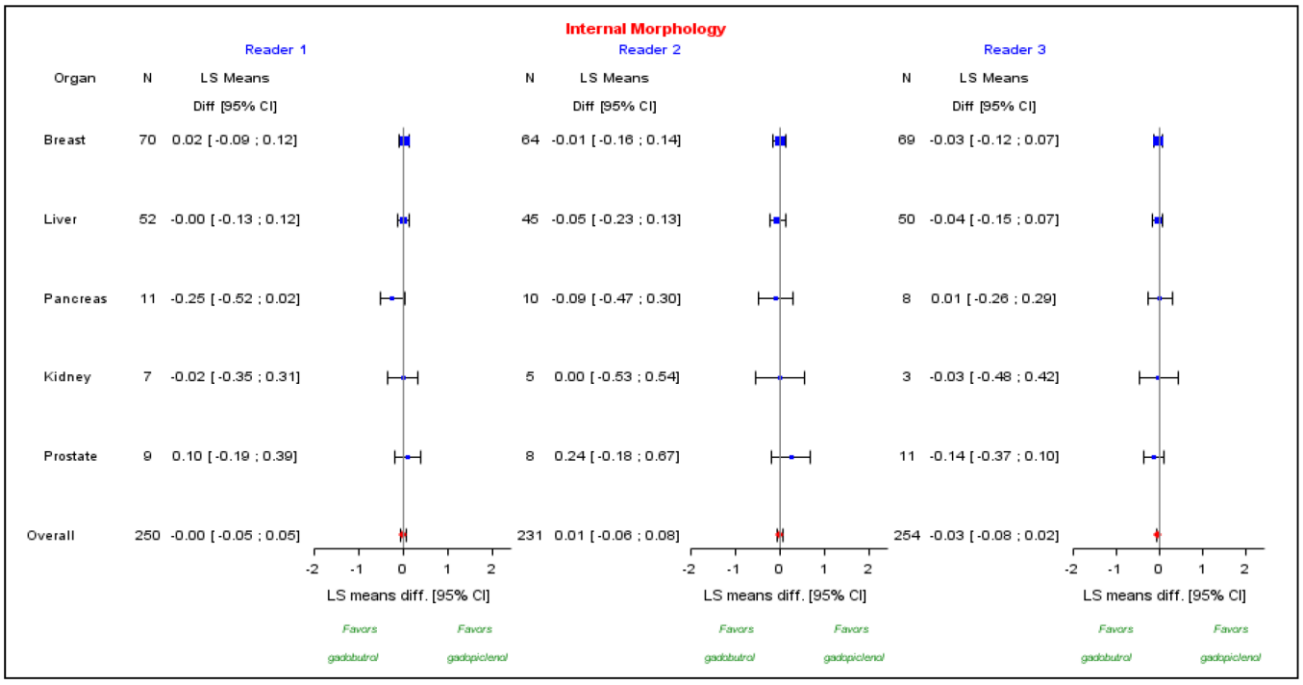
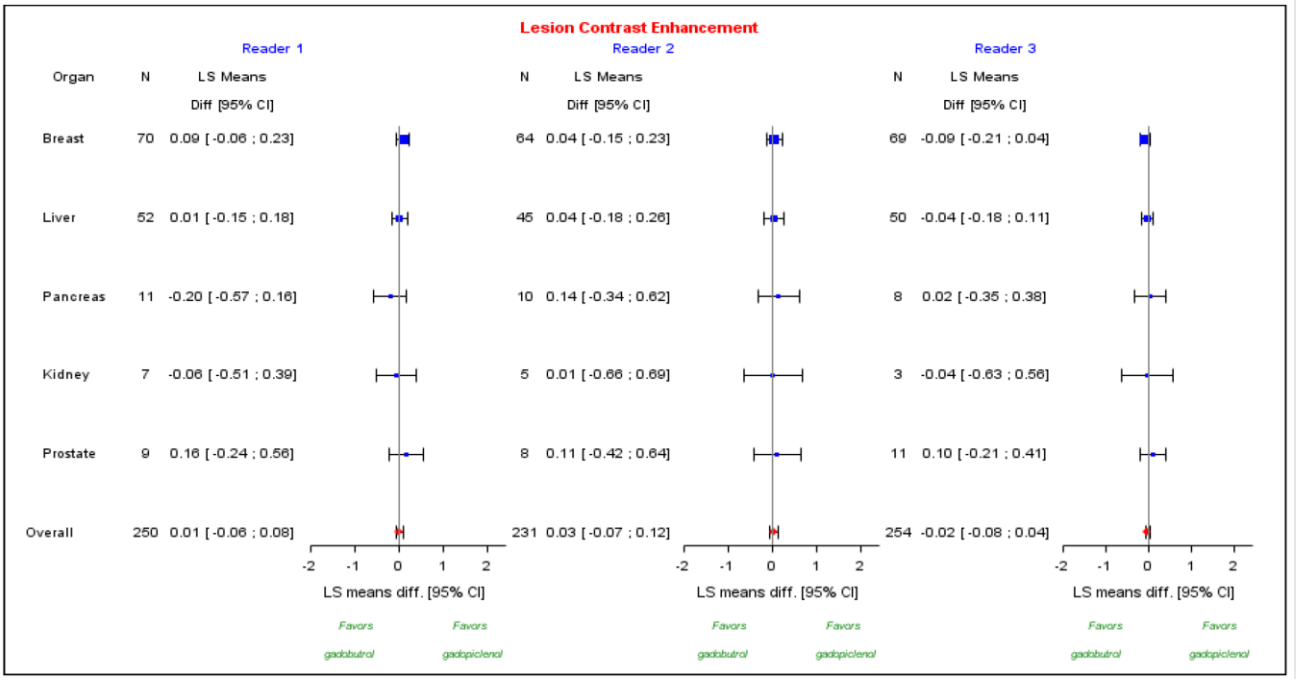


Figure 10. Lesion visualisation criteria - Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol - Forest Plot by organ – FAS 2 (N= 273)







Secondary criteria

Improvement in lesion visualisation score at patient-level

Improvement in lesion visualisation scores at patient-level was shown by Paired images with gadopiclenol, scoring better than Pre-contrast images in more than 97% of the patients for readers 1 and 3 and for all 3 co-primary visualisation criteria. For the reader 2, better score was reported for 42.2% for border delineation to 87.0% of the patients, for degree of contrast enhancement. Similar results were obtained with gadobutrol (table below).

Table 69. Body GDX-44-011- Improvement in lesion visualisation scores at patient-level - Off-Site Readings – FAS 1 and FAS 2

	MRI with Gadopiclenol FAS 1 (N= 278)			MRI with Gadobutrol FAS 2 (N= 273)		
	n	Not Better	Better	n	Not Better	Better
Border delineation						
Reader 1	251	7 (2.8%)	244 (97.2%)	247	8 (3.2%)	239 (96.8%)
Reader 2	230	133 (57.8%)	97 (42.2%)	224	147 (65.6%)	77 (34.4%)
Reader 3	262	5 (1.9%)	257 (98.1%)	246	5 (2.0%)	241 (98.0%)
Internal morphology						
Reader 1	251	3 (1.2%)	248 (98.8%)	247	2 (0.8%)	245 (99.2%)
Reader 2	230	130 (56.5%)	100 (43.5%)	224	130 (58.0%)	94 (42.0%)
Reader 3	262	4 (1.5%)	258 (98.5%)	246	3 (1.2%)	243 (98.8%)
Degree of contrast enhancement						
Reader 1	251	4 (1.6%)	247 (98.4%)	247	2 (0.8%)	245 (99.2%)
Reader 2	230	30 (13.0%)	200 (87.0%)	224	34 (15.2%)	190 (84.8%)
Reader 3	262	1 (0.4%)	261 (99.6%)	246	1 (0.4%)	245 (99.6%)

Lesion visualisation at lesion level

Lesion visualisation criteria at lesion level for paired images with gadopiclenol compared with pre-contrast images showed similar results to those obtained at patient level. Assessment of lesion visualisation criteria by the off-site readers at lesion level for MRI with Gadopiclenol vs MRI with Gadobutrol is also similar to those obtained at patient level. Lesion visualisation criteria by the off-site blinded readers at lesion level were also analysed according to lesion size (≤1 cm, >1 cm and ≤2 cm, >2 cm) (Table 70). No differences were observed for different lesion sizes.

Table 70. Lesion visualisation criteria at lesion level - Off-Site Readings – MRI with Gadopiclenol vs MRI with Gadobutrol – Lesion size analysis – Mixed Model – Extended FAS 2 (N=276)

		n lesions	LS Mean (SE)			95% CI difference
			Gadopiclenol	Gadobutrol	Difference (SE)	
Border delineation	**≤1 cm**					
	Reader 1	67	3.79 (0.06)	3.68 (0.06)	0.11 (0.08)	[-0.04 ; 0.26]
	Reader 2	52	3.34 (0.13)	3.31 (0.14)	0.03 (0.15)	[-0.27 ; 0.32]
	Reader 3	108	3.36 (0.07)	3.38 (0.07)	-0.02 (0.07)	[-0.16 ; 0.11]
	>1 cm and ≤2 cm					
	Reader 1	245	3.67 (0.04)	3.71 (0.04)	-0.04 (0.04)	[-0.12 ; 0.04]
	Reader 2	176	3.46 (0.08)	3.41 (0.08)	0.05 (0.06)	[-0.08 ; 0.17]
	Reader 3	224	3.43 (0.05)	3.53 (0.05)	-0.10 (0.04)	[-0.18 ; -0.01]
	>2 cm					
	Reader 1	401	3.80 (0.03)	3.78 (0.03)	0.02 (0.02)	[-0.03 ; 0.07]
	Reader 2	321	3.50 (0.07)	3.46 (0.07)	0.03 (0.04)	[-0.05 ; 0.11]
	Reader 3	324	3.53 (0.04)	3.53 (0.04)	-0.00 (0.03)	[-0.06 ; 0.06]
Internal morphology	**≤1 cm**					
	Reader 1	67	3.80 (0.06)	3.72 (0.06)	0.08 (0.08)	[-0.07 ; 0.23]
	Reader 2	52	3.46 (0.10)	3.39 (0.11)	0.07 (0.13)	[-0.18 ; 0.33]
	Reader 3	108	3.46 (0.06)	3.48 (0.06)	-0.02 (0.06)	[-0.14 ; 0.10]
	>1 cm and ≤2 cm					
	Reader 1	245	3.71 (0.04)	3.72 (0.04)	-0.02 (0.04)	[-0.09 ; 0.06]
	Reader 2	176	3.60 (0.06)	3.51 (0.06)	0.08 (0.06)	[-0.03 ; 0.20]
	Reader 3	224	3.64 (0.04)	3.70 (0.04)	-0.06 (0.04)	[-0.14 ; 0.01]
	>2 cm					
	Reader 1	401	3.82 (0.03)	3.81 (0.03)	0.01 (0.02)	[-0.04 ; 0.06]
	Reader 2	321	3.73 (0.05)	3.73 (0.05)	-0.01 (0.04)	[-0.08 ; 0.07]
	Reader 3	324	3.71 (0.04)	3.71 (0.04)	0.00 (0.03)	[-0.05 ; 0.06]
Degree of contrast enhancement	**≤1 cm**					
	Reader 1	67	3.74 (0.10)	3.67 (0.10)	0.08 (0.11)	[-0.14 ; 0.30]
	Reader 2	52	3.07 (0.18)	2.98 (0.20)	0.09 (0.20)	[-0.31 ; 0.49]
	Reader 3	108	3.28 (0.08)	3.20 (0.08)	0.08 (0.08)	[-0.07 ; 0.23]
	>1 cm and ≤2 cm					
	Reader 1	245	3.52 (0.06)	3.50 (0.06)	0.03 (0.06)	[-0.08 ; 0.14]
	Reader 2	176	2.91 (0.11)	2.84 (0.11)	0.07 (0.09)	[-0.10 ; 0.24]
	Reader 3	224	3.37 (0.06)	3.40 (0.06)	-0.03 (0.05)	[-0.13 ; 0.06]
	>2 cm					
	Reader 1	401	3.69 (0.05)	3.69 (0.05)	0.01 (0.04)	[-0.06 ; 0.08]
	Reader 2	321	2.84 (0.10)	2.82 (0.10)	0.02 (0.05)	[-0.08 ; 0.12]
	Reader 3	324	3.46 (0.05)	3.44 (0.05)	0.01 (0.03)	[-0.05 ; 0.08]

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error. Non-matching and matching lesions are considered.
The models include lesion visualization factor as dependent variable, contrast agent, lesion size, center, period and contrast agent*lesion size interaction as fixed factors, lesion as random factor.

Technical adequacy of images

The technical adequacy of images was graded similarly for Pre-contrast and Paired images, with a large majority of "good" adequacy for Paired images (87% to 93%) for Reader 1 and Reader 2 and 23% "fair" and 71% "good" for Reader 3. The technical adequacy of Paired images with gadobutrol was similar to the technical adequacy of Paired images with gadopiclenol, with more than 87% of the examinations graded good for readers 1 and 2 and more than 70% for reader 3.

Number, size, and location of lesions

The number of identified lesions was similar between Pre-contrast and Paired images with gadopiclenol (Table 71) and between Paired images with gadopiclenol and with gadobutrol (Table 72), with a median number of 1 lesion per patient for reader 2 and 2 lesions for readers 1 and 3. The negative binomial regression model

showed a statistically significant difference between Pre-contrast and Paired images with gadopiclenol for Reader 1 and no difference for the other readers. No differences were observed between Paired images with gadopiclenol and with gadobutrol for all readers.

The median largest diameter of the most representative lesion ranged from 29.6 to 31.3 mm on Pre-contrast images and 28.2 to 32.2 mm on Paired images, depending on the blinded reader. The range of lesion size was 3 to 210 mm. Distribution of lesions according to location was similar between Pre-contrast and Paired images with gadopiclenol and between gadopiclenol and gadobutrol. The most frequent locations were liver and breast, then uterus, prostate, pancreas, retroperitoneum and peritoneum.

Table 71. Number of Lesions - Off-Site Readings - MRI with Gadopiclenol - PAIRED vs PRE – Descriptive Statistics- Extended FAS 1 (N=286)

	Gadopiclenol					
	Reader 1		Reader 2		Reader 3	
	Pre (N=286)	Paired (N=286)	Pre (N=286)	Paired (N=286)	Pre (N=286)	Paired (N=286)
Number of lesion(s) per patient						
n	286	286	286	284	284	285
Mean (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	2.0	2.0	1.0	1.0	2.0	2.0
Min. ; Max.	0 ; 30	0 ; 30	0 ; 99	0 ; 99	0 ; 30	0 ; 30
Images not assessable	0	0	0	2	2	1
In categories						
No lesion	4 (1.4%)	5 (1.7%)	11 (3.8%)	14 (4.9%)	1 (0.4%)	1 (0.4%)
1 lesion	111 (38.8%)	131 (45.8%)	167 (58.4%)	175 (61.6%)	108 (38.0%)	137 (48.1%)
2 lesions	54 (18.9%)	48 (16.8%)	42 (14.7%)	39 (13.7%)	64 (22.5%)	65 (22.8%)
3 lesions	80 (28.0%)	50 (17.5%)	27 (9.4%)	20 (7.0%)	64 (22.5%)	42 (14.7%)
More than 3 lesions	37 (12.9%)	52 (18.2%)	39 (13.6%)	36 (12.7%)	47 (16.5%)	40 (14.0%)
Images not assessable	0	0	0	2	2	1

SD: Standard Deviation; Matching and not matching lesions are considered.

Table 72. Number of Lesions - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol – Descriptive Statistics – Extended FAS 2 – (N=276)

	Reader 1		Reader 2		Reader 3	
	Gadopiclenol (N=276)	Gadobutrol (N=276)	Gadopiclenol (N=276)	Gadobutrol (N=276)	Gadopiclenol (N=276)	Gadobutrol (N=276)
Number of lesion(s) per patient						
n	276	274	274	276	275	275
Mean (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	2.0	2.0	1.0	1.0	2.0	2.0
Min. ; Max.	0 ; 30	0 ; 20	0 ; 99	0 ; 99	0 ; 30	0 ; 35
Not assessable	0	2	2	0	1	1
In categories						
No lesion	5 (1.8%)	4 (1.5%)	13 (4.7%)	11 (4.0%)	1 (0.4%)	1 (0.4%)
1 lesion	124 (44.9%)	128 (46.7%)	169 (61.7%)	164 (59.4%)	132 (48.0%)	135 (49.1%)
2 lesions	47 (17.0%)	43 (15.7%)	39 (14.2%)	48 (17.4%)	62 (22.5%)	63 (22.9%)
3 lesions	49 (17.8%)	53 (19.3%)	19 (6.9%)	19 (6.9%)	41 (14.9%)	39 (14.2%)
More than 3 lesions	51 (18.5%)	46 (16.8%)	34 (12.4%)	34 (12.3%)	39 (14.2%)	37 (13.5%)
Not assessable	0	2	2	0	1	1

SD: Standard Deviation; Matching and not matching lesions are considered.

Diagnostic Confidence

The level of diagnostic confidence markedly improved with Paired images compared to Pre-contrast images, with a level of "excellent" reported in 2.8%, 39.3% and 0.7% with Pre-contrast images and 80.4%, 64.4% and 20.1% with Paired images, for Reader 1, 2 and 3, respectively. A diagnosis of "moderately high suspicion of malignancy" was more frequently reported with Paired images than with Pre-contrast images. The level of diagnosis confidence was similar for Paired images with gadopiclenol and Paired images with gadobutrol (Table 73).

Table 73. Body GDX-44-011- Radiological Diagnosis and Level of Diagnostic Confidence - Off-Site Readings -MRI with Gadopiclenol vs MRI with Gadubutrol – Extended FAS 2 (N=276)

	Reader 1		Reader 2		Reader 3	
	Gadopiclenol (N=271)	Gadobutrol (N=270)	Gadopiclenol (N=261)	Gadobutrol (N=265)	Gadopiclenol (N=274)	Gadobutrol (N=274)
Radiological diagnosis						
n	271	270	261	265	274	274
Negative	0	0	2 (0.8%)	0	0	0
Benign	12 (4.4%)	10 (3.7%)	40 (15.3%)	42 (15.8%)	46 (16.8%)	54 (19.7%)
Probably benign finding	17 (6.3%)	15 (5.6%)	13 (5.0%)	23 (8.7%)	28 (10.2%)	36 (13.1%)
Low suspicion of malignancy	27 (10.0%)	21 (7.8%)	12 (4.6%)	15 (5.7%)	34 (12.4%)	30 (10.9%)
Intermediate suspicion of malignancy	47 (17.3%)	46 (17.0%)	39 (14.9%)	36 (13.6%)	59 (21.5%)	41 (15.0%)
Moderately high suspicion of malignancy	168 (62.0%)	178 (65.9%)	155 (59.4%)	149 (56.2%)	107 (39.1%)	113 (41.2%)
Level of diagnostic confidence						
1 = Nil: very uncertain	0	0	0	1 (0.4%)	0	0
2 = Poor: uncertain	0	0	1 (0.4%)	3 (1.1%)	5 (1.8%)	2 (0.7%)
3 = Moderate: moderately certain	6 (2.2%)	4 (1.5%)	36 (13.8%)	30 (11.3%)	34 (12.4%)	20 (7.3%)
4 = High: good certainty	47 (17.3%)	63 (23.3%)	57 (21.8%)	50 (18.9%)	178 (65.0%)	188 (68.6%)
5 = Excellent: very certain	218 (80.4%)	203 (75.2%)	167 (64.0%)	181 (68.3%)	57 (20.8%)	64 (23.4%)
Mean (SD)	4.8 (0.5)	4.7 (0.5)	4.5 (0.7)	4.5 (0.8)	4.0 (0.6)	4.1 (0.6)
Median	5.0	5.0	5.0	5.0	4.0	4.0
Min. ; Max.	3 ; 5	3 ; 5	2 ; 5	1 ; 5	2 ; 5	2 ; 5

*Only patients with at least one lesion are presented; No missing data. SD: Standard Deviation.

Impact of contrast-enhanced MRI on subject treatment plan

The changes in treatment plan based on MRI results were similar for both contrast agents. The addition of contrast injection could change the treatment plan in 30.1% of the patients for gadopiclenol and 29.3% for gadobutrol (Table 74). Based on paired images, the proposed therapeutic management was more often biopsy, chemotherapy or surgery, while based on unenhanced MRI, the proposed therapeutic management was most often continued monitoring/observation without treatment, follow-up imaging examinations and lumpectomy/mastectomy (other treatment).

Table 74. Patient Treatment Plan Evaluation - On-Site Reading – MRI with Gadopiclenol vs MRI with Gadobutrol – Extended FAS 2 (N=276)

	Gadopiclenol (N=276)	Gadobutrol (N=276)
Could the treatment plan be changed?		
n	276	276
Yes	83 (30.1%)	81 (29.3%)
No	193 (69.9%)	195 (70.7%)
No opinion	0	0
If Yes, therapeutic management proposed:		
based on unenhanced MRI		
n	71	69
Surgery	14 (19.7%)	15 (21.7%)
Biopsy	18 (25.4%)	17 (24.6%)
Chemotherapy	2 (2.8%)	1 (1.4%)
Radiotherapy	1 (1.4%)	1 (1.4%)
Other treatment	41 (57.7%)	40 (58.0%)
Missing data	12	12
based on combined unenhanced and enhanced MRI		
n	83	81
Surgery	32 (38.6%)	31 (38.3%)
Biopsy	40 (48.2%)	37 (45.7%)
Chemotherapy	34 (41.0%)	32 (39.5%)
Radiotherapy	18 (21.7%)	18 (22.2%)
Other treatment	19 (22.9%)	19 (23.5%)

When analyzing the data according to tumour classification based on unenhanced MRI, treatment plan could be changed after MRI with gadopiclenol for 32% of 165 patients with malignant diagnosis and 14% of 64 patients with non-malignant diagnosis (Table 74). Treatment plan changes were reported for 41% of the 22 patients for whom the investigator considered that diagnosis was not assessable based on unenhanced MRI. Similar results were reported with gadobutrol.

Table 75. Patient Treatment Plan Evaluation by tumour classification before contrast agent administration - On-Site Reading - MRI with Gadopiclenol vs MRI with Gadobutrol – Extended FAS 2 (N= 276)

	Malignant		Non-Malignant		Not Assessable	
	Gadopiclenol (N=165)	Gadobutrol (N=168)	Gadopiclenol (N=64)	Gadobutrol (N=65)	Gadopiclenol (N=22)	Gadobutrol (N=21)
Could the treatment plan be changed?						
n	165	168	64	65	22	21
Yes	53 (32.1%)	53 (31.5%)	9 (14.1%)	9 (13.8%)	9 (40.9%)	9 (42.9%)
No	112 (67.9%)	115 (68.5%)	55 (85.9%)	56 (86.2%)	13 (59.1%)	12 (57.1%)
If Yes, therapeutic management proposed: based on unenhanced MRI						
n	41	41	9	9	9	9
Surgery	9 (22.0%)	11 (26.8%)	1 (11.1%)	1 (11.1%)	2 (22.2%)	1 (11.1%)
Biopsy	14 (34.1%)	13 (31.7%)	3 (33.3%)	3 (33.3%)	0	0
Chemotherapy	2 (4.9%)	1 (2.4%)	0	0	0	0
Radiotherapy	1 (2.4%)	1 (2.4%)	0	0	0	0
Other treatment	20 (48.8%)	20 (48.8%)	5 (55.6%)	5 (55.6%)	7 (77.8%)	8 (88.9%)
Missing data	12	12	0	0	0	0
based on combined unenhanced and enhanced MRI						
n	53	53	9	9	9	9
Surgery	24 (45.3%)	23 (43.4%)	2 (22.2%)	2 (22.2%)	1 (11.1%)	2 (22.2%)
Biopsy	29 (54.7%)	27 (50.9%)	4 (44.4%)	4 (44.4%)	2 (22.2%)	1 (11.1%)
Chemotherapy	27 (50.9%)	25 (47.2%)	1 (11.1%)	1 (11.1%)	2 (22.2%)	2 (22.2%)
Radiotherapy	15 (28.3%)	15 (28.3%)	0	0	0	0
Other treatment	7 (13.2%)	7 (13.2%)	4 (44.4%)	4 (44.4%)	4 (44.4%)	4 (44.4%)

Quantitative Parameters (percentage of lesion enhancement, lesion to background ratio)

The percentage of lesion enhancement was higher with gadopiclenol for two readers (p=0.0003 and p<0.0001). There were no significant differences between the two contrast agents for LBR (Table 76).

Table 76. Body GDX-44-011 - Percentage of enhancement and Lesion to Background Ratio - Off-Site Readings - MRI with Gadopiclenol vs MRI with Gadobutrol - Mixed Model – FAS 2 (N= 273)

	n	LS Mean (SE)			95% CI difference	p-value
		Gadopiclenol	Gadobutrol	Difference (SE)		
Percentage of enhancement*						
Reader 1	249	145.26 (6.95)	116.52 (6.95)	28.73 (7.85)	[13.27 ; 44.20]	0.0003
Reader 2	227	147.78 (6.78)	121.06 (6.78)	26.72 (4.90)	[17.05 ; 36.39]	<0.0001
Reader 3	249	219.95 (40.63)	211.49 (40.63)	8.46 (10.98)	[-13.16 ; 30.08]	0.4415
Lesion to Background Ratio**						
Reader 1	249	2.83 (0.13)	2.74 (0.13)	0.09 (0.12)	[-0.15 ; 0.32]	0.4633
Reader 2	227	3.51 (0.24)	3.72 (0.24)	-0.22 (0.19)	[-0.58 ; 0.15]	0.2418
Reader 3	249	4.36 (0.22)	4.41 (0.22)	-0.04 (0.17)	[-0.38 ; 0.29]	0.7976

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error; Only matching lesions are considered.

*The models include Percentage of enhancement as dependent variable, contrast agent and period as fixed factors, patient as random factor.

** The models include Lesion to Background Ratio as dependent variable, contrast agent, period and the unenhanced value (Pre) as fixed factors, patient as random factor.

Overall Diagnostic Preference

The three blinded readers expressed in the majority no preference between images with gadopiclenol and images with gadobutrol (74.6% to 82.6% of the images, depending on the reader). When readers reported a preference, it was more often for gadopiclenol (12% to 14.5% of the cases) than for gadobutrol (5.4% to 10.9% of the cases) (Table 77). The main reason for preference for gadopiclenol or gadobutrol was superior contrast enhancement, followed by better lesion visualisation (delineation and internal structure of the lesions) and greater diagnostic confidence.

Table 77. Body GDX-44-011- Overall Diagnostic Preference - Off-Site Readings - MRI with Gadopiclenol 0.05 mmol/kg vs MRI with Gadobutrol 0.1 mmol/kg

Dose of gadopiclenol	Reader	N	gadopiclenol preferred	No preference	gadobutrol preferred	p-value (a)
0.5 mmol/kg	4	276	36 (13.0%)	216 (78.3%)	24 (8.7%)	0.1223
	5	276	40 (14.5%)	206 (74.6%)	30 (10.9%)	0.2346
	6	276	33 (12.0%)	228 (82.6%)	15 (5.4%)	0.0079

(a) Wilcoxon signed-rank test. *multiple choices
Source: CSR GDX-44-011 in Module 5.3.5.1 Body

- **Ancillary analyses**

Expert concordance assessment

An additional image evaluation has been conducted to assess concordance in lesion detectability obtained with 0.05 mmol/kg gadopiclenol and 0.1 mmol/kg of comparator gadobutrol in MRI.

Methodology

This assessment was performed by a total of nine experienced radiologists ("Blinded Readers"), 3 reading MR images of Head and Neck (together with MR images of CNS from study GDX-44-010), 3 reading MR images of the thorax including breast and 3 reading MR images of abdomen, pelvis and musculoskeletal system, who were fully blinded to all patient clinical information and to the contrast agent used in each MR exam, and independently and separately reviewed all the investigational MRI images in a fully randomised order to assess the number of lesions and locate them in each MR exam from original study GDX-44-011 obtained with 0.05 mmol/kg gadopiclenol and 0.1 mmol/kg gadobutrol. Screen shots were obtained documenting the lesions that were marked and numbered on the images by each reader.

The following assessments were performed by each reader independently for each MRI exam based on the randomised order for presentation of exams:

- Technical adequacy (are the images interpretable?): Yes/No

If the whole MR exam was judged as technically inadequate, then the evaluation was stopped for that MR exam.

If the whole MR exam was judged as technically adequate, then the following was assessed:

- Lesions detected: yes/no? If yes, the table with lesion number/location was completed.
- For each detected lesion, the individual lesion location was defined based on the codes provided

Each detected lesion was marked together with its corresponding lesion number on the images and screenshots were obtained.

Three additional independent experienced radiologists (Concordance Readers), one for the Head and Neck MR images (together with MR images of CNS from study GDX-44-010), one for thorax including breast MR images and one for the MR images of abdomen, pelvis and musculoskeletal system, tracked all lesions detected on Exam 1 (Visit 2) and Exam 2 (Visit 4) across the evaluations of the blinded readers by assigning one unique reference number for each matched lesion. All patients were presented to the Concordance Readers even if the patient had no lesions identified by one or two Blinded Readers.

In case of discordant lesions, i.e., lesions seen on one exam but not in the other, respective Panels (Concordance Reader and each individual Blinded Reader) assessed the nature of the lesion (radiology diagnosis based on image interpretation in routine practice) and potential clinical impact of this non-concordance in detection of lesions. The patient profiles consisting of all the available clinical information (e.g., medical history and results of previous imaging studies) were provided to the Panels.

All the selected blinded and concordance readers had an extensive and significant experience in the assessment and interpretation of MRI examinations of other body regions. None of the readers was involved in the initial evaluation of the MR images from study GDX-44-011, or in the images analysis provided in March 2023 to EMA.

All the individual patient studies for which both paired images (unenhanced and contrast enhanced MRI) for gadopiclenol and gadobutrol MRIs were available and without major protocol deviations (Per Protocol Set of the original studies for the primary evaluation) were included in this assessment.

Additionally, 10% of the patient studies (both Exam 1 and Exam 2) were randomised and included twice in the read queue in a blinded manner. The first read of these patients was the basis of concordance/discordance analysis, while second read was the basis of intra-reader variability assessment.

Results

A total of 260 patients were included in this new blinded read to assess lesion detection rate with 0.05 mmol/kg gadopiclenol vs 0.1 mmol/kg gadobutrol:

- 17 patients for Head & Neck imaging (reading performed by readers 1, 2 and 3)
- 73 patients for Thorax imaging (reading performed by readers 4, 5 and 6)

170 patients for other body regions (reading performed by readers 7, 8 and 9): 95 for abdomen imaging, 58 for pelvis imaging and 17 for musculoskeletal system. Following concordance lesion tracking and at the time of clinical impact evaluation, images from the first MRI and images from the second MRI were not considered comparable by the panel for at least one blinded reader for 10 patients. Therefore, concordance in lesion detection was analysed for the following numbers of patients with comparable images:

Head & Neck	Reader 1: 17	Reader 2: 17	Reader 3:17
Thorax	Reader 4: 71	Reader 5: 73	Reader 6: 73
Other body regions	Reader 7: 165	Reader 8: 166	Reader 9: 165
• abdomen	94	94	94
• pelvis	56	56	56
• MSK	15	16	15

Lesion level

Among the lesions detected with gadobutrol, the overall percentage of lesions also detected with gadopiclenol (common lesions), ranged from (depending on the reader):

- 89.5% to 100% for head & neck imaging,
- 88.3%% to 93.2% for thorax imaging,
- 91.7% to 100% for pelvis imaging,
- 94.6% to 95.2% for abdomen imaging,
- 100% for musculoskeletal system imaging (for all 3 readers).

In the head & neck MR images (Table 79), no more than 8 lesions per patient were detected with gadobutrol. Whatever the total number of lesions detected with gadobutrol, 86% to 100% of these lesions were also detected with gadopiclenol in each case.

In the thorax MR images (Table 80), the majority of patients (62% to 69% depending on the reader) had no more than 3 lesions detected with gadobutrol, but readers detected more than 10 lesions (up to 24) in 2 to 4 patients. Even for these patients, the rate of lesions also detected with gadopiclenol was high, ranging from 81.8% to 100% for 11 to 18 lesions detected with gadobutrol by patient and 75% for the case with 24 lesions detected by one reader.

In the pelvis MR images (Table 81), 100% of the lesions detected with gadobutrol were also detected with gadopiclenol in patients with 1 to 4 lesions. In patients with 5 to 17 lesions detected with gadobutrol, the percentage of lesions also detected with gadopiclenol remains high: 90% to 100% except for 2 patients (with 9 and 11 lesions detected) for Reader 7 and patients with 6, 7, 8 and 10 lesions detected with gadobutrol for Reader 8. For Reader 9, a score of 100% was reported in all cases.

In the abdomen MR images (Table 82), more than 90% of the patients had no more than 10 lesions detected with gadobutrol, 1 to 5 lesions for most of them. The percentage of lesions also detected with gadopiclenol was high whatever the number of lesions per patient (up to 34): over 80% for all cases except one (76.5% for a patient with 17 lesions), and mainly between 90% and 100% (overall rate of 95% for all readers).

In the musculoskeletal system MR images (Table 83), whatever the number of lesions detected per patient (1 to 14), 100% of these lesions were also detected with gadopiclenol.

Table 78. Summary by body region of concordance in lesions detected with each GBCA

	N lesions detected with gadobutrol	Lesions seen with both contrast agents (matching lesions)	Lesions seen only with gadobutrol	Lesions seen only with gadopiclenol
GDX-44-011 (Body)				
Head & Neck				
Reader 1	19	**17 (89.5%)**	2	3
Reader 2	34	**32 (94.1%)**	2	6
Reader 3	22	**22 (100%)**	0	1
Thorax				
Reader 4	251	**234 (93.2%)**	17	20
Reader 5	234	**217 (92.7%)**	17	30
Reader 6	257	**227 (88.3%)**	30	26
Pelvis				
Reader 7	156	**143 (91.7%)**	13	10
Reader 8	141	**130 (92.2%)**	11	8
Reader 9	124	**124 (100%)**	0	4
Abdomen				
Reader 7	373	**355 (95.2%)**	18	18
Reader 8	352	**333 (94.6%)**	19	33
Reader 9	308	**292 (94.8%)**	16	23
Musculoskeletal				
Reader 7	19	**19 (100%)**	0	0
Reader 8	39	**39 (100%)**	0	0
Reader 9	32	**32 (100%)**	0	0

Table 79. GDX-44-011 -Head and Neck - Number of identical lesions ("common lesions") detected per patient using gadobutrol as standard of care, as per blinded unpaired assessments followed by concordance lesion tracking

Number of lesions detected per patient on gadobutrol MRI	Reader 1			Reader 2			Reader 3		
	N patients	No. of Lesions Detected		N patients	No. of Lesions Detected		N patients	No. of Lesions Detected	
		on gadobutrol MRIs	on both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)
01	15	15	13 (86.7%)	13	13	12 (92.3%)	14	14	14 (100%)
02	2	4	4 (100%)	1	2	2 (100%)	1	2	2 (100%)
03		.			.		2	6	6 (100%)
04		.		1	4	4 (100%)		.	
07		.		1	7	6 (85.7%)		.	
08		.		1	8	8 (100%)		.	

Number of lesions detected per patient on gadobutrol MRI	Reader 1			Reader 2			Reader 3		
	N patients	No. of Lesions Detected		N patients	No. of Lesions Detected		N patients	No. of Lesions Detected	
		on gadobutrol MRIs	on both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)
Total	***17***	***19***	***17 (89.5%)***	***17***	***34***	***32 (94.1%)***	***17***	***22***	***22 (100%)***

Patients with images assessable / interpretable / comparable for both scans **and at least one lesion detected with gadobutrol**

%: (number of common lesions detected on both MRIs / number of lesions detected on gadobutrol MR images) * 100.

Table 80. GDX-44-011 -Thorax - Number of identical lesions ("common lesions") detected per patient using gadobutrol as standard of care, as per blinded unpaired assessments followed by concordance lesion tracking

Number of lesions detected per patient on gadobutrol MRI	Reader 4			Reader 5			Reader 6		
	N patients	No. of Lesions Detected		N patients	No. of Lesions Detected		N patients	No. of Lesions Detected	
		on gadobutrol MRIs	on both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)
01	22	22	21 (95.5%)	26	26	26 (100%)	21	21	21 (100%)
02	9	18	17 (94.4%)	12	24	22 (91.7%)	13	26	23 (88.5%)
03	11	33	31 (93.9%)	12	36	35 (97.2%)	14	42	37 (88.1%)
04	7	28	26 (92.9%)	6	24	23 (95.8%)	5	20	19 (95%)
05	5	25	21 (84%)	4	20	19 (95%)	6	30	27 (90%)
06	4	24	22 (91.7%)	3	18	15 (83.3%)	4	24	23 (95.8%)
07	4	28	26 (92.9%)	3	21	19 (90.5%)	2	14	9 (64.3%)
08		.		3	24	21 (87.5%)		.	
09	1	9	9 (100%)	1	9	6 (66.7%)	2	18	16 (88.9%)
10	1	10	10 (100%)		.			.	
11	1	11	10 (90.9%)		.		1	11	9 (81.8%)
12	1	12	10 (83.3%)		.			.	
13		.			.		1	13	12 (92.3%)
14		.		1	14	13 (92.9%)	1	14	13 (92.9%)
15	1	15	15 (100%)		.			.	
16	1	16	16 (100%)		.			.	
18		.		1	18	18 (100%)		.	
24		.			.		1	24	18 (75%)
Total	***68***	***251***	***234 (93.2%)***	***72***	***234***	***217 (92.7%)***	***71***	***257***	***227 (88.3%)***

Patients with images assessable / interpretable / comparable for both scans **and at least one lesion detected with gadobutrol**

%: (number of common lesions detected on both MRIs / number of lesions detected on gadobutrol MR images) * 100.

Table 81. GDX-44-011 -Pelvis - Number of identical lesions ("common lesions") detected per patient using gadobutrol as standard of care, as per blinded unpaired assessments followed by concordance lesion tracking

Number of lesions detected per patient on gadobutrol MRI	Reader 7			Reader 8			Reader 9		
	N patients	No. of Lesions Detected		N patients	No. of Lesions Detected		N patients	No. of Lesions Detected	
		on gadobutrol MRIs	on both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)
01	20	20	20 (100%)	29	29	29 (100%)	18	18	18 (100%)
02	11	22	22 (100%)	11	22	22 (100%)	10	20	20 (100%)
03	6	18	18 (100%)	4	12	12 (100%)	5	15	15 (100%)
04		.		1	4	4 (100%)	1	4	4 (100%)
05	3	15	14 (93.3%)	1	5	5 (100%)	3	15	15 (100%)
06	1	6	6 (100%)	2	12	9 (75%)	1	6	6 (100%)
07	2	14	13 (92.9%)	1	7	6 (85.7%)	3	21	21 (100%)
08	1	8	8 (100%)	1	8	6 (75%)	1	8	8 (100%)
09	1	9	6 (66.7%)		.			.	
10	2	20	18 (90%)	3	30	25 (83.3%)		.	
11	1	11	6 (54.5%)		.			.	
12		.		1	12	12 (100%)		.	
13	1	13	12 (92.3%)		.			.	
17		.			.		1	17	17 (100%)
Total	***49***	***156***	***143 (91.7%)***	***54***	***141***	***130 (92.2%)***	***43***	***124***	***124 (100%)***

Patients with images assessable / interpretable / comparable for both scans **and at least one lesion detected with gadobutrol**

%: (number of common lesions detected on both MRIs / number of lesions detected on gadobutrol MR images) * 100.

Table 82. GDX-44-011 -Abdomen - Number of identical lesions ("common lesions") detected per patient using gadobutrol as standard of care, as per blinded unpaired assessments followed by concordance lesion tracking

Number of lesions detected per patient on gadobutrol MRI	Reader 7			Reader 8			Reader 9		
	N patients	No. of Lesions Detected		N patients	No. of Lesions Detected		N patients	No. of Lesions Detected	
		on gadobutrol MRIs	on both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)
01	38	38	38 (100%)	39	39	39 (100%)	36	36	36 (100%)
02	10	20	20 (100%)	14	28	26 (92.9%)	23	46	45 (97.8%)
03	12	36	35 (97.2%)	10	30	30 (100%)	6	18	18 (100%)
04	6	24	21 (87.5%)	5	20	19 (95%)	7	28	27 (96.4%)
05	4	20	19 (95%)	9	45	41 (91.1%)	4	20	19 (95%)
06	2	12	12 (100%)	1	6	6 (100%)	1	6	6 (100%)
07	2	14	12 (85.7%)	2	14	14 (100%)	2	14	14 (100%)
08	3	24	24 (100%)	1	8	8 (100%)	1	8	8 (100%)
09	3	27	27 (100%)	1	9	8 (88.9%)	1	9	8 (88.9%)
10	1	10	9 (90%)	2	20	19 (95%)		.	
11		.			.		3	33	30 (90.9%)

Number of lesions detected per patient on gadobutrol MRI	Reader 7			Reader 8			Reader 9		
	N patients	No. of Lesions Detected		N patients	No. of Lesions Detected		N patients	No. of Lesions Detected	
		on gadobutrol MRIs	on both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)
12		.		1	12	12 (100%)	2	24	23 (95.8%)
13	1	13	13 (100%)	1	13	13 (100%)		.	
14	1	14	14 (100%)	1	14	14 (100%)	1	14	12 (85.7%)
15	2	30	28 (93.3%)	1	15	15 (100%)		.	
17	1	17	13 (76.5%)	1	17	15 (88.2%)		.	
20	1	20	18 (90%)		.			.	
25		.			.		1	25	24 (96%)
26	1	26	25 (96.2%)		.			.	
27		.			.		1	27	22 (81.5%)
28	1	28	27 (96.4%)	1	28	25 (89.3%)		.	
34		.		1	34	29 (85.3%)		.	
Total	***89***	***373***	***355 (95.2%)***	***91***	***352***	***333 (94.6%)***	***89***	***308***	***292 (94.8%)***

Patients with images assessable / interpretable / comparable for both scans **and at least one lesion detected with gadobutrol**

%: (number of common lesions detected on both MRIs / number of lesions detected on gadobutrol MR images) * 100.

Table 83. GDX-44-011 -Musculoskeletal - Number of identical lesions ("common lesions") detected per patient using gadobutrol as standard of care, as per blinded unpaired assessments followed by concordance lesion tracking

Number of lesions detected per patient on gadobutrol MRI	Reader 7			Reader 8			Reader9		
	N patients	No. of Lesions Detected		N patients	No. of Lesions Detected		N patients	No. of Lesions Detected	
		on gadobutrol MRIs	on both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)		On gadobutrol MRIs	On both MRIs (common lesions)
01	9	9	9 (100%)	9	9	9 (100%)	7	7	7 (100%)
02	2	4	4 (100%)	3	6	6 (100%)	1	2	2 (100%)
03	2	6	6 (100%)	2	6	6 (100%)	3	9	9 (100%)
04		.		1	4	4 (100%)		.	
14		.		1	14	14 (100%)	1	14	14 (100%)
Total	***13***	***19***	***19 (100%)***	***16***	***39***	***39 (100%)***	***12***	***32***	***32 (100%)***

Patients with images assessable / interpretable / comparable for both scans **and at least one lesion detected with gadobutrol**

%: (number of common lesions detected on both MRIs / number of lesions detected on gadobutrol MR images) * 100.

Patient level

Depending on the reader, a perfect agreement (all lesions detected with both gadobutrol and gadopiclenol or no lesion seen with both GBCAs) was reported for:

- 70.6% to 94.1% of the patients in the Head & Neck group,
- 69.8% to 73.2% of the patients in the Thorax group,
- 87.5% to 94.6% of the patients in the Pelvis group,
- 84.0% to 87.2% of the patients in the Abdomen group
- 100% of the patients in the Musculoskeletal Group.

Table 85 presents the number (%) of patients with only lesions detected with both GBCAs (perfect matches), those with common lesions and additional lesions seen with only one GBCA (gadobutrol or gadopiclenol) and those who had only lesions detected with one or the other GBCA but none in common, for each body region.

Table 84. Summary by body region, of the number of patients with perfect and imperfect agreement between contrast agents in the set of lesions observed

		N patients	# patients in which more lesions detected by gadobutrol	# patients in which more lesions detected by gadopiclenol	# patients in which each GBCA detected the same number and set of lesions	# patients in which each GBCA detected the same number but a different set of lesions
Head & Neck (GDX-44-011)	**Reader 1**	17	0	1 (5.9%)	14 (82.4%)	2 (11.8%)
	Reader 2	17	1 (5.9%)	3 (17.6%)	12 (70.6%)	1 (5.9%)
	Reader 3	17	0	1 (5.9%)	16 (94.1%)	0
Thorax (GDX-44-011)	**Reader 4**	71	2 (2.8%)	5 (7.0%)	52 (73.2%)	12 (16.9%)
	Reader 5	73	4 (5.5%)	12 (16.4%)	53 (72.6%)	4 (5.5%)
	Reader 6	73	9 (12.3%)	8 (11.0%)	51 (69.8%)	5 (6.8%)
Pelvis (GDX-44-011)	**Reader 7**	56	4 (7.1%)	1 (1.8%)	49 (87.5%)	2 (3.6%)
	Reader 8	56	3 (5.4%)	2 (3.6%)	49 (87.5%)	2 (3.6%)
	Reader 9	56	-	3 (5.4%)	53 (94.6%)	0
Abdomen (GDX-44-011)	**Reader 7**	94	6 (6.4%)	3 (3.2%)	82 (87.2%)	3 (3.2%)
	Reader 8	94	4 (4.3%)	7 (7.4%)	80 (85.1%)	3 (3.2%)
	Reader 9	94	5 (5.3%)	8 (8.5%)	79 (84.0%)	2 (2.1%)
Musculoskeletal (GDX-44-011)	**Reader 7**	15	0	0	15 (100%)	0
	Reader 8	16	0	0	16 (100%)	0
	Reader 9	15	0	0	15 (100%)	0

Table 85. GDX-44-011 (Body) - Lesion detection at patient level, blinded unpaired assessment followed by concordance lesion tracking

	Head & Neck			Reader 1 (N=17*)	Reader 2 (N=17*)	Reader 3 ((N=17*)
	Patients with lesions detected on:					
	Both MRIs (common lesions)	Gadobutrol MRI only	Gadopiclenol MRI only			
Perfect matches (no lesions or only common lesions)	No lesion detected			**0 (0%)**	**0 (0%)**	**0 (0%)**
	Yes	None	None	**14 (82.4%)**	**12 (70.6%)**	**16 (94.1%)**
Common lesions + additional lesions seen with only one GBCA	Yes	Yes	None	-	1 (5.9%)	-
	Yes	None	Yes	1 (5.9%)	3 (17.6%)	1 (5.9%)
	Yes	Yes	Yes	-	-	-
No common lesions	None	Yes	None	-	-	-
	None	None	Yes	-	-	-
	None	Yes	Yes	2 (11.8%)	1 (5.9%)	-
	Thorax			**Reader 4 (N=71*)**	**Reader 5 (N=73*)**	**Reader 6 ((N=73*)**
	Patients with lesions detected on:					
	Both MRIs (common lesions)	Gadobutrol MRI only	Gadopiclenol MRI only			
Perfect matches (no lesions or only common lesions)	No lesion detected			**3 (4.2%)**	**1 (1.4%)**	**2 (2.7%)**
	Yes	None	None	**49 (69%)**	**52 (71.2%)**	**49 (67.1%)**
Common lesions + additional lesions seen with only one GBCA	Yes	Yes	None	2 (2.8%)	4 (5.5%)	7 (9.6%)
	Yes	None	Yes	4 (5.6%)	10 (13.7%)	3 (4.1%)
	Yes	Yes	Yes	12 (16.9%)	6 (8.2%)	12 (16.4%)
No common lesions	None	Yes	None	-	-	-
	None	None	Yes	-	-	-
	None	Yes	Yes	1 (1.4%)	-	-
	Pelvis			**Reader 7 (N=56*)**	**Reader 8 (N=56*)**	**Reader 9 (N=56*)**
	Patients with lesions detected on:					
	Both MRIs (common lesions)	Gadobutrol MRI only	Gadopiclenol MRI only			
Perfect matches (no lesions or only common lesions)	No lesion detected			**7 (12.5%)**	**2 (3.6%)**	**13 (23.2%)**
	Yes	None	None	**42 (75%)**	**47 (83.9%)**	**40 (71.4%)**
Common lesions + additional lesions seen with only one GBCA	Yes	Yes	None	2 (3.6%)	1 (1.8%)	-
	Yes	None	Yes	1 (1.8%)	1 (1.8%)	3 (5.4%)
	Yes	Yes	Yes	4 (7.1%)	5 (8.9%)	-
No common lesions	None	Yes	None	-	-	-
	None	None	Yes	-	-	-
	None	Yes	Yes	-	-	-

	Abdomen			Reader 7 (N=94*)	Reader 8 (N=94*)	Reader 9 ((N=94*)
	Patients with lesions detected on:					
	Both MRIs (common lesions)	Gadobutrol MRI only	Gadopiclenol MRI only			
Perfect matches (no lesions or only common lesions)	No lesion detected			**5 (5.3%)**	**3 (3.2%)**	**4 (4.3%)**
	Yes	None	None	**77 (81.9%)**	**77 (81.9%)**	**75 (79.8%)**
Common lesions + additional lesions seen with only one GBCA	Yes	Yes	None	2 (2.1%)	2 (2.1%)	4 (4.3%)
	Yes	None	Yes	2 (2.1%)	5 (5.3%)	4 (4.3%)
	Yes	Yes	Yes	8 (8.5%)	7 (7.4%)	6 (6.4%)
No common lesions	None	Yes	None	-	-	-
	None	None	Yes	-	-	1 (1.1%)
	None	Yes	Yes			
	Musculoskeletal system			**Reader 7 (N=15*)**	**Reader 8 (N=16*)**	**Reader 9 (N=15*)**
	Patients with lesions detected on:					
	Both MRIs (common lesions)	Gadobutrol MRI only	Gadopiclenol MRI only			
Perfect matches (no lesions or only common lesions)	No lesion detected			**2 (13.3%)**	**0 (0%)**	**3 (20%)**
	Yes	None	None	**13 (86.7%)**	**16 (100%)**	**12 (80%)**
Common lesions + additional lesions seen with only one GBCA	Yes	Yes	None	-	-	-
	Yes	None	Yes	-	-	-
	Yes	Yes	Yes	-	-	-
No common lesions	None	Yes	None	-	-	-
	None	None	Yes	-	-	-
	None	Yes	Yes	-	-	-

Discordant lesions

In head & neck imaging (Table 86), 0 to 2 lesions were only detected with gadobutrol while 1 to 6 lesions were only detected with gadopiclenol, depending on the reader. Among the lesions only seen with gadobutrol, one was assessed as a primary malignant lesion and all others were assessed as "not a true lesion". The cause of discordance was attributed to the reader in all cases. The lesions only seen with gadopiclenol were also assessed as "not a true lesion", (1/3 and 5/6 for Reader 1 and Reader 2, respectively) or primary malignant lesions. The cause of discordance was attributed to the reader except for 2 lesions in the same patient (indicated as: not discordant lesions / overlooked by concordance reader due to the confluent nature of the lesions).

In thorax imaging (Table 87), there was a similar number of lesions only detected with gadobutrol (17 to 30) and only detected with gadopiclenol (20 to 30, depending on the reader). These lesions were mainly assessed as non-malignant by Reader 4 (9/17 and 11/20 for lesions only seen with gadobutrol and gadopiclenol, respectively) and Reader 6 (25/30 and 22/26, respectively) and malignant by Reader 5 (7/17 and 9/30, respectively), rarely not a true lesion (0 to 1 case per reader with gadobutrol or gadopiclenol). The nature of the lesion was indicated as "unknown" for 4 to 9 lesions for gadobutrol and 2 to 15 lesions for gadopiclenol. The cause of discordance was attributed to the reader for all lesions only seen with gadobutrol and most lesions only seen with gadopiclenol. Other reasons were mentioned for 6 lesions: "technical discrepancies with poor comparability for this small lesion" for 3 lesions in the same patient, "technical discrepancies for motion artifact with poor comparability for this small lesion" for one lesion and "not discordant lesions /

overlooked by concordance reader due to the multiple lesions (or due to the confluent nature of the lesions) for 2 lesions.

In pelvis imaging (Table 88), again the numbers of lesions only seen by one GBCA were similar for gadobutrol (0 to 13 lesions) and gadopiclenol (4 to 10 lesions). These lesions were non-malignant for all lesions only seen with gadobutrol and the majority of lesions only seen with gadopiclenol (9/10, 8/8 and 2/4 for Reader 7, 8 and 9, respectively). The reason for discordance was attributed to the reader or another reason reported as a technical issue (motion, partial volume, volume averaging), similarly for gadobutrol and gadopiclenol.

In abdomen imaging (Table 89), 16 to 19 lesions were only seen with gadobutrol, and 23 to 33 lesions were only seen with gadopiclenol. The nature of the lesion was variable as shown in Table 89: not a true lesion, non-malignant or secondary malignant lesion in most cases. The cause of discordance was attributed to the reader in the majority of cases (12/18, 13/19, 15/16 for gadobutrol and 12/18, 26/33 and 14/23 for gadopiclenol), but also to other technical reasons (partial volume, motion artefact, motion and contrast timing, volume averaging).

No discordant lesions were detected for MSK imaging (100% concordance for all readers).

The contrast agent was identified as the potential cause of discordance by 2 readers for a total of 7 lesions, all in MR images with gadopiclenol from the same patient. These readers reported better contrast enhancement allowing more lesions to be detected at V2 (with gadopiclenol). For this patient, multiple discordant lesions were reported for the 3 readers, and the other reasons for discordance were the reader or technical reason (partial volume). None of these discordances were assessed to have a potential clinical impact, because they were identified in a clinical situation (>10 hepatic metastases) when the number of lesions has no longer potential impact on patient management decision since the patient undergoes systemic chemotherapy.

Table 86. GDX-44-011 - Head & Neck - Assessment of discordance in lesion detection following concordance lesion tracking

Reader	**Reader 1**	**Reader 2**	**Reader 3**
N Total lesions	**22**	**40**	**23**
N lesions detected with gadobutrol	**19**	**34**	**22**
Lesion detected on gadobutrol MR images but not detected on gadopiclenol MR images	2 (10.5%)	2 (5.9%)	0 (0%)
Not a true lesion	1 (5.3%)	2 (5.9%)	-
Malignant	1 (5.3%)	-	-
Primary	1 (5.3%)	-	-
Discordance potentially due to:			
Reader	2 (10.5%)	2 (5.9%)	-
N lesions detected with gadopiclenol	**20**	**38**	**23**
Lesion detected on gadopiclenol MR images but not detected on gadobutrol MR images	3 (15%)	6 (15.8%)	1 (4.3%)
Not a true lesion	1 (5%)	5 (13.2%)	-
Malignant	2 (10%)	1 (2.6%)	1 (4.3%)
Primary	2 (10%)	1 (2.6%)	1 (4.3%)
Discordance potentially due to:			
Reader	3 (15%)	4 (10.5%)	1 (4.3%)
Other reasons	-	2 (5.3%)	-

Patients with images assessable / interpretable / comparable for both scans
%: (n row / Total number of lesions detected either on gadobutrol MR images or on gadopiclenol MR images as appropriate) * 100.

Table 87. GDX-44-011 Thorax - Assessment of discordance in lesion detection following concordance lesion tracking

Reader	**Reader 4**	**Reader 5**	**Reader 6**
N Total lesions	**271**	**264**	**283**
N lesions detected with gadobutrol	**251**	**234**	**257**
Lesion detected on gadobutrol MR images but not detected on gadopiclenol MR images	17 (6.8%)	17 (7.3%)	30 (11.7%)
Unknown	4 (1.6%)	9 (3.8%)	4 (1.6%)
Not a true lesion	1 (0.4%)	-	-
Non-malignant	9 (3.6%)	1 (0.4%)	25 (9.7%)
Malignant	3 (1.2%)	7 (3%)	1 (0.4%)
Primary	2 (0.8%)	4 (1.7%)	1 (0.4%)
Secondary	1 (0.4%)	3 (1.3%)	-
Discordance potentially due to:			
Reader	17 (6.8%)	17 (7.3%)	30 (11.7%)
N lesions detected with gadopiclenol	**254**	**247**	**253**
Lesion detected on gadopiclenol MR images but not detected on gadobutrol MR images	20 (7.9%)	30 (12.1%)	26 (10.3%)
Unknown	3 (1.2%)	15 (6.1%)	2 (0.8%)
Not a true lesion	1 (0.4%)	1 (0.4%)	-
Non-malignant	11 (4.3%)	5 (2%)	22 (8.7%)
Malignant	5 (2%)	9 (3.6%)	2 (0.8%)
Primary	5 (2%)	6 (2.4%)	2 (0.8%)
Secondary	-	3 (1.2%)	-
Discordance potentially due to:			
Reader	19 (7.5%)	25 (10.1%)	26 (10.3%)
Other reasons	1 (0.4%)	5 (2%)	

Patients with images assessable / interpretable / comparable for both scans
%: (n row / Total number of lesions detected either on gadobutrol MR images or on gadopiclenol MR images as appropriate) * 100.

Table 88. GDX-44-011 Pelvis - Assessment of discordance in lesion detection following concordance lesion tracking

Reader	**Reader 7**	**Reader 8**	**Reader 9**
N Total lesions	**166**	**149**	**128**
N lesions detected with gadobutrol	**156**	**141**	**124**
Lesion detected on gadobutrol MR images but not detected on gadopiclenol MR images	13 (8.3%)	11 (7.8%)	0 (0%)
Non-malignant	13 (8.3%)	11 (7.8%)	-
Discordance potentially due to:			
Reader	5 (3.2%)	4 (2.8%)	-
Other reasons	8 (5.1%)	7 (5%)	-
N lesions detected with gadopiclenol	**153**	**138**	**128**
Lesion detected on gadopiclenol MR images but not detected on gadobutrol MR images	10 (6.5%)	8 (5.8%)	4 (3.1%)
Non-malignant	9 (5.9%)	8 (5.8%)	2 (1.6%)
Malignant	1 (0.7%)	-	2 (1.6%)
Secondary	1 (0.7%)	-	2 (1.6%)
Discordance potentially due to:			
Reader	6 (3.9%)	2 (1.4%)	1 (0.8%)
Other reasons	4 (2.6%)	6 (4.3%)	3 (2.3%)

Patients with images assessable / interpretable / comparable for both scans
%: (n row / Total number of lesions detected either on gadobutrol MR images or on gadopiclenol MR images as appropriate) * 100.

Table 89. GDX-44-011 Abdomen - Assessment of discordance in lesion detection following concordance lesion tracking

Reader	**Reader 7**	**Reader 8**	**Reader 9**
N Total lesions	**391**	**385**	**331**
N lesions detected with gadobutrol	**373**	**352**	**308**
Lesion detected on gadobutrol MR images but not detected on gadopiclenol MR images	18 (4.8%)	19 (5.4%)	16 (5.2%)
Unknown	5 (1.3%)	-	1 (0.3%)
Not a true lesion	-	7 (2%)	8 (2.6%)
Non-malignant	-	5 (1.4%)	1 (0.3%)
Malignant	13 (3.5%)	7 (2%)	6 (1.9%)
Primary	-	-	1 (0.3%)
Secondary	13 (3.5%)	7 (2%)	5 (1.6%)
Discordance potentially due to:			
Reader	12 (3.2%)	13 (3.7%)	15 (4.9%)
Other reasons	6 (1.6%)	6 (1.7%)	1 (0.3%)
N lesions detected with gadopiclenol	**373**	**366**	**315**
Lesion detected on gadopiclenol MR images but not detected on gadobutrol MR images	18 (4.8%)	33 (9%)	23 (7.3%)
Unknown	4 (1.1%)	-	2 (0.6%)
Not a true lesion	1 (0.3%)	12 (3.3%)	5 (1.6%)
Non-malignant	2 (0.5%)	4 (1.1%)	1 (0.3%)
Malignant	11 (2.9%)	17 (4.6%)	15 (4.8%)
Primary	-	1 (0.3%)	-
Secondary	11 (2.9%)	16 (4.4%)	15 (4.8%)
Discordance potentially due to:			
Reader	12 (3.2%)	26 (7.1%)	14 (4.4%)
Contrast agent	-	4 (1.1%)	3 (1%)
Other reasons	6 (1.6%)	3 (0.8%)	6 (1.9%)

Patients with images assessable / interpretable / comparable for both scans
%: (n row / Total number of lesions detected either on gadobutrol MR images or on gadopiclenol MR images as appropriate) * 100.

Clinical impact

In most cases (75/84 patients), the discordances had no impact on the patient management. The rationale for considering that the lesions detected with only one GBCA had no impact were mostly "potentially not a true lesion" in head & neck imaging, "potentially malignant lesion in a clinical situation when numbers do not matter any longer" or "potentially non-malignant lesion to be left untouched" in thorax imaging, and "potentially non-malignant lesion to be left untouched" in pelvis imaging.

Overall, lesions detected with only gadobutrol and not gadopiclenol or vice versa had a potential impact on patient management according to at least one reader for 9 patients: due to lesions only seen with gadobutrol for 1 patient, lesions only seen with gadopiclenol for 6 patients, and both cases (lesions only detected with gadobutrol and lesions only detected with gadopiclenol in the same patient) for 2 patients (Table 90). The rationale for clinical impact was mainly "possible target for therapy"; other reasons mentioned different surgical approach or additional treatment planning. For 7 patients, the discordance was attributed to the reader. In two cases, the lesion was not detected because of only partial volume seen. In no case the contrast agent was mentioned as reason for discordance.

Table 90. GDX-44-011 (Body) - Patients with discordant lesions that could have a potential impact on patient management

Body region	Patient	Reader Body region	Discordant Lesion/s Detected with	Rationale for clinical impact	Discordance potentially due to
Head & Neck	1	Reader 3	gadopiclenol	Target of therapy	Reader
	2	Reader 1	gadopiclenol and gadobutrol (clinical impact for both)	possible target for therapy	Reader Reader
		Reader 2	gadopiclenol and gadobutrol (clinical impact for both)	LES003 in v2 no true lesion, LES004 in V4 the true lesion	Reader Reader
	3	Reader 1	gadopiclenol and gadobutrol (clinical impact for both)	possible target for therapy	Reader
	4	Reader 1	gadopiclenol	possible target for therapy	Reader
Thorax	5	Reader 6	gadopiclenol	Potentially more extensive surgery	Reader
	6	Reader 6	gadobutrol	LES002 may be either cancer or abscess, anyway clinically evident. the impact would be significant after biopsy confirmation	Reader
Abdomen	7	Reader 8	gadopiclenol	At V2, two malignant lesions were detected (versus 1 malignant lesion at V4). Additional lesion seen at V2 would require additional treatment planning.	Other =Partial volume
	8	Reader 8	gadopiclenol	3 malignant lesions detected at V2 versus 2 malignant lesions detected at V4. In case of surgical treatment, additional lesion could require different surgical approach.	Reader
	9	Reader 9	gadopiclenol	Lesion detected in V2 requires additional treatment planning	Other =Partial volume

Intra-reader and inter-reader variability

The intra-reader agreement was assessed on 10% of the images. There was a very good level of intra-reader agreement: 100% with all images for all 3 readers for head & neck (assessed on 2 patients), 92.9% to 98% with gadopiclenol and 90.4% to 93.9% with gadobutrol for thorax images, and 85.7% to 96.7% with gadopiclenol and 88.5% to 91.5% with gadobutrol for images from other body regions.

The inter-reader agreement was assessed on all images following the concordance lesion tracking. At least 2 out of 3 readers agree for 60.8% of the images with gadopiclenol and 51% of the images with gadobutrol for head & neck (Readers 1, 2 and 3), 60.8% and 62.8%, respectively, for thorax (Readers 4, 5 and 6) and 75.9% and 77.7%, respectively, for the other body regions (Readers 7, 8 and 9).

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 91. Summary of efficacy for GDX-44-010, Phase III pivotal study in CNS MRI

Title: Efficacy and Safety of gadoPIClenol for CenTral NervoUs System (CNS) Magnetic REsonance Imaging (MRI) (PICTURE trial)			
Study identifier	GDX-44-010 (PICTURE) EudraCT No.: 2018-003988-54 ClinicalTrials.gov Identifier: NCT03996447		
Design	prospective, multicentre, randomised, double-blind, controlled and cross-over study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		4 to 23 days per patient not applicable not applicable
Hypothesis	• Superiority of gadopiclenol-enhanced MRI at 0.05 mmol/kg body weight (BW) compared to unenhanced MRI for patient referred for contrast-enhanced MRI of CNS, in terms of 3 lesion visualisation co-primary criteria using the patient as his/her own control. • Non-inferiority of gadopiclenol at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg in terms of 3 lesion visualisation co-primary criteria for patient referred for contrast-enhanced MRI of CNS.		
Treatments groups	Pre-contrast images before gadopiclenol injection		Images from unenhanced MRI before gadopiclenol injection Number randomised: 251 (126 in the arm gadopiclenol at first MRI and gadobutrol at second MRI and 125 in the arm gadobutrol at first MRI and gadopiclenol at second MRI)
	Paired images with gadopiclenol		Images from MRI performed with gadopiclenol (Paired images= images pre- and post-contrast injection) Number randomised: 251 (126 in the arm gadopiclenol at first MRI and gadobutrol at second MRI and 125 in the arm gadobutrol at first MRI and gadopiclenol at second MRI)
	Paired images with gadobutrol		Images from MRI performed with gadobutrol(Paired images = images pre- and post-contrast injection) Number randomised: 251 (126 in the arm gadopiclenol at first MRI and gadobutrol at second MRI and 125 in the arm gadobutrol at first MRI and gadopiclenol at second MRI)
Endpoints and definitions	Co-Primary endpoints	Border delineation Internal morphology Degree of contrast enhancement	Lesion visualisation (based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement), assessed by 3 independent off-site blinded readers using a 4-point scale, from 1 (none, poor) to 4 (excellent). The mean of scores for each of the 3 lesion visualisation co-criteria was 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). The mean of scores for each visualisation endpoint could range from 1 to 4. For each reader, only matching lesions were considered.

Title: Efficacy and Safety of gadoPIClenol for CenTral NervoUs System (CNS) Magnetic REsonance Imaging (MRI) (PICTURE trial)

	Secondary endpoint	CNR LBR %E	Quantitative assessments based on signal intensity (SI): Quantitative criteria were calculated by patient and by independent blinded reader and the result was provided by examination for each reader by averaging the parameter for maximum 3 most representative lesions. Only lesions that matched on both MRIs after lesion tracking were considered. **Contrast to Noise Ratio (CNR):** $CNR = \frac{SI_{lesion} - SI_{ht}}{SD_{noise}}$ SI_{lesion} = SI of lesion. SI_{ht} = SI of healthy tissue (brain or spinal cord). SD_{noise} = Standard Deviation of background noise. **Percentage of Lesion Enhancement (%E):** $E\% = \frac{SI_{post} - SI_{pre}}{SI_{pre}} x100$ SI_{post} = SI of lesion on post injection images. SI_{pre} = SI of lesion on pre injection images. **Lesion to Background Ratio (LBR)**: $LBR = \frac{SI_{lesion}}{SI_{ht}}$ SI_{lesion} = SI of lesion. SI_{ht}= SI of background (healthy tissue in brain or spinal cord).
	Secondary endpoint	Overall preference	Evaluated in a global matched-pairs fashion: for each randomised patient, Paired images from the first MR examination, labeled as examination 1, were displayed simultaneously with the corresponding Paired images from the second MR examination, labeled as examination 2. The assessment was performed by 3 additional independent readers as: 2 examination 1 is preferred to examination 2 3 no preference is observed 4 examination 2 is preferred to examination 1
	Secondary endpoint	Impact on patient treatment	At the end of visit 2 (first MRI) and at the end of visit 4 (second MRI), after having completed all the sequences of images required by the protocol (Paired images), the investigator had to document if the subject treatment plan could have been changed based on the images obtained (yes/no) and if yes, he/she had to specify the therapeutic management proposed based on radiological assessment (based on unenhanced MRI and based on combined unenhanced and enhanced MRI): Surgery, biopsy, chemotherapy, radiotherapy, other treatment (specify).
Database lock	17 November 2020		

Results and Analysis

Analysis description	**Primary Analysis 1 – Superiority of Paired images (Pre- and Post-contrast) with gadopiclenol versus Pre-contrast images for lesion visualisation**						
Analysis population and time point description	Full Analysis Set (FAS) 1: all patients who have both Pre and Paired images with gadopiclenol assessable for at least one matching lesion for at least one off-site reader (N=239) time point: NA						
Descriptive statistics and estimate variability	Treatment group	Paired images with gadopiclenol			Pre-contrast images before gadopiclenol		
	Reader	1	2	3	1	2	3
	Number of subjects	227	229	202	227	229	202
	Border delineation						

Title: Efficacy and Safety of gadoPIClenol for CenTral NervoUs System (CNS) Magnetic REsonance Imaging (MRI) (PICTURE trial)								
	Mean of scores		3.90	3.64	3.97	2.08	1.74	2.61
	Standard deviation		0.29	0.61	0.17	0.43	0.61	0.53
	Internal morphology							
	Mean of scores		3.92	3.65	3.97	1.66	1.88	2.01
	Standard deviation		0.29	0.59	0.17	0.47	0.31	0.73
	Degree of contrast enhancement							
	Mean of scores		3.77	3.58	3.90	1.00	1.00	1.00
	Standard deviation		0.62	0.72	0.37	0.00	0.00	0.00
Effect estimate per comparison	Border delineation	Comparison groups	Paired images with gadopiclenol versus pre-contrast images					
		Reader	1			2		3
		Difference between groups (least square mean)	1.82			1.90		1.36
		95%Confidence interval	[1.76 ; 1.88]			[1.81 ; 2.00]		[1.29 ; 1.44]
		P-value (two-sided paired t-tests)	<0.0001			<0.0001		<0.0001
	Internal morphology	Comparison groups	Paired images with gadopiclenol versus pre-contrast images					
		Difference between groups (least square mean)	2.26			1.77		1.96
		95%Confidence interval	[2.20 ; 2.33]			[1.69 ; 1.85]		[1.85 ; 2.06]
		P-value (two-sided paired t-tests)	<0.0001			<0.0001		<0.0001
	Degree of contrast enhancement	Comparison groups	Paired images with gadopiclenol versus pre-contrast images					
		Difference between groups (least square mean)	2.77			2.58		2.90
		95%Confidence interval	[2.69 ; 2.85]			[2.49 ; 2.67]		[2.84 ; 2.95]
		P-value (two-sided paired t-tests)	<0.0001			<0.0001		<0.0001
Analysis description	**Primary Analysis 2 - Non-inferiority of paired images with gadopiclenol at 0.05 mmol/kg compared to paired images with gadobutrol at 0.1 mmol/kg for lesion visualisation**							
Analysis population and time point description	Per-Protocol Set (PPS) 2: all patients who have both gadopiclenol and gadobutrol Paired images assessable for at least one matching lesion for at least one off-site reader and no major protocol deviations (N=236) time point: NA							
Descriptive statistics and estimate variability	Treatment group		Paired images with gadopiclenol			Paired images with gadobutrol		
	Reader		1	2	3	1	2	3
	Number of subjects		227	231	220	227	231	220
	Border delineation							
	Mean of scores		3.91	3.64	3.97	3.93	3.60	3.95
	Standard deviation		0.28	0.60	0.15	0.25	0.63	0.21
	Internal morphology							
	Mean of scores		3.93	3.64	3.97	3.93	3.62	3.92
	Standard deviation		0.28	0.58	0.16	0.25	0.56	0.28
	Degree of contrast enhancement							
	Mean of scores		3.78	3.57	3.89	3.77	3.52	3.81

Title: Efficacy and Safety of gadoPIClenol for CenTral NervoUs System (CNS) Magnetic REsonance Imaging (MRI) (PICTURE trial)								
	Standard deviation		0.62	0.70	0.38	0.58	0.67	0.59
Effect estimate per comparison	Border delineation	Comparison groups			Paired images with gadopiclenol versus Paired images with gadobutrol			
		Reader			1	2	3	
		Difference between groups (least square mean)			-0.02	0.03	0.02	
		95%Confidence interval			[-0.06; 0.02]	[-0.04; 0.11]	[-0.01; 0.05]	
		P-value (two-sided paired t-tests)			<0.0001	<0.0001	<0.0001	
	Internal morphology	Comparison groups			Paired images with gadopiclenol versus Paired images with gadobutrol			
		Difference between groups (least square mean)			-0.01	0.02	0.05	
		95%Confidence interval			[-0.04; 0.03]	[-0.05; 0.09]	[0.01; 0.08]	
		P-value (two-sided paired t-tests)			<0.0001	<0.0001	<0.0001	
	Degree of contrast enhancement	Comparison groups			Paired images with gadopiclenol versus Paired images with gadobutrol			
		Difference between groups (least square mean)			0.01	0.05	0.09	
		95%Confidence interval			[-0.04 ;0.07]	[-0.03 ;0.12]	[0.03 ;0.15]	
		P-value (two-sided paired t-tests)			<0.0001	<0.0001	<0.0001	
Notes	In order to statistically demonstrate the superiority of the "Paired" MRI over the Pre-contrast MRI, a statistically significant (one-sided p-value ⩽0.025) positive difference in mean scores in border delineation, internal morphology and degree of contrast enhancement of lesions had to be demonstrated for at least 2 out of 3 readers. Non-inferiority between gadopiclenol and gadobutrol could be concluded if the lower bound of the 95% CI was above the non-inferiority margin (-0.35) for at least 2 out of 3 readers and for the 3 co-primary criteria. Both primary objectives had to be achieved.							
Analysis description	**Secondary analysis - Quantitative parameters: Contrast to Noise Ratio (CNR), Percentage of Lesion Enhancement (%E) and Lesion to Background Ratio (LBR)**							
Analysis population and time point description	FAS2: all patients who have both gadopiclenol and gadobutrol Paired images assessable for at least one matching lesion for at least one off-site reader (N=239) Time point: NA							
Descriptive statistics and estimate variability	Treatment group	Paired images with gadopiclenol			Paired images with gadobutrol			
	Reader	1	2	3	1	2	3	
	Number of subjects	230 (%E) 228 (CNR and LBR)	233	223	230	233	223	
	CNR							
	Mean	178.28	115.39	60.58	153.11	96.04	46.96	
	Standard deviation	186.16	99.73	48.39	207.94	121.71	37.63	
	% E							
	Mean	195.1	221.7	196.5	158.5	184.6	153.7	
	Standard deviation	135.8	156.7	145.6	101.3	126.1	106.8	
	LBR							
	Mean	2.03	2.18	2.03	1.83	1.97	1.79	
	Standard deviation	0.70	0.75	0.69	0.54	0.59	0.52	

Title: Efficacy and Safety of gadoPIClenol for CenTral NervoUs System (CNS) Magnetic REsonance Imaging (MRI) (PICTURE trial)

Effect estimate per comparison	CNR	Comparison groups	Paired images with gadopiclenol versus Paired images with gadobutrol		
		Reader	1	2	3
		Difference between groups (least square mean)	25.26	18.33	13.46
		95%Confidence interval	[-0.21; 50.72]	[3.14; 33.52]	[8.70; 18.22]
		P-value (two-sided paired t-tests)	0.0519	0.0182	<0.0001
	%E	Comparison groups	Paired images with gadopiclenol versus Paired images with gadobutrol		
		Difference between groups (least square mean)	36.41	36.80	42.85
		95%Confidence interval	[27.63; 45.18]	[23.58; 50.01]	[32.57; 53.14]
		P-value (two-sided paired t-tests)	<0.0001	<0.0001	<0.0001
	LBR	Comparison groups	Paired images with gadopiclenol versus Paired images with gadobutrol		
		Difference between groups (least square mean)	0.20	0.21	0.24
		95%Confidence interval	[0.16 ; 0.24]	[0.16 ; 0.26]	[0.19 ; 0.28]
		P-value (two-sided paired t-tests)	<0.0001	<0.0001	<0.0001

Analysis description	**Secondary analysis - Overall Diagnostic Preference**			
Analysis population and time point description	Extended FAS2: all patients who have both gadopiclenol and gadobutrol Paired images assessable (N=241) Time point: NA			
Descriptive statistics and estimate variability		Reader 4	Reader 5	Reader 6
	n	241	241	241
	Gadopiclenol is preferred to gadobutrol	108 (44.8%)	131 (54.4%)	138 (57.3%)
	No preference is observed	98 (40.7%)	52 (21.6%)	56 (23.2%)
	Gadobutrol is preferred to gadopiclenol	35 (14.5%)	58 (24.1%)	47 (19.5%)
	p-value (Wilcoxon signed-rank test)	<0.001	<0.001	<0.001

Analysis description	**Secondary analysis - Impact of contrast-enhanced MRI on subject treatment plan**		
Analysis population and time point description	Extended FAS2: all patients who have both gadopiclenol and gadobutrol Paired images assessable (N=241) Time point: NA		
Descriptive statistics	Treatment group	Paired images with gadopiclenol	Paired images with gadobutrol
	Number of subjects	240	241
	n (%) treatment plan changed	56 (23.3%)	57 (23.7%)

Table 92. Summary of efficacy for GDX-44-011, Phase III pivotal study in MRI in body regions

Title: Efficacy and safety of gadopiclenol foR bOdy MagnetIc reSonancE imaging (MRI) (PROMISE trial)			
Study identifier	GDX-44-011 (PROMISE) EudraCT No.: 2018-003946-18 ClinicalTrials.gov Identifier: NCT03986138		
Design	prospective, multicentre, randomised, double-blind, controlled and cross-over study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		4 to 23 days per patient not applicable not applicable
Hypothesis	• Superiority of gadopiclenol-enhanced MRI at 0.05 mmol/kg body weight (BW) compared to unenhanced MRI for patient referred for contrast-enhanced MRI of body regions, in terms of 3 lesion visualisation co-primary criteria using the patient as his/her own control. • Non-inferiority of gadopiclenol at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg in terms of 3 lesion visualisation co-primary criteria for patient referred for contrast-enhanced MRI of body regions.		
Treatments groups	Pre-contrast images before gadopiclenol injection		Images from unenhanced MRI before gadopiclenol injection Number randomised: 300 (151 in the arm gadopiclenol at first MRI and gadobutrol at second MRI and 149 in the arm gadobutrol at first MRI and gadopiclenol at second MRI)
	Paired images with gadopiclenol		Images from MRI performed with gadopiclenol (Paired images= images pre- and post-contrast injection) Number randomised: 300 (151 in the arm gadopiclenol at first MRI and gadobutrol at second MRI and 149 in the arm gadobutrol at first MRI and gadopiclenol at second MRI)
	Paired images with gadobutrol		Images from MRI performed with gadobutrol(Paired images = images pre- and post-contrast injection) Number randomised: 300 (151 in the arm gadopiclenol at first MRI and gadobutrol at second MRI and 149 in the arm gadobutrol at first MRI and gadopiclenol at second MRI)
Endpoints and definitions	Co-Primary endpoints	Border delineation Internal morphology Degree of contrast enhancement	Lesion visualisation (based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement), assessed by 3 independent off-site blinded readers using a 4-point scale, from 1 (none, poor) to 4 (excellent). The mean of scores for each of the 3 lesion visualisation co-criteria was 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). The mean of scores for each visualisation endpoint could range from 1 to 4. For each reader, only matching lesions were considered.

	Secondary endpoint	LBR %E	Quantitative assessments based on signal intensity (SI): Quantitative criteria were calculated by patient and by independent blinded reader and the result was provided by examination for each reader by averaging the parameter for maximum 3 most representative lesions. Only lesions that matched on both MRIs after lesion tracking were considered. **Percentage of Lesion Enhancement (%E):** $E\% = \frac{SI_{post} - SI_{pre}}{SI_{pre}} x100$ SI_{post} = SI of lesion on post injection images. SI_{pre} = SI of lesion on pre injection images. **Lesion to Background Ratio (LBR)**: $LBR = \frac{SI_{lesion}}{SI_b}$ SI_{lesion} = SI of lesion. SI_b= SI of background (surrounding healthy tissue of the lesion).
	Secondary endpoint	Overall preference	Evaluated in a global matched-pairs fashion: for each randomised patient, Paired images from the first MR examination, labeled as examination 1, were displayed simultaneously with the corresponding Paired images from the second MR examination, labeled as examination 2. The assessment was performed by 3 additional independent readers as: 5 examination 1 is preferred to examination 2 6 no preference is observed 7 examination 2 is preferred to examination 1
	Secondary endpoint	Impact on patient treatment	At the end of visit 2 (first MRI) and at the end of visit 4 (second MRI), after having completed all the sequences of images required by the protocol (Paired images), the investigator had to document if the subject treatment plan could have been changed based on the images obtained (yes/no) and if yes, he/she had to specify the therapeutic management proposed based on radiological assessment (based on unenhanced MRI and based on combined unenhanced and enhanced MRI): Surgery, biopsy, chemotherapy, radiotherapy, other treatment (specify).
Database lock	26 January 2021		
Results and Analysis			
Analysis description	**Primary Analysis 1 – Superiority of Paired images (Pre- and Post-contrast) with gadopiclenol versus Pre-contrast images for lesion visualisation**		
Analysis population and time point description	Full Analysis Set (FAS) 1: all patients who have both Pre and Paired images with gadopiclenol assessable for at least one matching lesion for at least one off-site reader (N=278) Time point: NA		

Descriptive statistics and estimate variability	Treatment group	Paired images with gadopiclenol			Pre-contrast images before gadopiclenol		
	Reader	1	2	3	1	2	3
	Number of subjects	251	230	262	251	230	262
	Border delineation						
	Mean of scores	3.79	3.48	3.49	2.26	3.01	1.78
	Standard deviation	0.42	0.77	0.57	0.44	0.96	0.51
	Internal morphology						
	Mean of scores	3.80	3.75	3.72	1.99	3.22	1.69
	Standard deviation	0.42	0.54	0.48	0.17	0.84	0.52

	Degree of contrast enhancement							
	Mean of scores		3.64	2.82	3.33	1.00	1.00	1.00
	Standard deviation		0.65	1.07	0.59	0.00	0.00	0.00
Effect estimate per comparison	Border delineation	Comparison groups			Paired images with gadopiclenol versus pre-contrast images			
		Reader			1	2	3	
		Difference between groups (least square mean)			1.53	0.47	1.71	
		95%Confidence interval			[1.46 ; 1.60]	[0.36 ; 0.58]	[1.65 ; 1.78]	
		P-value (two-sided paired t-tests)			<0.0001	<0.0001	<0.0001	
	Internal morphology	Comparison groups			Paired images with gadopiclenol versus pre-contrast images			
		Difference between groups (least square mean)			1.81	0.53	2.03	
		95%Confidence interval			[1.76 ; 1.87]	[0.42 ; 0.64]	[1.95 ; 2.11]	
		P-value (two-sided paired t-tests)			<0.0001	<0.0001	<0.0001	
	Degree of contrast enhancement	Comparison groups			Paired images with gadopiclenol versus pre-contrast images			
		Difference between groups (least square mean)			2.64	1.82	2.33	
		95%Confidence interval			[2.56 ; 2.72]	[1.68 ; 1.96]	[2.26 ; 2.41]	
		P-value (two-sided paired t-tests)			<0.0001	<0.0001	<0.0001	
Analysis description	**Primary Analysis 2 - Non-inferiority of paired images with gadopiclenol at 0.05 mmol/kg compared to paired images with gadobutrol at 0.1 mmol/kg for lesion visualisation**							
Analysis population and time point description	Per-Protocol Set (PPS) 2: all patients who have both gadopiclenol and gadobutrol Paired images assessable for at least one matching lesion for at least one off-site reader and no major protocol deviations (N=260) Time point: NA							
Descriptive statistics and estimate variability	Treatment group		Paired images with gadopiclenol			Paired images with gadobutrol		
	Reader		1	2	3	1	2	3
	Number of subjects		240	223	243	240	223	243
	Border delineation							
	Mean of scores		3.82	3.56	3.53	3.81	3.53	3.57
	Standard deviation		0.38	0.69	0.53	0.39	0.74	0.49
	Internal morphology							
	Mean of scores		3.83	3.75	3.74	3.83	3.75	3.77
	Standard deviation		0.37	0.53	0.45	0.38	0.54	0.40
	Degree of contrast enhancement							
	Mean of scores		3.69	2.88	3.35	3.68	2.86	3.37
	Standard deviation		0.58	1.07	0.58	0.58	1.04	0.60

Effect estimate per comparison	Border delineation	Comparison groups	Paired images with gadopiclenol versus Paired images with gadobutrol		
		Reader	1	2	3
		Difference between groups (least square mean)	0.00	0.02	-0.04
		95%Confidence interval	[-0.05; 0.05]	[-0.05; 0.10]	[-0.10; 0.01]
		P-value (two-sided paired t-tests)	<0.0001	<0.0001	<0.0001
	Internal morphology	Comparison groups	Paired images with gadopiclenol versus Paired images with gadobutrol		
		Difference between groups (least square mean)	-0.00	-0.00	-0.03
		95%Confidence interval	[-0.06; 0.05]	[-0.07; 0.07]	[-0.08; 0.02]
		P-value (two-sided paired t-tests)	<0.0001	<0.0001	<0.0001
	Degree of contrast enhancement	Comparison groups	Paired images with gadopiclenol versus Paired images with gadobutrol		
		Difference between groups (least square mean)	0.01	0.03	-0.02
		95%Confidence interval	[-0.06; 0.09]	[-0.07; 0.12]	[-0.08; 0.04]
		P-value (two-sided paired t-tests)	<0.0001	<0.0001	<0.0001
Notes	In order to statistically demonstrate the superiority of the "Paired" MRI over the Pre-contrast MRI, a statistically significant (one-sided p-value $\leqslant$0.025) positive difference in mean scores in border delineation, internal morphology and degree of contrast enhancement of lesions had to be demonstrated for at least 2 out of 3 readers. Non-inferiority between gadopiclenol and gadobutrol could be concluded if the lower bound of the 95% CI was above the non-inferiority margin (-0.35) for at least 2 out of 3 readers and for the 3 co-primary criteria. Both primary objectives had to be achieved.					
Analysis description	**Secondary analysis - Quantitative parameters: Percentage of Lesion Enhancement (%E) and Lesion to Background Ratio (LBR)**				
Analysis population and time point description	FAS2: all patients who have both gadopiclenol and gadobutrol Paired images assessable for at least one matching lesion for at least one off-site reader (N=273) Time point: NA				

Descriptive statistics and estimate variability	Treatment group	Paired images with gadopiclenol			Paired images with gadobutrol		
	Reader	1	2	3	1	2	3
	Number of subjects	249	227	249	249	227	249
	% E						
	Mean	145.1	147.8	219.9	116.7	121.1	211.5
	Standard deviation	127.1	113.2	568.6	88.9	89.7	706.3
	LBR						
	Mean	2.82	3.45	4.29	2.74	3.77	4.44
	Standard deviation	3.76	4.85	5.50	3.31	5.63	6.00

Effect estimate per comparison	%E	Comparison groups	Paired images with gadopiclenol versus Paired images with gadobutrol		
		Reader	1	2	3
		Difference between groups (least square mean)	28.73	26.72	8.46
		95%Confidence interval	[13.27; 44.20]	[17.05 ; 36.39]	[-13.16 ; 30.08]
		P-value (two-sided paired t-tests)	0.0003	<0.0001	0.4415
	LBR	Comparison groups	Paired images with gadopiclenol versus Paired images with gadobutrol		
		Difference between groups (least square mean)	0.09	-0.22	-0.04
		95%Confidence interval	[-0.15 ; 0.32]	[-0.58 ; 0.15]	[-0.38 ; 0.29]
		P-value (two-sided paired t-tests)	0.4633	0.2418	0.7976
Analysis description	**Secondary analysis - Overall Diagnostic Preference**				
Analysis population and time point description	Extended FAS2: all patients who have both gadopiclenol and gadobutrol Paired images assessable (N=276) Time point: NA				
Descriptive statistics and estimate variability			Reader 4	Reader 5	Reader 6
	n		276	276	276
	Gadopiclenol is preferred to gadobutrol		36 (13.0%)	40 (14.5%)	33 (12.0%)
	No preference is observed		216 (78.3%)	206 (74.6%)	228 (82.6%)
	Gadobutrol is preferred to gadopiclenol		24 (8.7%)	30 (10.9%)	15 (5.4%)
	p-value (Wilcoxon signed-rank test)		0.1223	0.2346	0.0079
Analysis description	**Secondary analysis - Impact of contrast-enhanced MRI on subject treatment plan**				
Analysis population and time point description	Extended FAS2: all patients who have both gadopiclenol and gadobutrol Paired images assessable (N=276) Time point: NA				
Descriptive statistics	Treatment group		Paired images with gadopiclenol	Paired images with gadobutrol	
	Number of subjects		276	276	
	n (%) treatment plan changed		83 (30.1%)	81 (29.3%)	

2.6.5.3. Clinical studies in special populations

Paediatric population (GDX-44-007)

GDX-44-007- Pharmacokinetics, safety and efficacy of a new gadolinium-based contrast agent, gadopiclenol, in paediatric patients from 2 to 17 years of age undergoing contrast-enhanced MRI

Study GDX-44-007 is an open-label, uncontrolled multicentre, international study to evaluate the pharmacokinetics, safety and efficacy of gadopiclenol-enhanced MRI (0.05 mmol/kg) in CNS and body in paediatric patients from 2 to 17 years of age.

Methods

Main inclusion criterion was female or male paediatric patient aged 2 to 17 years with a known or suspected lesion(s) scheduled to undergo routine contrast-enhanced MRI of CNS or of other organs (head and neck, thorax, abdomen, pelvis or musculoskeletal system [including extremities]).

Four visits were scheduled for each patient: screening visit (up to 14 days before inclusion), inclusion visit during which the patients underwent unenhanced and gadopiclenol-enhanced MRI and started confinement (for 1 day but could be reduced to 8 hours under certain conditions) and two follow-up visits, 1 week and 3 months after inclusion. Reading of images was performed on-site.

Two cohorts of patients were included in this study:

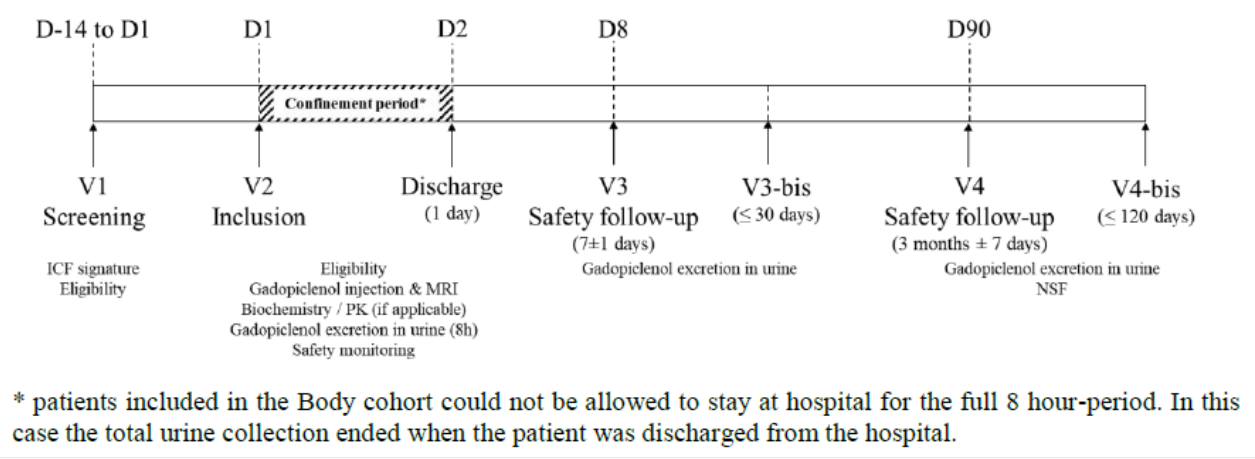
- CNS cohort: In this cohort paediatric patients undergo CNS contrast-enhanced MRI.
- Body cohort: In this cohort, paediatric patients undergoing contrast-enhanced MRI of other body organs (head and neck, thorax, abdomen, pelvis or musculoskeletal system)

An age-down staggered approach was used.

The efficacy of gadopiclenol-enhanced MRI for CNS and other body regions was assessed as a secondary objective. The following efficacy endpoints were assessed: technical adequacy for diagnosis, assessment of contrast quality (percentage of lesion enhancement, lesion to background ratio), lesion visualisation variables (border delineation, internal morphology, and degree of contrast enhancement) and change in diagnostic confidence. Efficacy assessment were performed for both CNS and Body cohorts by on site radiologist. In this paediatric study, the same definitions as those in the pivotal studies are used (see Table 16).

Figure 11 below represents the study schema.

Figure 11. Schematic of study design



* patients included in the Body cohort could not be allowed to stay at hospital for the full 8 hour-period. In this case the total urine collection ended when the patient was discharged from the hospital.

Results

Population characteristics

Eighty patients were included the study and all patients completed the study. The CNS cohort included 60 patients, distributed in three age groups (20 patients per group): 2-6 years, 7-11 years and 12-17 years. The Body cohort included 20 patients (6 aged 2-6 years, 3 aged 7-11 years and 11 aged 12-17 years).

The main diagnosis made after the CNS MRI examination was most frequently congenital malformation (26.5%) followed by primary tumour (14.7%), inflammatory disease (11.8%) and vascular or neurodegenerative disease (8.8% each). Other various diagnosis included mainly cysts and neurofibromatosis. Among the 20 patients of the Body cohort, vascular diseases and inflammatory diseases were diagnosed in 3 patients each (27.3%) and congenital malformation in one patient (9.1%). Other diagnosis included cysts and cryptorchism.

Efficacy

Technical adequacy

Table 93. Images Adequacy and Number of Lesions Detected – by Cohort and Overall– FAS

	CNS Cohort (N=60)		Body Cohort (N=20)		Total (N=80)	
	Pre	Pre+Post	Pre	Pre+Post	Pre	Pre+Post
Technical adequacy for diagnosis						
Nondiagnostic	0	0	0	0	0	0
Poor	0	0	1 (5.0%)	0	1 (1.3%)	0
Fair	3 (5.0%)	1 (1.7%)	3 (15.0%)	2 (10.0%)	6 (7.5%)	3 (3.8%)
Good	57 (95.0%)	59 (98.3%)	16 (80.0%)	18 (90.0%)	73 (91.3%)	77 (96.3%)
Images assessable						
Yes	60 (100%)	60 (100%)	20 (100%)	20 (100%)	80 (100%)	80 (100%)
Total number of detected lesions per patient						
Mean (SD)	2.1 (4.6)	2.2 (4.6)	0.6 (0.6)	0.6 (0.6)	1.7 (4.1)	1.8 (4.1)
Median	1.0	1.0	1.0	1.0	1.0	1.0
Min. ; Max.	0 ; 25	0 ; 25	0 ; 2	0 ; 2	0 ; 25	0 ; 25
No lesion	**28 (46.7%)**	**26 (43.3%)**	9 (45.0%)	9 (45.0%)	37 (46.3%)	35 (43.8%)
1 lesion	**15 (25.0%)**	**17 (28.3%)**	10 (50.0%)	10 (50.0%)	25 (31.3%)	27 (33.8%)
2 lesions	5 (8.3%)	5 (8.3%)	1 (5.0%)	1 (5.0%)	6 (7.5%)	6 (7.5%)
3 lesions	5 (8.3%)	5 (8.3%)	0	0	5 (6.3%)	5 (6.3%)
More than 3 lesions	7 (11.7%)	7 (11.7%)	0	0	7 (8.8%)	7 (8.8%)

Number of lesions- Overall, lesions were identified in 32 patients (53.3%) with Pre-contrast images and 34 patients (56.7%) with Paired images. For two patients (one in the 12-17 and one in the 7-11 years group), lesions were visible on post-contrast images only (Table 94). When considering up to 3 most representative lesions, in the CNS cohort, a total of 63 lesions were detected with Paired images: 26 in 14 patients aged 12-17 years, 31 in 16 patients aged 7-11 years and 6 in 4 patients aged 2-6 years. In patients aged 12-17 years, lesions were mainly located in lobar regions of the brain (mainly frontal temporal), in patients aged 7-11 years in other brain locations such as the basal ganglia and in patients aged 2-6 years in lateral ventricle. The two lesions only detected on Paired images were located in the pineal region and the pituitary area. There was no obvious difference in mean or median value of signal intensity of the lesions (up to 3 most representative lesions) between pre and pre+post images in the CNS cohort for the age groups 12-17 and 7-11 years; the increase in median signal intensity of the lesions was more pronounced in the 2-6 years group (6 lesions).

Table 94. Images Adequacy and Number of Lesions Detected – CNS Cohort by Age group - FAS

	12-17 years (N=20)		7-11 years (N=20)		2-6 years (N=20)	
	Pre	**Pre+Post**	**Pre**	**Pre+Post**	**Pre**	**Pre+Post**
Technical adequacy for diagnosis						
Nondiagnostic	0	0	0	0	0	0
Poor	0	0	0	0	0	0
Fair	1 (5.0%)	0	2 (10.0%)	1 (5.0%)	0	0
Good	19 (95.0%)	20 (100%)	18 (90.0%)	19 (95.0%)	20 (100%)	20 (100%)
Images assessable						
Yes	20 (100%)	20 (100%)	20 (100%)	20 (100%)	20 (100%)	20 (100%)
Total number of detected lesions per patient						
Mean (SD)	3.8 (7.1)	3.8 (7.1)	2.3 (3.1)	2.4 (3.0)	0.3 (0.7)	0.3 (0.7)
Median	1.0	1.0	1.0	1.0	0.0	0.0
Min. ; Max.	0 ; 25	0 ; 25	0 ; 13	0 ; 13	0 ; 2	0 ; 2
No lesion	**7 (35.0%)**	**6 (30.0%)**	**5 (25.0%)**	**4 (20.0%)**	16 (80.0%)	16 (80.0%)
1 lesion	**7 (35.0%)**	**8 (40.0%)**	**6 (30.0%)**	**7 (35.0%)**	2 (10.0%)	2 (10.0%)
2 lesions	0	0	3 (15.0%)	3 (15.0%)	2 (10.0%)	2 (10.0%)
3 lesions	2 (10.0%)	2 (10.0%)	3 (15.0%)	3 (15.0%)	0	0
More than 3 lesions	4 (20.0%)	4 (20.0%)	3 (15.0%)	3 (15.0%)	0	0

No missing data; Pre: Unenhanced MRI; Pre+Post: Unenhanced + Contrast-Enhanced MRI

In the Body cohort 0 to 2 lesions were detected per patient (median 1). Overall, 12 lesions were detected in 11 patients (55.0%) both with Pre-contrast images and Paired images (Table 93). The lesions were located in the head (2 lesions), within abdomen and pelvis (5 lesions), in the right lower limb (1 lesion) or at other locations such as testicles or perianal region (4 lesions). The median signal intensity of the detected lesions was 550 with Paired images compared to 318 with Pre images.

Contrast quality- The percentage of enhancement and LBR in patients of the CNS cohort and Body cohort are presented in Table 95. According to the applicant, the low mean level of percentage of enhancement in the CNS cohort can be explained with high number of lesions with no contrast enhancement due to the nature of the lesions, such as congenital malformations and neurodegenerative diseases.

Table 95. Assessment of Contrast Quality – Full Analysis Set

	CNS Cohort			CNS Cohort (N=60)	Body Cohort (N=20)	Total (N=80)
	12-17 years (N=20)	7-11 years (N=20)	2-6 years (N=20)			
Percentage of enhancement (E%)						
Total number of lesions	25	30	6	61	12	73
Mean (SD)	11.4 (39.7)	10.7 (49.4)	20.0 (29.7)	11.9 (43.5)	101.1 (65.6)	26.6 (57.8)
Median	7.4	1.6	9.3	6.0	88.4	7.0
Min. ; Max.	-57 ; 137	-56 ; 161	-12 ; 62	-57 ; 161	6 ; 199	-57 ; 199
Missing data*	1	1	0	2	0	2
Lesion to background ratio (LBR)						
Total number of lesions	26	31	6	63	12	75
Mean (SD)	0.90 (0.47)	0.85 (0.39)	1.17 (0.68)	0.90 (0.46)	1.68 (2.25)	1.03 (1.01)
Median	0.80	0.81	1.22	0.81	0.98	0.84
Min. ; Max.	0.4 ; 2.5	0.3 ; 2.1	0.2 ; 1.9	0.2 ; 2.5	0.3 ; 8.6	0.2 ; 8.6

*Percentage of enhancement not calculated for lesions not seen with unenhanced images.

Lesion visualisation variables-

For the CNS cohort, the mean (SD) sum of lesions scores for unenhanced and contrast-enhanced 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 1.7 (1.1) for the degree of contrast enhancement, respectively (

Table **96**). According to the applicant, the mean difference in the sum of lesion scores between unenhanced and contrast-enhanced MRI was negligible for lesion border delineation and internal morphology, and the mean (SD) difference for the degree of contrast enhancement was 0.6 (1.1).

When analysed by age group, there was no difference between groups in terms of lesion border delineation and internal morphology, with a median difference of 0 in all cases. For the degree of contrast enhancement, the difference in the sum of lesions scores was more pronounced for the 4 patients of the 2-6 years group (mean difference [SD] 2.0 [1.1] versus 0.5 [1.0] for patients aged 12-17 years and 0.5 [1.0] for those aged 7-11 years).

Table 96. Sum of Lesions Scores and Variation – CNS and Body Cohorts – FAS

	CNS Cohort			Body cohort		
	Unenhanced MRI (N=60)	Contrast-Enhanced MRI (N=60)	Difference (N=60)	Unenhanced MRI (N=20)	Contrast-Enhanced MRI (N=20)	Difference (N=20)
Number of patients with lesion detected	32	34		11	11	
Total number of lesions	61	63	61	12	12	12
Lesion border delineation						
Mean (SD)	2.9 (0.8)	3.0 (0.8)	0.0 (0.6)	2.7 (0.7)	3.2 (0.7)	0.5 (0.9)
Median	3.0	3.0	0.0	3.0	3.0	0.0
Min. ; Max.	1 ; 4	1 ; 4	-1 ; 3	2 ; 4	2 ; 4	-1 ; 2
Internal morphology						
Mean (SD)	2.9 (1.0)	3.0 (0.9)	0.1 (0.3)	2.6 (0.9)	2.9 (0.9)	0.3 (1.1)
Median	3.0	3.0	0.0	3.0	3.0	0.0
Min. ; Max.	1 ; 4	1 ; 4	0 ; 2	1 ; 4	1 ; 4	-1 ; 2
Degree of contrast enhancement						
Mean (SD)	1.0 (0.0)	1.7 (1.1)	0.6 (1.1)	1.0 (0.0)	3.4 (0.7)	2.4 (0.7)
Median	1.0	1.0	0.0	1.0	3.5	2.5
Min. ; Max.	1 ; 1	1 ; 4	0 ; 3	1 ; 1	2 ; 4	1 ; 3

SD: Standard Deviation; Difference: Contrast-Enhanced minus Unenhanced

Change in diagnosis confidence- The investigator's confidence in diagnosis improved for 25 patients (55.6%) and remained unchanged for 20 patients (44.4%) among the 45 patients with detected lesions (Table 97). The improvement in investigator's diagnosis confidence was more frequent in the Body cohort (63.6%) compared to the CNS cohort (52.9%).

Table 97. Change in Diagnosis Confidence – Full Analysis Set

	CNS Cohort			CNS Cohort (N=60)	Body Cohort (N=20)	Total (N=80)
	12-17 years (N=20)	7-11 years (N=20)	2-6 years (N=20)			
Patients with detected lesion						
Yes	14 (70.0%)	16 (80.0%)	4 (20.0%)	34 (56.7%)	11 (55.0%)	45 (56.3%)
No	6 (30.0%)	4 (20.0%)	16 (80.0%)	26 (43.3%)	9 (45.0%)	35 (43.8%)
If yes, investigator's diagnosis confidence following injection						
Improved	6 (42.9%)	9 (56.3%)	3 (75.0%)	18 (52.9%)	7 (63.6%)	25 (55.6%)
Remains unchanged	8 (57.1%)	7 (43.8%)	1 (25.0%)	16 (47.1%)	4 (36.4%)	20 (44.4%)
Main diagnosis according to MRI examination						
Primary tumor	1 (7.1%)	4 (25.0%)	0	5 (14.7%)	0	5 (11.1%)
Inflammatory disease	3 (21.4%)	1 (6.3%)	0	4 (11.8%)	3 (27.3%)	7 (15.6%)
Vascular disease	2 (14.3%)	1 (6.3%)	0	3 (8.8%)	3 (27.3%)	6 (13.3%)
Congenital malformation	3 (21.4%)	5 (31.3%)	1 (25.0%)	9 (26.5%)	1 (9.1%)	10 (22.2%)
Neurodegenerative disease	1 (7.1%)	0	2 (50.0%)	3 (8.8%)	0	3 (6.7%)
Other*	4 (28.6%)	5 (31.3%)	1 (25.0%)	10 (29.4%)	4 (36.4%)	14 (31.1%)

Patients with impaired renal function

As patients with an eGFR <60 mL/min/1.73 m² were included in the phase III studies, representing about 7.5% of the study population, a post hoc descriptive analysis was performed to assess the co-primary criteria in this population compared to patients with eGFR ≥60 mL/min/1.73 m². For both pivotal studies, the results observed in the patients with eGFR<60 mL/min/1.73 m² were similar to those observed in patients with eGFR ≥60 mL/min/1.73 m² for both primary objectives.

Elderly

Out of 522 patients included in these trials (GDX-44-004 and GDX-44-010), 119 (22.8%) were 65 to 74 years old, 31 (5.9%) were 75 to 84 years old, and only one (0.2%) was older than 84 years (88-years old patient).

Table 98. Elderly patients repartition by age class in controlled trials

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	119 (22.8%)/522	31 (5.9%)/522	1(0.2%)/522

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Even though the two Phase III studies were conducted for different indications, the pooling of their data is considered appropriate as the assessments and timing of assessments for the primary and key secondary endpoints are identical between the studies. The pool included 551 patients having performed at least one MRI examination with injection of contrast agent, aged from 18 to 86 years (mean 57±13). Despite this increased heterogeneity of readers, pooled results were consistent with the results of each individual study, showing the superiority of Paired images with gadopiclenol compared to Pre-contrast images and the non-inferiority of gadopiclenol at 0.05 mmol/kg to gadobutrol at 0.1 mmol/kg in terms of lesion visualisation.

Table 99. Lesion Visualisation – Off-Site Readings – Full Analysis Set

	n patients	LS Mean (SE)			95% CI difference	p-value
		Gadopiclenol	Gadobutrol	Difference		
Study GDX-44-010 (PICTURE)						
Border delineation	239	3.83 (0.02)	3.82 (0.02)	0.01 (0.02)	[-0.02 ; 0.05]	0.5025
Internal morphology	239	3.83 (0.02)	3.81 (0.02)	0.02 (0.02)	[-0.01 ; 0.05]	0.2006
Degree of contrast enhancement	239	3.73 (0.03)	3.68 (0.03)	0.05 (0.02)	[0.01 ; 0.09]	0.0172
Study GDX-44-011 (PROMISE)						
Border delineation	273	3.60 (0.03)	3.60 (0.03)	-0.00 (0.02)	[-0.05 ; 0.04]	0.8987
Internal morphology	273	3.75 (0.02)	3.76 (0.02)	-0.01 (0.02)	[-0.05 ; 0.03]	0.6822
Degree of contrast enhancement	273	3.30 (0.04)	3.29 (0.04)	0.01 (0.03)	[-0.05 ; 0.07]	0.8546

CI: Confidence Interval ; LS: Least Squares ; SE: Standard Error.

Table 100. Results on overall diagnostic preference for Study GDX-44-010 (CNS) and Study GDX-44-011 (Body)

	Reader	N	gadopiclenol preferred	No preference	gadobutrol preferred	p-value*
Study GDX-44-010 (CNS)	4	241	108 (44.8 %)	98 (40.7 %)	35 (14.5 %)	< 0.0001
	5	241	131 (54.4 %)	52 (21.6 %)	58 (24.1 %)	< 0.0001
	6	241	138 (57.3 %)	56 (23.2 %)	47 (19.5 %)	< 0.0001
Study GDX-44-011 (Body)	4	276	36 (13.0 %)	216 (78.3 %)	24 (8.7 %)	0.1223
	5	276	40 (14.5 %)	206 (74.6 %)	30 (10.9 %)	0.2346
	6	276	33 (12.0 %)	228 (82.6 %)	15 (5.4 %)	0.0079

* Wilcoxon signed-rank test.

A change in patient treatment plan was reported after administration of gadopiclenol at 0.1 mL/kg BW (equivalent to 0.05 mmol/kg BW) in 23.3 % and 30.1 % of patients in Study GDX-44-10 (CNS) and Study GDX-44-011 (Body), respectively.

Analysis per subgroups in the CNS study (GDX-44010) revealed that treatment plan could be changed for 64 % of the 22 patients for whom the investigator considered that diagnosis was not assessable (or grade of glial tumour could not be determined) based on unenhanced MRI, 28 % of 81 patients with malignant diagnosis and about 12 % of 111 patients with non-malignant diagnosis.

In the Body study (GDX-44-011), treatment plan could be changed after MRI with gadopiclenol for 41 % of the 22 patients with non-assessable diagnosis based on unenhanced MRI, 32 % of 165 patients with malignant diagnosis and 14 % of 64 patients with non-malignant diagnosis.

A post-hoc reading of all images from both pivotal studies for CNS and Body indications was conducted in a fully blinded, unpaired, randomised manner. A high level of concordance in lesion detectability between gadopiclenol at 0.05 mmol/kg and gadobutrol at 0.1 mmol/kg was observed at lesion and at patient level. The results are summarised in Table 101 below.

Table 101. Concordance in lesion detectability between gadopiclenol at 0.05 mmol/kg and gadobutrol at 0.1 mmol/kg

	Perfect match at lesion level*	Perfect match at patient level*
Study 1 (CNS)	88.0% to 89.8%	84.3% to 86.0%
Study 2 (Body) overall	92.3% to 95.5%	81.3% to 85.0%
Head & Neck	89.5% to 100%	70.6% to 94.1%
Thorax	88.3% to 93.2%	69.8% to 73.2%
Pelvis	91.7% to 100%	87.5% to 94.6%
Abdomen	94.6% to 95.2%	84.0% to 87.2%
Musculoskeletal	100%	100%

*Range of values according to the reader (3 readers per region)

2.6.5.6. Supportive study(ies)

GDX-44-008 - Proof of Concept study concerning efficacy of P03277 MR Imaging in hepatocellular carcinoma (HCC) diagnosis

This proof-of-concept study on liver imaging was a double-centre, non-randomised, open-label Phase IIa exploratory in female or male adult patients with liver cirrhosis or chronic liver disease.

Methods

The study included two cohorts of patients:

- a first cohort of 30 patients who were administered gadopiclenol at 0.1 mmol/kg
- a second cohort of 10 patients who were administered gadopiclenol at 0.05 mmol/kg.

The main inclusion criteria were:

- Female or male adult patient presenting with liver cirrhosis or chronic liver disease as shown by previous liver biopsy or by a combination of clinical, endoscopic, biological, ultrasound parameters, and elastography,
- Patient presenting with one to a maximum of 3 untreated hepatic nodules ≤3 cm (long axis) previously identified and/or characterised through enhanced CT and/or MRI within a maximum of 21 days before gadopiclenol MR imaging, confirmed for HCC or not.

The primary objective was to evaluate the diagnostic value (sensitivity and specificity) for hepatocellular carcinoma (HCC) of gadopiclenol-enhanced MRI in patients with small suspected nodules and chronic liver disease. The secondary objectives were to evaluate multiple quantitative and qualitative efficacy parameters and the safety profile (clinical and biological) of gadopiclenol following single administration in patients with suspected HCC.

The study included 4 visits: a screening visit, an inclusion visit with unenhanced and contrast-enhanced MRI performed according to the required sequences, a safety follow-up visit one day after the inclusion visit and a fourth optional visit.

Between 3 days after the inclusion visit and up to 13 weeks maximum, a biopsy was performed, or a surgically resected specimen was collected at the time of loco-regional treatment and analysed for histology by a local pathologist. Alternatively, it was acceptable to record results from histology performed within 2 months prior to the inclusion visit.

For each investigational site, an expert radiologist in liver diseases was appointed for on-site readings and provided on-site reading results. Investigational sites were requested to send anonymous images of patients to Guerbet in a specific format. Two expert radiologists, having expertise in the interpretation of MR images of liver diseases and HCC were appointed from the participating sites. Expert readers were not involved in the on-site reading. To guarantee an unambiguous assignment (matching) of the liver nodules between standard of reference and expert readings, nodule tracking was performed using a liver map according to Couinaud segmentation drawings completed on-site and by expert readers.

The diagnostic performance of gadopiclenol-enhanced MRI for HCC was assessed using a standard of reference based on previous imaging and/or histology. Images were read by two experts.

Results

Among the 39 patients included in the FAS, a total of 56 suspected nodules were analysed: 43 from cohort 1 (gadopiclenol at 0.1 mmol/kg) and 13 from cohort 2 (gadopiclenol at 0.05 mmol/kg).

Crossing of diagnosis showed that with gadopiclenol at 0.1 mmol/kg, 8 of 21 HCC nodules were considered as not having the typical HCC features according to EASL criteria (false negative), and 3 of 22 non-HCC nodules were characterised as having the typical HCC features on MR examination (false positive). Therefore, the diagnostic performance for gadopiclenol-enhanced MR at 0.1 mmol/kg showed a sensitivity and specificity of 62% and 86%, respectively (**Table 102**). With gadopiclenol at 0.05 mmol/kg, 1 of 5 HCC nodules was considered as not having the typical HCC features (false negative), while all non-HCC nodules were also characterised as not having the typical HCC features on MR examination (no false positive). Therefore, the diagnostic performance for gadopiclenol-enhanced MR at 0.05 mmol/kg showed a sensitivity and specificity of 80% and 100%, respectively.

Accuracy, positive and negative predictive values were 74%, 81% and 70%, respectively, for gadopiclenol at 0.1 mmol/kg and 92%, 100% and 89% for gadopiclenol at 0.05 mmol/kg.

Table 102. Diagnostic performance

			Standard of reference		
			HCC	Not HCC	Total
Expert reading	Gadopiclenol 0.1 mmol/kg	HCC	13	3	16
		Not HCC	8	19	27
	Gadopiclenol 0.05 mmol/kg	HCC	4	0	4
		Not HCC	1	8	9

Most patients had only one nodule (62.1% and 80% of patients who have received gadopiclenol at 0.1 and 0.05 mmol/kg, respectively). The size of the detected nodules ranged between 3 mm and 3 cm, with a mean size around 15 mm.

Overall, 90 to 100% of images from cohort 1 and 100% of images from cohort 2 were considered as technically adequate by on-site and expert readers. All images from both cohorts were considered assessable.

In both cohorts, quantitative evaluation of nodule intensity showed in HCC nodules a substantial increase in median CNR from unenhanced T1 sequence at the arterial phase then a decrease at the portal phase and stabilisation at the delayed phase. In non-HCC nodules, the same pattern was observed for CNR but to a lower extent.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

This application is based on efficacy data from the (phase 2b) dose-finding study GDX-44-004, two pivotal confirmatory (phase 3) studies for CNS MRI (GDX-44-010) and Body MRI (GDX-44-011) conducted with the same study design, and a dedicated phase 2 study GDX-44-007 in paediatric patients of 2 -17 years old in order to support a CNS and another whole body MRI indication in adults and the paediatric population for gadopiclenol. Supportive data are obtained from the (phase 2a) proof-of-concept study GDX-44-008 on liver imaging for hepatocellular carcinoma (HCC).

- ***Dose selection.***

The selection of the dose for the confirmatory studies GDX-44-010 and GDX-44-011 is based on data of first-in human study GDX-44-001 and the dose-finding study GDX-44-004. Notably, the dose of 0.1 mmol/kg is the standard dose for most approved gadolinium-based contrast agents (GBCAs). In the dose-finding study, for all three independent off-site blinded readers, gadopiclenol at the dose of 0.1 and 0.2 mmol/kg showed significantly higher CNR compared with gadobenate dimeglumine at 0.1 mmol/kg, whereas gadopiclenol at 0.05 mmol/kg showed similar efficacy in CNR compared with gadobenate dimeglumine at 0.1 mmol/kg. A similar pattern for all three blinded readers was observed for CNR based on cerebrospinal fluid, lesion-to-brain ratio (LBR), contrast enhancement percentage, and lesion visualisation criteria. Moreover, a linear dose-response relationship between increasing doses of gadopiclenol (0.025, 0.05, 0.1, and 0.2 mmol/kg) and increases in CNR for all 3 independent off-site readers has been observed. Consequently, the recommended dose of Elucirem is 0.1 mL/kg body weight (BW) (equivalent to 0.05 mmol/kg BW) to provide diagnostically adequate contrast for all indications. The dose should be calculated based on the patient's BW and should not exceed the recommended dose per kilogram of BW detailed in Table 1.

In children, Elucirem in vials with a single use syringe of a volume adapted to the amount to be injected should be used in order to have better precision of the injected volume.

Contrast-enhanced MRI can start after the injection depending on the pulse sequences used and the protocol for the examination. Optimal signal enhancement is generally observed during arterial phase and within a period of about 15 minutes after injection. Longitudinal relaxation times (T1)-weighted sequences are particularly suitable for contrast-enhanced examinations.

- ***Design of the main clinical studies (GDX-44-010 and GDX-44-011)***

Both studies were prospective, multicentre, randomised, double-blind, controlled, cross-over studies to evaluate the safety and efficacy of gadopiclenol at 0.05 mmol/kg compared with gadobutrol at 0.1 mmol/kg for CNS and body MRI. The design generally appeared to achieve both primary objectives of the studies. The cross-over design intended to increase the study quality (reducing the variability and increasing the power of

the study) and to ensure that each patient would receive an MRI with an approved GBCA. Two MRI examinations were performed at visit 2 and visit 4 for each patient. Patients were randomised in a 1:1 ratio for the order of receiving the contrast agents in order to avoid bias. The interval between the 2 MRIs was 2-14 days to minimise the risk of disease progression or lesion evolution, which is considered appropriate.

Moreover, as stated in the guideline (CPMP/EWP/1119/98/Rev.1), a sufficient number of patients with other conditions that could affect the interpretation of the imaging results should be included. It is known that MRI scan with contrast is particularly difficult in patients with heart failure, but these patients (class III/IV NYHA) were excluded from the study. In this respect, the applicant has clarified that the degree of contrast enhancement between normal tissues/structures and the diagnostic quality of MR images does not depend on first-pass effect but depends on the steady state concentrations in abnormal vasculature CNS areas with abnormal BBB/BSCB. Therefore, ideal timing tends to be spread over long windows for opportunity for steady-state acquisitions, which is endorsed.

The image reading procedures are deemed adequate. Off-site blinded image evaluations by three independent readers for the primary analysis in confirmatory trials is in line with the "Appendix 1 to the guideline on clinical evaluation of diagnostic agents" (CPMP/EWP/1119/98 Rev.1) on imaging agents. Three additional independent blinded radiologists were appointed for the global matched-pairs assessment for overall diagnostic preference, which is considered appropriate. As different body regions were included in the body study, readers with different expertise were involved, resulting in 18 independent blinded readers which is appropriate.

Regarding the imaging procedure, the same MR equipment had to be used for the two MRI examinations required by the protocol for a single patient. Additionally, the same parameter setting for the same sequence had to be used for unenhanced and for contrast-enhanced images in each patient. In the study the Contrast-enhanced 2D T1-weighted SE/TSE images 3D T1-weighted GRE images were performed.

Another independent radiologist was involved in lesion tracking for the exact matching of lesions between imaging modalities (pre-contrast and paired images), or between the two MR examinations for the same patient and between readers. Once the concordance process was done, lesions could be compared for analysis within readers; Only matching lesions were included in the primary criteria analyses. As previously indicated by CHMP, with such an approach, important and clinically relevant information about the difference between gadopiclenol-enhanced and gadobutrol-enhanced MRI may get lost. For example, the issue of potential false positive was raised. The number of lesions observed with each contrast medium not identified with the other contrast medium were provided, showing that the percentage of extra lesions observed was well-balanced between the gadopiclenol and gadobutrol groups.

Nevertheless, concordance analyses in the pivotal studies showed that the percentage of patients with the same number of lesions identified with both gadopiclenol and gadobutrol was only around 75% of the CNS lesions and around 62% lesions for other body regions MRI. This level of concordance is considered relatively low and indicates that similarity (or non-inferiority) of diagnostic efficacy of gadopiclenol vs. gadobutrol cannot be claimed. In the absence of analysis of a suitable SOT, further information on discordant lesions and discussion of the clinical impact of these discordances were provided based on an additional assessment of concordance in lesion detectability (see below).

The confirmatory studies included two co-primary objectives, i.e., the superiority of combined unenhanced/enhanced imaging with gadopiclenol vs unenhanced imaging and non-inferiority of gadopiclenol (0.05 mmol/kg) vs gadobutrol (0.1 mmol/kg) enhanced imaging in terms of 3 qualitative lesion visualisation criteria (border delineation, internal morphology, and degree of contrast enhancement) as judged by 3

independent blinded readers. A comparison of enhanced to non-enhanced images is considered necessary, as this is what happens in clinical practice. In this respect, demonstrating the superiority of gadopiclenol-enhanced vs unenhanced is considered appropriate. According to the above-mentioned Appendix 1 (CPMP/EWP/119/98 Rev.1), for all imaging contrast agents developed as alternative (or improvement) over registered diagnostic agents, comparative studies are required. Gadopiclenol (0.05mmol/kg) is developed as an alternative (or improvement) for other macrocyclic GBCAs. In this respect, demonstration of non-inferiority of gadopiclenol at 0.05 mmol/kg against comparator gadobutrol at 0.1 mmol/kg, an approved GBCA, is considered appropriate.

The 3 co-primary lesion visualisation criteria of border delineation, internal morphology, and degree of contrast enhancement are clinically relevant, in line with the EMA guideline on imaging agents (CPMP/EWP/119/98 Rev.1) and therefore acceptable. However, these co-primary criteria represent qualitative (subjective) assessments of the technical performance of gadopiclenol but do not directly evaluate diagnostic performance or clinical outcome. This shortcoming is mostly due to the lack of a standard of truth. According to the applicant, no standard of truth could be added for any subset of patients. Based on the applicant's experience in previous studies, the expected **CNS study** population should include about 20% to 30% glial tumours with high grade III/IV i.e., 50-60 patients, for some of whom it would be possible to confirm the diagnosis with surgery. This number of patients would still not be sufficient to conclude on the impact of gadopiclenol on diagnostic thinking, and it would be even more difficult to link its value to the clinical outcome, considering the many confounders involved in the therapeutic plans of patients. As such, it would be difficult to conduct such a study due to a lack of sensitivity as well as ethical reasons. For the **body study** GDX-44-011, CHMP previously recommended obtaining a standard of truth for a subset of patients and subsequently generalising it to others for which it cannot be obtained. Meanwhile, CHMP also acknowledged previously that extending one organ to other body regions will be very difficult due to the different lesion types and organ specificities. Therefore, it is acknowledged that a study incorporating such a standard of truth and corresponding outcome measures (e.g., via surgery-confirmed diagnosis) may be difficult. In the same EMA guideline on imaging agents (CPMP/EWP/119/98 Rev.1) is stated as a general principle that a standard of truth is required to assess the diagnostic performance of a diagnostic agent. However, in cases when it might not be feasible or ethical to obtain a standard of truth or to determine it in an accurate manner, "concordance" with a well-documented comparator in a cross-over study can be used as an outcome measure. In this respect, the cross-over design of the two pivotal studies with an approved comparator permits the evaluation of concordance of the diagnosis between contrast agents and within and across readers. Based on the above, the co-primary objectives and corresponding criteria are considered acceptable. Notably, the applicant evaluated the diagnostic performance of gadopiclenol in a proof-of-concept study in adult patients with liver cirrhosis or chronic liver disease (GDX-44-008)(see below). Nevertheless, there appears to be significant non-concordance findings between gadopiclenol and gadobutrol in the number of lesions detected for both CNS and body, and that the nature of this non-concordance remained unclear. Therefore, an additional assessment of concordance in lesion detectability was conducted (see below).

The applicant has aggregated lesion visualisation scores per subject by using the mean of up to the three most representative lesions. In general, however, the benefit of aggregating scores on the subject level is criticised as averaging ratings for subjects with different numbers of lesions or averaging over lesions of different types may introduce heteroscedasticity and dependence between samples which ultimately may undermine key assumptions of the statistical inference. Furthermore, capping the number of lesions to be included in the analysis set at three "representative lesions" (defined according to lesion size and contrast enhancement) runs the risk of introducing bias in the assessment and could compromise the external validity of the trial as results may only apply to "representative lesions". It is not clear whether the restriction to

three representative lesions, thus exclusion of smaller lesions and less enhanced lesions, leads to a decrease in sensitivity of detection of differences between gadopiclenol or gadobutrol. CHMP therefore advised the applicant to consider direct comparison (e.g. in a paired manner) between individual ratings of all matched lesions. In this respect, a hierarchical modelling procedure could be used to correctly account for the fact that not all patients will contribute the same number of lesions to the data set. Additional sources of variation (e.g. subject, centre, and rater) should have been included as adjustment factors. This advice has been followed. Furthermore, the primary criteria 2 analyses according to lesion size (≤1 cm, >1 cm and ≤2 cm, >2 cm) for both the CNS study GDX-44-010 and body study GDX-44-011 have been provided, which showed that there is no trend for lower lesion visualisation scores with smaller lesions, i.e. the results were consistent overall lesion size categories, which is reassuring. Moreover, considering that in both CNS and body studies, only a minority of patients (~9.2-18.5%) for extended FAS 2 presented more than 3 lesions, the selection of up to three most representative lesions is not expected to have had a major impact on the outcome.

The applicant has used a non-inferiority margin of 0.35 on the lesion visualisation scale, which refers to 10% of the effect size (3.5) found in previous trials. The applicant's clinical justification for this margin is that with the assumed effect size of 3.5 this would still ensure an average rating above a score of 3, representing 'good' score. Whether this would exclude a clinically important difference remains questioned. However, since for the primary comparisons, the mean scores are well above 3.5, and the 95% CI of the difference in scores is well above the margin, this is not further pursued. Furthermore, non-inferiority between gadopiclenol and gadobutrol was concluded if the lower bound of the 95% CI was above the non-inferiority margin set to 0.35 for at least 2 out of 3 blinded readers and for the 3 co-primary criteria simultaneously. The applicant argued that at least 2 out of 3 readers follow the method employing two readers with a third consensus reader in case of disagreement. Although this is not an uncommon method, it was not applied in these studies, which used three readers in all cases, nor will it be used in clinical practice. Nevertheless, if the applicant had used an all three readers method, they would have demonstrated superiority and non-inferiority for the two co-primary endpoints. Notably, regarding primary objective 2, the non-inferiority margin of 0.35 and demonstration of non-inferiority by 2 out of 3 blinder readers instead of all 3 readers are no issues for discussion for the overall population since the 95% CI of the difference was far above the non-inferiority margin for all three readers. However, in some subgroup analyses of the body study GDX-44-011 the 95% CI of the difference was close to the non-inferiority margin or under the non-inferiority margin for at least one reader, likely due to the limited sample size in these subgroups.

The secondary endpoints of improvement in lesion visualisation scores at patient-level, technical adequacy of images, number, size and location of lesions, diagnostic confidence, impact on patient treatment plan, quantitative criteria, and overall diagnostic preference were assessed to further evaluate the diagnostic value of gadopiclenol, which is considered appropriate.

While the proposed sample size for both confirmatory studies appears to be sufficient to provide 90% (or 80% for the NI comparison) power for a single comparison, the success criterion proposed by the applicant comprises a combination of 2 times 3 times 3 hypothesis tests. For each of the two primary objectives and for all three criteria at least 2 hypothesis tests out of 3 for each reader need to be statistically significant. The exact performance characteristics of such a decision rule depend on the correlation between different criteria and the concordance between readers but will likely have a largely reduced power (under identical assumptions) compared to a single comparison. Consequently, the stated power may be substantially overestimated for the proposed sample size. In addition, it is unclear which error rate is controlled when a statistically significant improvement (non-inferiority) in ratings for 2 out of 3 readers is required. The CHMP

advised the applicant to clarify the null hypothesis and consider whether a multiplicity correction is required. Although this advice has not been followed, this issue has not been pursued.

The randomisation and blinding procedures were acceptable.

- ***Design of the additional image evaluation to assess concordance***

The applicant has conducted an additional image evaluation to assess concordance in lesion detectability obtained with 0.05 mmol/kg gadopiclenol and 0.1 mmol/kg of comparator gadobutrol in MRI. This additional assessment was performed by a total of nine experienced radiologists ("Blinded Readers"):

- three experienced neuroradiologists reading MR images of CNS (MR images of brain and spine from study GDX-44-010) and Head and Neck (MR images from study GDX-44-011);
- three experienced radiologists reading MR images of the thorax (essentially breast imaging) from study GDX-44-011
- three experienced radiologists reading MR images of other body regions (abdomen, pelvis, MSK) from study GDX-44-011.

All readers were fully blinded to all patient clinical information and to the contrast agent used in each MR exam, and independently and separately reviewed all the investigational MRI images in a fully randomised in order to assess the number and location of all lesions in each MR exam. Screenshots were obtained documenting the lesions that were marked and numbered on the images by each reader. All patients were included as part of this new assessment, even those with only one lesion agree across 3 readers in the original technical performance assessment. Three additional independent experienced radiologists (Concordance Readers), one for the CNS and Head and Neck MR images, one for thorax including breast MR images and one for the MR images of abdomen, pelvis and musculoskeletal system, tracked all lesions detected on Exam 1 (Visit 2, V2) and Exam 2 (Visit 4, V4) across the evaluations of the blinded readers by assigning one unique reference number for each matched lesion. These readers were also fully blinded to all patient clinical information and to the contrast agent used in each MR exam. Screenshots taken during unpaired reading sessions were available for the Concordance Reader to do the lesion tracking and matching (Concordance Read). In case of discordant lesions, i.e., lesions seen on one exam but not in the other, respective Panels (Concordance Reader and each individual Blinded Reader; n=2) will assess the nature of the lesion (radiology diagnosis based on image interpretation in routine practice) and potential clinical impact of this non-concordance in detection of lesions. The patient profiles consisting of all the available clinical information (e.g., medical history and results of previous imaging studies) will be provided to the Panels. The concordance in lesion detection was analysed using gadobutrol as validated comparator. The percentage of lesions detected with gadobutrol that were also detected with gadopiclenol was calculated, overall and according to the number of lesions detected with gadobutrol per patient. The design of this new assessment is considered acceptable. All readers were fully blinded to patient clinical information and to the contrast agent used in each MR exam, and the readers reviewed the MRI images independently and separately in a fully randomised order to assess all lesions.

Efficacy data and additional analyses

- ***Study GDX-44-010 for CNS imaging***

In the pivotal CNS study, 256 subjects (128 subjects in each arm) presenting with known or highly suspected CNS lesions with focal areas of disrupted BBB (e.g. primary and secondary tumours) were randomised, of

which 125 in each arm received the first contrast agent. Subsequently, 242 subjects (94.5%) received the second contrast agent (gadobutrol (n=120) or gadopiclenol (n=122)). The percentage of subjects who completed the study was high (94.5%). In total, 14 patients (5.5%) discontinued the study, of which 6 were before receiving the first and 8 were before receiving the second contrast agent. The most common reason was the withdrawal of patient's consent (n=4) and adverse events other than COVID-19 (n=4). There were no differences in participant flow between the two randomised arms.

The applicant has comprehensively monitored the major protocol deviations (n=27 (10.5%). The percentage of protocol deviations is slightly higher in the gadopiclenol/gadobutrol arm (12.5%) compared with the gadobutrol/gadopiclenol arm (8.6%); however, no pattern could be observed. As described, the COVID-19 pandemic did not have a major impact on the conduct of the study.

The majority of patients (72%) presented with brain tumours, 20% had brain or spine metastases and 8% presented with other pathologies. The recruited patients presented a population of which the most (~92%) disease diagnoses were related to the system organ class (SOC) "*neoplasms benign, malignant and unspecified (including cysts and polyps)"* with meningioma (29.3 to 29.7%), metastases to the central nervous system (18.0 to 19.2%), glioblastoma (10.5 to 10.9%) and acoustic neuroma (8.4 to 8.8%) as the most frequent diseases (preferred terms (PT)), whereas in the SOC "*nervous system disorders*" (~6.5%), the most frequent disease (PT) was central nervous system lesion (4.2 to 4.6%). In the other SOC of "infections and infestations", "Injury, poisoning and procedural complications" and "Investigations" only single disease diagnoses were reported. Some disorders (demyelinating (brain and spinal cord) disorders, non-acute vascular lesions, parasitic and infectious disorders and immune or toxic driven encephalopathies) appear to be under – or not represented. In this respect, the applicant substantiated the different factors determining differential SI enhancement between abnormal and normal CNS tissues/structures: 1) extravasation of GBCAs through an abnormal blood-brain barrier (BBB) and its functional equivalent, the blood-spinal cord barrier (BSCB); 2) vascular abnormalities, such as neovascularity, vasodilatation or hyperaemia; and 3) presence of necrotic, non-enhancing tissue or viable, enhancing tissue within a lesion. A combination of the above is also possible. Subsequently, the applicant divided the heterogeneous group of CNS diseases/conditions, including the under – or not represented conditions of inflammatory and autoimmune disorders, demyelination, infectious disorders, and vascular malformation, over the different determinants of contrast enhancement and stated that the study covered all possible mechanisms of contrast enhancement. Based on these principles, the applicant considers that the data obtained in patients with Intra-axial neoplastic conditions or other mass conditions of the brain parenchyma, either primary or secondary (n = 109 including 55 metastases and 51 gliomas) can be extrapolated to conditions underrepresented in the study such as patients intramedullary spine lesions (n=4), patients with inflammatory and autoimmune disorders, including disorders of demyelination (none in the study), patients with infectious disorders: encephalitis, meningitis, empyema, abscess (neurocysticercosis = 1) and patients suffering from acute and chronic infarct (1 stroke and 1 subacute ischemic lesion). While this justification provided by the applicant is acknowledged, the limited availability of data in patients with inflammatory, infectious, autoimmune or demyelinating disorders (such as multiple sclerosis), patients with with acute or chronic infarct, or patients with intramedullary spine lesions remains of concern. Therefore, information on no or limited data in specific conditions has been included in section 4.4, which is considered appropriate.

The demographics and other baseline characteristics are well distributed across the two randomised groups.

In the pivotal CNS study, both primary objectives were achieved for all three blinded readers. For the primary objective 1 (superiority over unenhanced MRI images), 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 0.025 in favour of paired images (pre-contrast/contrast-enhanced images) compared to pre-contrast images for all three readers ($p<0.0001$ in all cases). Based on these results, superiority of combined unenhanced/contrast-enhanced MRI (paired) with gadopiclenol over unenhanced MRI (pre-contrast) has been demonstrated. For the primary objective 2 (non-inferiority to gadobutrol at 0.1 mmol/kg), the differences in mean of scores for border delineation, internal morphology and degree of contrast enhancement were close to 0 in all cases, with a lower limit of the 95% CI of the difference not lower than -0.06, that is largely above the non-inferiority margin of -0.35 for all three readers ($p<0.0001$ in all cases), indicating non-inferiority of gadopiclenol to gadobutrol. These findings were confirmed in the supportive analyses performed on the PSS1 for criterion 1 and FAS 2 for criterion 2. Additionally, the investigator observed similar results with on-site reading for the two primary objectives. Furthermore, the analysis of the difference "Paired - Pre" for 3 co-primary criteria for MRI with gadobutrol showed similar results to those obtained with gadopiclenol, confirming the assay sensitivity.

Both primary analyses 1 and 2 were repeated using the extended FAS 1 and extended FAS 2, which included matching and non-matching lesions, lesions seen with both contrast agents and lesions only seen with one contrast agent. In these analyses, no imputation of missing data is performed as the applicant considered that not having matching lesions has no link with the lesion visualisation scores, so data are missing at random. In this respect, using a mixed model without imputation was considered the most appropriate for this sensitivity analysis, according to the applicant. The results of the extended FAS analyses were similar to those provided by the main analysis. Nevertheless, the applicant has also performed an additional sensitivity analyses in which a non-matching lesion was theoretically coupled to a non-existing lesion with a mean score of 1 for each criterion as requested by the CHMP. The results of this analysis were consistent with the previous analysis, i.e. non-inferiority of gadopiclenol compared to gadobutrol was demonstrated for all endpoints and all three readers in both studies, which is reassuring.

Intra-reader variability was generally good as well as inter-reader variability, showing consistent results between readers.

Subgroup analyses concerning demographic parameters and magnetic field strength showed consistent results in terms of primary efficacy criteria 1 and 2. The majority of patients investigated in the pivotal study CNS changes/ abnormities were located in the brain and to a lesser extent in the spinal cord. Therefore, the subgroup analysis of the primary endpoints for patients with brain neoplasms and patients with other diseases (including spine disease, n=5 out of 6) have been provided, showing comparable lesion visualisation scores for images of patients with brain tumours and patients with other diseases. Moreover, despite the low sample size in the subgroup of patients with other diseases (n=5/6), the primary objective has almost been met in this subgroup since non-inferiority has been demonstrated for 2 out of 3 readers for the lesion visualisation criteria border delineation and internal morphology and for 1 out of 3 readers for the degree of contrast enhancement. Regarding the degree of contrast enhancement, reader 2 had a lower limit of the 95% CI of the difference of -0.40, which was just below the non-inferiority margin of – 0.35 limit, despite very high mean visualisation scores of 4.0, indicating that the primary analysis was borderline negative for this subgroup. To note, for images of patients with a brain tumour, non-inferiority of gadopiclenol compared to gadobutrol was demonstrated for all endpoints and all three readers. Furthermore, the data of the CNS study GDX-44-010 was pooled with the data from study GDX-44-004 in which four doses of gadopiclenol (0.025, 0.05, 0.1, and 0.2 mmol/kg) were compared with gadobenate dimeglumine (MultiHance; linear GBCA) at 0.1 mmol/kg. The pooled data set supported the non-inferiority of gadopiclenol at 0.5 nmol/kg to other GBCAs at 0.1 nmol/kg.

Paired images with gadopiclenol showed improvements compared to pre-contrast images for all secondary endpoints. More importantly, for all secondary endpoints, similar or better results between paired images with gadopiclenol and paired images of gadobutrol were observed. More specifically, for evaluation of improvement in lesion visualisation scores at patient-level, both paired images with gadopiclenol and paired images with gadobutrol scored better than pre-contrast images in more than 95% of the evaluations for all three readers and for all three visualisation criteria. Assessment of lesion visualisation criteria at lesion level by MRI modality and by contrast agents showed similar results to those obtained at patient level. Regarding the technical adequacy of images, there was some variability in the assessment of pre-contrast images, with the large majority of images (>95%) considered good by reader 1, poor by reader 2 and fair by reader 3. Nevertheless, as expected, with paired images with gadopiclenol, the majority of images were rated as being of good quality (94.3, 80.5, and 95.1% for readers 1, 2, and 3, respectively). Similar results were obtained with gadobutrol (good quality: 95.1, 80.4, and 97.6 for readers 1, 2, and 3, respectively). The majority of patients presented only one lesion (64.2 to 75.9% for extended FAS 1 and 63.9 to 67.4% for extended FAS 2). Generally, more lesions were identified with paired images with gadopiclenol compared with pre-contrast images for all three readers, which can be expected with contrast enhancement. Furthermore, the number of lesions identified with gadopiclenol was generally comparable to those identified with gadobutrol, with a mean of 2.1-2.9 lesions depending on the reader. Nevertheless, although the number of lesions was generally comparable, there appeared to be a relatively large number of patients with non-matching lesions (see also number analysed). Therefore, the number of lesions observed with each contrast medium which is not identified with the other contrast medium, has been provided, which showed that the percentage of extra lesions observed was well-balanced between the gadopiclenol and gadobutrol groups. It appears that differences in observed lesions were more related to intra-reader variability than different visualisation/detection capacities between the two agents. Furthermore, the primary criteria 2 analyses according to lesion size (≤1 cm, >1 cm and ≤2 cm, >2 cm) showed that there is no trend for lower lesion visualisation scores with smaller lesions, i.e., the results were consistent overall lesion size categories, which is reassuring. The level of diagnostic confidence markedly improved with paired images compared to pre-contrast images. The percentage of the excellent level of diagnostic confidence was slightly higher for gadopiclenol compared with gadobutrol (67.4% vs 64.6%, 66.0% vs 63.1% and 93.0% vs 89.1% for readers 1, 2, and 3, respectively). Regarding radiological diagnosis, the largest difference between pre-contrast and paired images was found for glial tumours, for which tumour grade could be determined in more cases than paired images. No differences could be observed for radiological diagnosis between gadopiclenol and gadobutrol. The percentage of treatment plan changes based on paired images compared with pre-contrast images was similar between both contrast agents (23.3% of the patients for gadopiclenol and 23.7% for gadobutrol), which is expected considering the non-inferiority claim. When analysing the data according to tumour classification, treatment plan could be changed after MRI with gadopiclenol for 28% of 81 patients with malignant diagnosis, for 12% of 111 patients with non-malignant diagnosis and for 64% of the 22 patients for whom the investigator considered that diagnosis was not assessable (or grade of glial tumour could not be determined) based on unenhanced MRI, indicating that in all types of lesions contrast-enhancement of images affect patient management. Additionally, there was also no difference between both contrast agents for the change on treatment plan according to tumour classification. Regarding the quantitative parameters, lesion to background ratio (LBR) and percentage of lesion enhancement were significantly higher with gadopiclenol than with gadobutrol for all three blinded readers ($p<0.0001$). For CNR, the difference was statistically significant for the two readers. These findings indicate a better technical performance of gadopiclenol compared with gadobutrol based on objective quantitative assessment. Global matched-pairs assessment for overall diagnostic preference by 3 additional independent blinded radiologists showed that images with gadopiclenol were in majority preferred to images with gadobutrol (44.8%, 54.4%

and 57.3% for readers 4, 5, and 6, respectively; p< 0.0001), whereas no preference was reported for 40.7%, 21.6% and 23.2% of the images by reader 4, 5 and 6, respectively, indicating a similar or better technical performance of gadopiclenol compared with gadobutrol.

- ***Study GDX-44-011 for body imaging***

In the confirmatory body study, 304 patients (152 subjects in each arm) with known or suspected abnormalities or lesions in other body regions (8% in head and neck, 28% in thorax, 35% in abdomen, 22% in pelvis and 7% in musculo-skeletal system) both based on results of a previous imaging procedure such as CT or MRI, were randomised, of which 151 subjects (99.3%) received the first MRI with gadopiclenol, and 149 subjects (98.0%) received the first MRI with gadobutrol. Subsequently, 277 subjects (91.1%) received the second contrast agent (gadobutrol (n=141) or gadopiclenol (n=136)). The most frequent pathologies were breast tumours (23%) and liver tumours (21%). The percentage of subjects who completed the study was high (90.5%). In total, 29 patients (9.5%) discontinued the study, of which 4 were before receiving the first and 23 were before receiving the second contrast agent and 2 subjects were after receiving the second contrast agent. Most common reasons were withdrawal of patient's consent (n=7) and other reasons (n=9). There were no differences in participant flow between the two randomised arms.

The applicant has comprehensively monitored the major protocol deviations (n=50 (16.4%). The percentage of protocol deviations is slightly higher in the gadobutrol/gadopiclenol arm (14.5%) compared with the gadopiclenol/gadobutrol arm (18.4%); however, no pattern could be observed. As described, the COVID-19 pandemic did not have a major impact on the conduct of the study.

The recruited patients presented a population of patients with known or suspected enhancing abnormality(ies) and/or lesion(s) in at least one body region among head & neck (n=22 in FAS 2), thorax (n=76), abdomen (n=95), pelvis (n=59) and musculoskeletal (n=22 and n=21). The majority (65.8%) of the disease diagnoses were related to the SOC "*neoplasms benign, malignant and unspecified (incl cysts and polyps)*" with metastasis to the liver (9.4%) and breast cancer (8.6%) as the most frequent diseases (PT). Other most frequent diseases (PT) were breast mass (9.0%; SOC "*reproductive system and breast disorders*") and hepatic lesion (4.7%; SOC "*hepatobiliary disorders*"). Some body regions, i.e., head & neck and musculoskeletal (both n=~21), appear to be underrepresented (see below for further details). For the overall population and per body region, the demographics and other baseline characteristics are well distributed across the two randomised groups, with the exception of the thorax region. The population of the thorax region included a large majority of women and were younger compared with the other body regions, due to breast MRI imaging.

In the confirmatory body study, both primary objectives were achieved for all three blinded readers. For the primary objective 1 (superiority over unenhanced MRI images), 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 0.025 in favour of paired images (pre-contrast/contrast-enhanced images) compared to pre-contrast images for all three readers (p<0.0001 in all cases). Based on these results, the superiority of combined unenhanced/contrast-enhanced MRI (paired) with gadopiclenol over unenhanced MRI (pre-contrast) has been demonstrated. For the primary objective 2 (non-inferiority to gadobutrol), the differences in mean of scores for border delineation, internal morphology and degree of contrast enhancement were close to 0 in all cases, with a lower limit of the 95% CI of the difference not lower than -0.10, that is largely above the non-inferiority margin of -0.35 for all three readers (p<0.0001 in all cases), indicating non-inferiority of gadopiclenol to gadobutrol. These findings were confirmed in the supportive analyses performed on the PSS1 for criteria 1 and FAS 2 for criteria 2. Additionally, the investigator observed

similar results with on-site reading for the two primary objectives. Furthermore, the analysis of the difference "Paired - Pre" for each of 3 co-primary criteria for MRI with gadobutrol showed similar results to those obtained with gadopiclenol, confirming the assay sensitivity.

Similar to the CNS study, both primary analyses 1 and 2 were repeated using the extended FAS 1 and extended FAS 2, respectively, which included matching and non-matching lesions, lesions seen with both contrast agents and lesions only seen with one contrast agent. In these analyses, no imputation of missing data is performed as the applicant considered the fact of not having matching lesions has no link with the lesion visualisation scores, and so data are missing at random. In this respect, using a mixed model without imputation was considered the most appropriate for this sensitivity analysis, according to the applicant. The results of the extended FAS analyses were similar to those provided by the main analysis. Nevertheless, the applicant has performed an additional sensitivity analysis in which a non-matching lesion was theoretically coupled to a non-existing lesion with a mean score of 1 for each criterion as requested by the CHMP. The results of this analysis were consistent with the previous analysis, i.e. non-inferiority of gadopiclenol compared to gadobutrol was demonstrated for all endpoints and all three readers in both studies, which is reassuring.

Analysis of intra-readers' and inter-readers' variability, overall and by body region, showed generally good reproducibility of readings.

Subgroup analyses with respect to demographic parameters and magnetic field strength showed consistent results in terms of primary efficacy criteria 1 and 2. Subgroup analyses for the lesion visualisation criteria showed in general consistent results between body regions. The superiority of paired images with gadopiclenol compared to pre-contrast images has been demonstrated in all body regions for all lesion visualisation criteria for all three readers, except for border delineation in musculoskeletal assessments by reader 2, which is likely due to the limited number of patients (n=17) enrolled in the musculoskeletal body region population. Furthermore, non-inferiority (95% CI of the difference above the non-inferiority margin of -0.35) has been demonstrated in all body regions for all lesion visualisation criteria for all three readers, except for lesion contrast enhancement in musculoskeletal assessments by reader 1 (on 16 patients) and by reader 3 (on 18 patients) and in internal morphology in head & neck assessments by reader 2 (on 18 patients). These findings indicate that the primary objective 2 has not been met for the body region musculoskeletal, since to be successful at least 2 out of 3 readers should have shown non-inferiority for all 3-coprimary criteria simultaneously. This negative finding is likely due to the limited number of patients enrolled in the musculoskeletal body region population. Subgroup analyses for the lesion visualisation criteria showed, in general also, consistent results between body organs (breast, liver, kidney, pancreas, and prostate). More specifically, the primary objective 1 for the body organs breast, liver, pancreas, kidney and prostate, was met. Furthermore, the primary objective 2 has been met for the body organs breast, and liver, but not for the body organs pancreas (n= 8-10 depending on the reader), kidney (n=3-7), and prostate (n=8-11). These negative findings are also likely due to the very limited number of patients enrolled in these specific organ subsets. In this respect, the applicant was requested to justify that the results can be extrapolated to these specific body regions/organs which appeared to be underrepresented. According to the Appendix 1 of the Guideline on Clinical evaluation of diagnostic agents (CPMP/EWP/1119/98 rev. 1), major systems that should be systematically included in trials for a whole-body indication concern those in which the imaging agent would be expected to exhibit different pharmacokinetic behaviours. These systems include the brain, liver, and blood vessels. No discussion on the technical performance of gadopiclenol on MRI imaging of the heart and blood vessels has been provided by the applicant since no indication for heart and blood vessels has been requested. Regarding kidneys which were underrepresented in the study, the

applicant classified all body organs and conditions in the determinants of contrast enhancement "blood perfusion and vessel permeability" in their response to LoQ, as such, no discrimination between, for example, the organs liver and kidney has been made, which is not in line with the guideline stating that different pharmacokinetic behaviours can be expected between the liver and kidneys. Nevertheless, although the primary objective 2 has not been met for kidneys, considering that subgroup analyses for the lesion visualisation criteria showed in general consistent results for MRI of the kidneys compared with other organs and that the active comparator is also indicated for MRI of the kidneys, it is considered acceptable to extrapolate the positive results of the other organs to the underrepresented body regions/organs, including head & neck and musculoskeletal and pancreas, kidneys, and prostate. Furthermore, a specific discussion or data on the subgroup analyses of the primary endpoints regarding different stages of the underlying diseases, lesion type (malignant tissue, neovascular lesions or different extent of vascular barrier changes) or for patients who underwent surgery or radiation therapy (yes/no) have not been provided. Instead, the applicant substantiated that three factors determine the behaviour of extracellular GBCA in tissues: 1) blood perfusion; 2) transport of contrast agent across vessel walls; and 3) diffusion of contrast medium in the interstitial space, which all lead back to different tissue perfusion independently of their nature, e.g., neoplastic vs inflammatory, their organ location, e.g., breast vs prostate, their stage, e.g., in-situ cancer vs advanced cancer and patient population, i.e., adults vs children. Although the three factors determining the behaviour of extracellular GBCA in tissues are acknowledged, there are no clinical data to support the applicant's claims that gadopiclenol and gadobutrol will exhibit similar patterns of contrast enhancement and consequently similar diagnostic performance for body imaging of patients with inflammatory, infectious or autoimmune conditions. Such conditions include acute/chronic pancreatitis, inflammatory bowel disease, inflammatory diseases of the head and neck region and endometriosis. Similarly, there are no clinical data to support the similar diagnostic performance of these agents for body imaging in patients following neoadjuvant chemotherapy. Therefore, information on no or limited data in specific conditions has been included in section 4.4., which is considered appropriate. It is known that the MRI diagnosis is particularly difficult in patients who underwent surgery or radiation therapy. A such, a subgroup analysis of the primary endpoints for patients who underwent surgery or radiation therapy (yes/no) has been provided. This analysis showed that non-inferiority of gadopiclenol compared to gadobutrol was demonstrated for all endpoints and all three readers (a lower limit of the 95% CI of the difference not lower than -0.14, that is largely above the non-inferiority margin of – 0.35) in both patient populations, indicating that both contrast agents showed adequate technical performance regardless of previously treated or not with surgery or chemotherapy.

Paired images with gadopiclenol showed improvements compared to pre-contrast images for all secondary endpoints. More importantly, similar or better results for all secondary endpoints were observed for paired images with gadopiclenol compared with paired images of gadobutrol. More specifically, for evaluation of improvement in lesion visualisation scores at patient-level, both paired images with gadopiclenol and paired images with gadobutrol scored better than pre-contrast images in more than 97% of the evaluations for two readers for all three criteria. In contrast, somewhat lower scores (34.4% to 84.8%) were observed with the other reader, which were, however, slightly higher with gadopiclenol compared with gadobutrol, which is reassuring. Assessment of lesion visualisation criteria at lesion level by MRI modality and by contrast agents showed similar results to those obtained at patient level. for paired images with gadopiclenol compared with pre-contrast images, and for MRI with gadopiclenol vs MRI in gadobutrol showed similar results to those obtained at patient level. Additionally, assessments based on lesion size for MRI with gadopiclenol compared with MRI with gadobutrol showed that the differences in mean of scores for each criterion was close to 0 in all cases, with a lower limit of the 95% CI of the difference not lower than -0.31 for each lesion size category (≤ 1 cm, >1 cm and ≤2 cm, >2 cm), indicating that also for smaller lesions (≤1 cm) gadopiclenol is non-inferior

to gadobutrol. Moreover, there is no trend for lower lesion visualisation scores with smaller lesions, i.e., the results were consistent overall lesion size categories. Regarding technical adequacy of images, similar ratings were found for pre-contrast and paired images with a large majority of "good" adequacy (pre-contrast images: 96.5%, 83.6%, and 73.9% and for paired images: 93.4%, 87.1%, and 70.6% for reader 1, 2, and 3 respectively). Paired images with gadopiclenol or gadobutrol showed similar technical adequacy scores, with more than 87% of the examinations graded good for readers 1 and 2 and more than 80% for reader 3. Most of the patients presented only one *lesion* (38.8 to 61.6% for extended FAS 1 and 48.0 to 61.7% for extended FAS 2), whereas 12.6 to 18.2% of the subjects for extended FAS 1 and 12.3 to 18.5% of the subjects for extended FAS 2 presented more than 3 lesions. Generally, more lesions were identified with pre-contrast lesions compared with paired images with gadopiclenol (570 vs 533, 449 vs 421, and 569 vs 513 for reader 1, 2 and 3 respectively, see section numbers analysed). The applicant clarified that it is known in routine clinical practice that some lesions can be seen on pre-contrast images but not confirmed with paired images, depending on the pathology. The level of diagnostic confidence markedly improved with paired images compared to pre-contrast images. The level of diagnostic confidence was similar with gadopiclenol and gadobutrol (excellent: 80.4% vs 75.2%, 64.0% vs 68.3%, and 20.8% vs 23.4% for readers 1, 2, and 3, respectively). Regarding radiological diagnosis, the largest difference between pre-contrast and paired images was found for intermediate or moderately high suspicion of malignancy, for which more cases of moderately high suspicion of malignancy in paired images compared with pre-contrast images. No differences could be observed for radiological diagnosis between gadopiclenol and gadobutrol. The percentage of treatment plan changes based on paired images compared with pre-contrast images was similar between both contrast agents (30.1% of the patients for gadopiclenol and 29.3% for gadobutrol), which is expected considering the non-inferiority claim. Furthermore, when analysing the data according to tumour classification based on unenhanced MRI, treatment plan could be changed after MRI with gadopiclenol for 32% of 165 patients with malignant diagnosis, for 14% of 64 patients with non-malignant diagnosis and for 41% of the 22 patients for whom the investigator considered that diagnosis was not assessable (or grade of glial tumour could not be determined) based on unenhanced MRI, indicating that in all types of lesions contrast-enhancement of images affect patient management. There was also no difference between both contrast agents for the change on treatment plan according to tumour classification. Regarding the quantitative parameters, a significantly higher percentage of lesion enhancement was observed for two readers, whereas there was no difference in LBR for all readers. These findings indicate a better/equivalent technical performance of gadopiclenol compared with gadobutrol based on objective quantitative parameters.

Global matched-pairs assessment for overall diagnostic preference by 3 additional independent blinded radiologists showed no clear preference for gadopiclenol or gadobutrol (78.3%, 74.6%, and 82.6% for reader 4, 5, and 6, respectively), whereas preference for gadopiclenol was reported for 13.0%, 14.5%, and 12.0% of the images by reader 4, 5, and 6, respectively, indicating the generally similar or better technical performance of gadopiclenol compared to gadobutrol.

Supportive data was obtained from Study GDX-44-008, a double-centre, non-randomised, open-label exploratory study in female or male adult patients with liver cirrhosis or chronic liver disease. In this proof-of-concept study, a small number of patients (30 patients receiving gadopiclenol 0.1 mmol/kg (cohort 1) and 10 patients receiving gadopiclenol 0.05 mmol/kg (cohort 2)) and nodules were analysed using a standard of reference based on previous imaging and/ or histology. The diagnostic performance (primary objective) for gadopiclenol-enhanced MR showed a sensitivity and specificity of 62% and 86% at the dose of 0.1 mmol/kg, and 80% and 100% at the dose of 0.05 mmol/kg, respectively, in lesions between 3 mm and 3 cm. Accuracy, positive and negative predictive values were 74%, 81% and 70%, respectively, for gadopiclenol at 0.1 mmol/kg and 92%, 100% and 89% for gadopiclenol at 0.05 mmol/kg. These findings suggest that

gadopiclenol at 0.05 mmol/kg may be more appropriate for HCC diagnosis than gadopiclenol at 0.1 mmol/kg. However, the number of patients and number of nodules in each cohort was considered too limited to draw firm conclusions on the appropriate dose. For comparison, in a liver study with gadobutrol, average sensitivity in combined pre and post-contrast MRI for Gadovist-treated patients was 79 % and specificity was 81 % for lesion detection and classification of suspected malignant liver lesions (patient-based analysis)(SPC Gadovist), suggesting that the diagnostic performance of gadopiclenol in patients with liver disease is similar or better compared with gadobutrol. Nevertheless, firm conclusions cannot be made due to the limited number of patients.

For both pivotal studies, similar results were observed in patients with eGFR between 30 and 60 mL/min/1.73m^2 and patients with eGFR above 60 mL/min/1.73 m^2 for both primary objectives.

- ***Additional image evaluation to assess concordance***

GDX-44-010 (CNS)

Lesion level. The additional assessment showed that, at lesion level, 88.0% to 89.8% of the lesions detected with gadobutrol were also detected with gadopiclenol ("perfect matching lesions"), depending on the blinded reader. In patients with a single lesion detected with gadobutrol, this lesion was also detected with gadopiclenol in all cases except 2 (perfect agreement 98.7% to 100% of the cases). Further, the large majority of patients (95%) had no more than 10 lesions in the CNS, and among the patients with no more than 10 lesions, the percentage of perfect matching lesions was even higher (92.5% to 94.6%). This indicates that discordances were mostly reported in patients with a high number of lesions (>10 lesions), that is, in clinical situations where the number of lesions does not matter anymore for patient management, according to the applicant. Importantly, there was approximately a similar number of additional lesions seen only with gadobutrol (61 to 90, depending on the reader) or seen only with gadopiclenol (54 to 78, depending on the reader).

Patient level. At patient level, a relatively high perfect agreement between gadopiclenol and gadobutrol was observed (84.3% to 86.0% of the patients). Depending on the reader, among the 235 assessed patients, in addition to the perfect matches, 31 to 36 patients (13.2% to 15.3%) had perfect matching lesions and additional lesions seen with only one of the contrast agents. Only 1 or 2 patients (0.4% to 0.9%) had no perfect matching lesions.

Discordant lesions. Between 10% and 12% of the lesions detected with gadobutrol (61 to 90 lesions, depending on the reader) were not detected with gadopiclenol. It was highlighted by the applicant that 43 out of the 90 discordant lesions reported for Reader 3 were from only 3 patients with 61 to 100 lesions detected with gadobutrol, which is in a clinical situation where numbers do not matter any longer as far as potential implications on patient management are concerned, which is acknowledged. The lesions only detected with gadobutrol were mostly secondary malignant lesions. In the majority of the discordant lesions (73% to 89%) the readers attributed the reason for discordance to themselves, i.e. lesion overlooked. Importantly, a similar pattern was observed for the 6.4% to 12.3% lesions detected with gadopiclenol (54 to 78 lesions) but not detected with gadobutrol, which is reassuring.

Clinical impact. Among the 60 patients with discordant lesions for at least one reader, no potential clinical impact was identified for 40 patients. The main reason was that the discordant lesions were identified/not identified in patients with multiple brain metastases, when additional identified lesions do not have impact on patient management any longer (e.g., if already a whole brain radiation therapy would be the treatment of choice for the patient). Lesions detected with only gadobutrol and not gadopiclenol or vice versa had a

potential impact on patient management according to at least one reader for 20 patients (8.5%): due to lesions only seen with gadobutrol for 6 patients, lesions only seen with gadopiclenol for 7 patients, and both cases for 7 patients for at least one reader. The clinical impact was indicated as "possible target for stereotactic radiosurgery (SRS)" for 16 patients with brain metastatic disease, which was the patient population with the largest number of discordances, or a modification in the indication to different techniques of radiotherapy in the 4 other patients. For 17 patients, the cause of discordance was only attributed to the reader. In two cases, the lesion was not detected because it was covered by artifacts or not covered by the exam. The contrast agent was the potential cause of discordance for 2 patients: in one patient, the lesion was only seen with gadopiclenol and in the other patient 2 lesions were seen only with gadopiclenol and one only with gadobutrol. Therefore, only one discordance due to a lesion seen with gadobutrol but not with gadopiclenol could have had a potential clinical impact on patient management, which is reassuring.

Intra-reader and inter-reader variability. The intra-reader agreement was assessed on 10% of the images by all reader. The intra-reader agreement was 92.1% with both contrast agents for Reader 2, 100% with gadopiclenol and 96.1% with gadobutrol for Reader 3 and 85.7% with gadopiclenol and 89.1% with gadobutrol for Reader. Overall, there are no large differences in the intra-reader variability between the two contrast agents, which is reassuring. Regarding inter-reader agreement, at least 2 out of 3 readers agree for 74.8% of the lesions with gadopiclenol and 75.4% of the lesions with gadobutrol. The inter-reader agreement was similar for lesions seen with gadobutrol or lesions seen with gadopiclenol, which is reassuring.

GDX-44-011 (Body)

Lesion level. Relatively high percentages of perfect matching lesions were observed in the body MRI study (89.5% to 100% for head & neck, 88.3% to 92.2% for thorax, 91.7% to 100% for pelvis, 94.6% to 95.2% for abdomen, and 100% for musculoskeletal, depending on the blinded reader). Similar as observed with CNS, there was a comparable number of additional lesions seen only with gadobutrol or seen only with gadopiclenol.

Patient level. At patient level, a relatively high perfect agreement between gadopiclenol and gadobutrol was observed for pelvis (87.5% to 94.6% of the patients, depending on reader), abdomen (84.0% to 87.2%), and musculoskeletal (100%). A lower percentage of perfect agreement between gadopiclenol and gadobutrol was observed for head & neck (70.6% to 94.1%) and thorax (69.8% and 73.2%). An explanation for these lower percentages has not been provided. Although the lower percentage of perfect agreement for reader 2 in the head & neck group of 70.6% might be explained by the low number of patients (n=17), an explanation for the thorax results is not at hand. Nevertheless, the discordances in lesions in the thorax group were almost all attributed to the reader. Additionally, the discordances did not highlight any concern regarding clinical impact (see below), which is reassuring.

Discordant lesions. In head & neck imaging, 0 to 2 lesions were only detected with gadobutrol while 1 to 6 lesions were only detected with gadopiclenol, depending on the reader. Among the lesions only seen with gadobutrol, one was assessed as a primary malignant lesion and all others were assessed as "not a true lesion". The cause of discordance was attributed to the reader in all cases, which is reassuring.

In thorax imaging (including breast imaging), there was a similar number of lesions only detected with gadobutrol (17 to 30) and only detected with gadopiclenol (20 to 30, depending on the reader). These lesions were mainly assessed as "non-malignant" and rarely as "not a true lesion". The cause of discordance was attributed to the reader for all lesions only seen with gadobutrol or only seen with gadopiclenol, with the exception of 6 lesions detected only with gadopiclenol, which were identified as "other reasons", which is reassuring.

In pelvis imaging, again the numbers of lesions only seen by one GBCA were similar for gadobutrol (0 to 13 lesions) and gadopiclenol (4 to 10 lesions, depending on the reader). These lesions were non-malignant for all lesions only seen with gadobutrol and the majority of lesions only seen with gadopiclenol. The reason for discordance was attributed to the reader or another reason reported as a technical issue (motion, partial volume, volume averaging), similarly for gadobutrol and gadopiclenol, which is reassuring.

In abdomen imaging, 16 to 19 lesions were only seen with gadobutrol, and 18 to 33 lesions were only seen with gadopiclenol. The nature of the lesion was variable for gadobutrol as well as for gadopiclenol The cause of discordance was attributed to the reader in the majority of cases, but also to other technical reasons (partial volume, motion artefact, motion and contrast timing, volume averaging).

No discordant lesions were detected for musculoskeletal imaging (100% concordance for all readers).

Clinical impact. Among the 84 patients with discordant lesions for at least one reader, no potential impact on patient management was identified for 75 patients. The rationale for considering that the lesions detected with only one contrast agent had no impact were mostly "potentially not a true lesion" in head & neck imaging, "potentially malignant lesion in a clinical situation when numbers do not matter any longer" or "potentially non-malignant lesion to be left untouched" in thorax imaging, and "potentially non-malignant lesion to be left untouched" in pelvis imaging. Lesions detected with only gadobutrol and not gadopiclenol or vice versa had a potential impact on patient management according to at least one reader for 9 patients: due to lesions only seen with gadobutrol for 1 patient, lesions only seen with gadopiclenol for 6 patients, and both cases (lesions only detected with gadobutrol and lesions only detected with gadopiclenol for the same patient) for 2 patients. The rationale for clinical impact was mainly "possible target for therapy". The cause of discordance was attributed to the reader for 7 patients and to "partial volume effect" in 2 patients. Importantly, in no case the contrast agent was mentioned as reason for discordance, which is reassuring.

Intra-reader and inter-reader variability. The intra-reader agreement was 100% with all images for all 3 readers for head & neck (assessed on 2 patients), 92.9% to 98% with gadopiclenol and 90.4% to 93.9% with gadobutrol for thorax images, and 85.7% to 96.7% with gadopiclenol and 88.5% to 91.5% with gadobutrol for images from other body regions. Overall, the intra-reader agreement was relatively high and there are no large differences in the intra-reader agreement between the two contrast agents, which is reassuring. Regarding inter-reader agreement, at least 2 out of 3 readers agree for 60.8% of the images with gadopiclenol and 51% of the images with gadobutrol for head & neck, 60.8% and 62.8%, respectively, for thorax and 75.9% and 77.7%, respectively, for the other body regions. The inter-reader agreement was approximately similar for lesions seen with gadobutrol or lesions seen with gadopiclenol, which is reassuring.

Overall, it can be concluded that the assessment of lesion detectability showed a good concordance between gadopiclenol at 0.05 mmol/kg and gadobutrol at 0.1 mmol/kg, and did not highlight any concern regarding clinical impact of discordant findings.

Additional expert consultation

Not applicable.

Assessment of paediatric data on clinical efficacy

The paediatric study GDX-44-007 was an open-label, uncontrolled multi-centre international study to evaluate the PK, safety, and efficacy of gadopiclenol-enhanced MRI (0.05 mmol/kg) in CNS and body in

paediatric patients from 2 to 17 years of age to support the proposed paediatric indication. The study included two cohorts, i.e., a CNS and a Body cohort. The CNS cohort included 60 patients distributed in three age groups, i.e., 2-6, 7-11 and 12-17 years (20 patients in each group), whereas the Body cohort included 20 patients (6 aged 2-6, 3 aged 7-11 and 11 aged 12-17 years).

In the CNS cohort of study GDX-44-007, the main diagnosis was congenital brain abnormality (26.5%), followed by primary tumour (14.7%), inflammatory disease (11.8%) and vascular or neurodegenerative disease (8.8% each). Other various diagnoses (29.4%) included mainly cysts and neurofibromatosis. The included CNS disorders can be considered adequately represented and are in line with the CNS disorders encountered in clinical practice. It is obvious that due to the limited number of patients included in the body cohort that several lesion types are under- or not represented.

The technical adequacy was improved for paired images compared with pre-contrast images in the Body cohort (level of good: 90.0% vs 80.0%), whereas the difference was less pronounced in the CNS cohort (level of good: 98.3% vs 95.0%). The observation of low contrast enhancement can be explained by the high number of lesions with no contrast enhancement due to the nature of the lesions, such as congenital malformation and neurodegenerative diseases. Nevertheless, the findings of the paired images are generally comparable with the technical adequacy rated as being good in the adult population (CNS: 80.5 to 95.1% and Body: 70.6 to 93.4% depending on the reader). In the CNS cohort, lesions were observed in 32 patients (53.3%) with pre-contrast images and in 34 patients (56.7%) with paired images with gadopiclenol, indicating that for 2 patients the lesions were only visible with paired images, i.e., after contrast MRI. Regarding the signal intensity of the lesion, there were no clear differences in mean or median signal intensity in the CNS age groups of 12-17 and 7-11 years, whereas there was an increase in mean and median signal intensity of the lesion in paired images compared to pre-contrast images in the 2-6 years group. In the Body cohort, 12 lesions were detected in 11 patients (55.0%) in both pre-contrast and paired images. The median signal intensity of the lesions was increased in paired images compared with pre-contrast images (550 vs 318, respectively).

Regarding quantitative assessment, the mean percentage of lesion enhancement was 11.9% and 101.1% in the paediatric patients of the CNS and Body cohorts, respectively. As already described above, the low percentage of lesion enhancement in the CNS cohort was due to the nature of the lesions. The LBR were 0.9 and 1.68 in the patients of the CNS and Body cohort, respectively. These findings were much lower than those observed in the adult population (% of enhancement of ~200 for CNS and 145 to 220 for Body; LBR of 2.1 for CNS and 2.8 to 4.4 for Body). The observed lower values of % enhancement and LBR can be explained by the difference in the type of disease included in the paediatric and adult studies. The low mean level of percentage of enhancement in the CNS cohort can be explained with high number of lesions with no contrast enhancement due to the nature of the lesions, such as congenital malformations and neurodegenerative diseases. Congenital anomalies, which represent a frequent indication for paediatric MRI, may not necessarily cause contrast enhancement. Overall, no enhancement was observed in the majority of lesions, namely 44 lesions (69.8%) in the paediatric study. In contrast, in the adult CNS study, most patients had some type of brain tumour of which the majority such as meningiomas, metastases, and most gliomas, are known to enhance after contrast injection. Notably, similar to signal intensity of the lesion, subgroup analyses by age group showed a higher percentage of enhancement and LBR for the age group 2-6 years compared with the age groups 12-17 years and 7-11 years. The applicant argued that although the 4 patients in the low age group 2-6 years have lesions with a low potential for contrast enhancement, it is likely that some of the 6 lesions had some degree of contrast enhancement. However, the variability was significant so that the higher mean and median E% and LBR values compared with the other age groups can

be explained by the low number of lesions that were used for SI measurements and quantitative assessment in the age group of 2-6 years. This rationale cannot be completely followed, considering that the variability was even higher in the other age groups. Nevertheless, considering the results found in the adult MRI study can be extrapolated to the paediatric population since the determinants of contrast enhancements in paediatric and adult diseases are the same and the PK profile of gadopiclenol in paediatric patients aged 2 to 18 years are comparable to the PK profile in adults, this issue is not further pursued.

With respect to lesion visualisation criteria, contrast enhancement did not improve lesion border delineation and internal morphology scores compared with pre-contrast images in the CNS cohort (differences of 0.0 and 0.1, respectively). At the same time, a small increase was observed in the degree of contrast enhancement (difference of 0.6). As described above, subgroup analyses by age group showed similar results for lesion border delineation and internal morphology, whereas the degree of contrast enhancement was more pronounced in the 4 patients in the 2-6 years age group. For the Body cohort, slightly higher scores in lesion border delineation and internal morphology scores compared with pre-contrast images were observed (differences of 0.5 and 0.3, respectively), while the improvement in contrast enhancement was more pronounced (difference of 2.4). As with the quantitative objective measurements, the differences in the lesion visualisation scores between pre-contrast and paired images in the paediatric population were smaller than those observed in the adult population. Likewise, as with the quantitative assessment, smaller differences in the lesion visualisation scores between pre-contrast and paired images in the paediatric population compared to the adult population can be explained by the lack of enhancement of some lesions in the paediatric population due to the different histology of paediatric lesions included in the study compared to the adult population. Although less pronounced improvements concerning quantitative parameters and lesion visualisation scores in the paediatric population compared with the adult population have been observed, the investigator's confidence in diagnosis was still improved for most examinations (52.9% for CNS and 63.3% for body MRI).

Overall, administration of gadopiclenol at 0.05 mmol/kg in paediatric subjects 2-17 years old results in enhancement of the CNS and body images in terms of the quantitative parameters (signal intensity, percentage of lesion enhancement and LBR (only for body)) and the qualitative parameters (lesion visualisation score). Diagnostic efficacy was evaluated and there was no difference among the paediatric age groups. Moreover, the applicant has adequately substantiated that results found in the adult CNS and body MRI studies can be extrapolated to the paediatric populations since the determinants of contrast enhancements in paediatric and adult diseases are the same and the PK profile of gadopiclenol in paediatric patients aged 2 to 18 years are comparable to the PK profile in adults.

2.6.7. Conclusions on the clinical efficacy

The superiority of gadopiclenol-enhanced MRI at 0.05 mmol/kg compared to unenhanced MRI (primary objective 1) and non-inferiority of gadopiclenol at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg (primary objective 2) based on a qualitative assessment of 3 lesion visualisation co-primary criteria (border delineation, internal morphology, and degree of contrast enhancement) has been demonstrated in both pivotal studies with CNS and body imaging. The results of the primary objectives were supported by (almost) all secondary endpoints. Nevertheless, there were significant non-concordance findings between gadopiclenol and gadobutrol in the number of lesions detected for both CNS and body, and the nature and the clinical impact of these non-concordance findings remained unclear. In response, an additional assessment of concordance in lesion detectability has been conducted, which showed a good concordance between gadopiclenol at 0.05 mmol/kg and gadobutrol at 0.1 mmol/kg, and did not highlight any concern regarding

clinical impact of discordant findings. Additionally, there were no large differences in the intra- and inter-reader agreement between the two contrast agents. Further, administration of gadopiclenol at 0.05 mmol/kg in paediatric subjects 2-17 years old results in enhancement of the CNS and body images in terms of the quantitative parameters (signal intensity, percentage of lesion enhancement and LBR (only for body)) and the qualitative parameters (lesion visualisation score). Moreover, the applicant has adequately substantiated that results found in the adult CNS and body MRI studies can be extrapolated to the paediatric populations since the determinants of contrast enhancements in paediatric and adult diseases are the same and the PK profile of gadopiclenol in paediatric patients aged 2 to 18 years are comparable to the PK profile in adults.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Among the 1097 subjects included in the eight clinical studies, 1047 were exposed to gadopiclenol: 92 healthy volunteers and 955 patients. Among the patients, exposed to gadopiclenol, 80 (7.6%) were aged 2 to 17 years. CNS imaging was performed for 515 (49.2%) adults and 60 (5.7%) paediatric patients while Body imaging was performed for 328 (31.3%) adults and 20 (25%) paediatric patients. Most subjects (n=708; 67.6%) A total of 999 subjects received only one dose of gadopiclenol and 48 healthy volunteers received two doses of gadopiclenol, one of 0.1 mmol/kg and another of 0.3 mmol/kg in the thorough QT study (GDX-44-006).

Different rates of administration were used for adults compared to children. The injection rate in adults was between 2 and 3 mL/s in adults. In paediatric patients (GDX-44-007 study), the injection rate was 1 to 2 mL/s for patients aged 7 to 17 years (median of 2 mL/s) and 0.3 to 2 mL/s for patients aged 2-6 years (median of 1 mL/s).

Gadopiclenol was administered using manual and power injector. The mode of injection was well balanced between manual (46.8%) and power injector (45.2%).

In cross-over comparative studies, the characteristics of the population were similar for all study products as the same patients received both contrast agents and premature discontinuations were well balanced between randomisation groups. In GDX-44-003 study, demographic characteristics were similar for healthy subjects receiving placebo and those receiving gadopiclenol.

Among the subjects exposed to gadopiclenol, there were more female patients (54%) and age ranged from 2 to 88 years, with a median of 55 years. Most of the subjects (66.6%) were aged 18 to 64 years, nearly 20% were aged 65 to 74 years and 6% were at least 75 years old. Paediatric patients represented 7.6% of the study population exposed to gadopiclenol. The large majority of subjects (82.9%) were White, 9.5% were Asian, 4.8% American Indian or Alaska native, 2.5% Black or African American, 0.3% Native Hawaiian Or Other Pacific Islander. The majority (67.3%) were enrolled in European countries, 12.8% in the USA, 11.6% in Mexico and 8.3% in Asia-Pacific countries.

Regarding risk factors, the population exposed to gadopiclenol included 5.5% of patients with moderate renal impairment (eGFR ≥30 to <60 ml/min/1.73m^2) and 1.5% with severe renal impairment (eGFR <30 ml/min/1.73m^2 + dialysed patients), 11.6% with a history of hypersensitivity (allergic disease), 9.1% with cardiac diseases (coronary heart disease of any type and rhythm disorders), 8.6% with a medical history of convulsions and 6.1% with hepatic insufficiency.

Patients with severe renal impairment were only included in GDX-44-005 study and therefore only received the dose 0.1 mmol/kg. The rate of patients with a history of convulsions was higher among patients receiving gadopiclenol at 0.2 mmol/kg (20.0%).

Most patients (92.9%) who received gadopiclenol had at least one past or current disease. The most common ongoing pathologies at study inclusion were vascular disorders (35.2%, mainly hypertension [31.9%]), nervous system disorders (31.0%, mainly headache [6.6%], epilepsy [4.2%] and seizure [3.5%]), metabolism and nutrition disorders (27.5%, mainly diabetes mellitus [7.6%], Type 2 diabetes mellitus [4.6%], hypercholesterolaemia [5.1%] and hyperlipidaemia [3.8%]), and neoplasms (22.8%, mainly lung adenocarcinoma [2.6%], lung neoplasm malignant [2.5%], breast cancer [2.0%] and invasive ductal breast carcinoma [1.5%]).

2.6.8.2. Adverse events

Overall, 367 subjects (33.5%) experienced at least one AE and the AEs were considered related to the study product for 151 subjects (13.8%). The rates of adverse events were similar between contrast agents (Table 103).

A higher rate of adverse events was reported in Phase I studies including healthy subjects and this rate was similar for gadopiclenol and placebo or with the positive control moxifloxacin in the QT study (GDX-44-006).

Table 103. Overview of Adverse Events by Study Product – All Subjects Exposed (N= 1097)

	Gadopiclenol All doses (N=1047)	Gadobenate dimeglumine (N=256)	Gadobutrol (N=535)	Placebo (N=66)	Moxifloxacin (N=48)	All subjects (N=1097)
At least one AE						
n (%) patients	247 (23.6%)	59 (23.0%)	101 (18.9%)	33 (50.0%)	16 (33.3%)	367 (33.5%)
n AEs	390	95	147	49	18	699
At least one AE related to study product (ADR)						
n (%) patients	89 (8.5%)	31 (12.1%)	33 (6.2%)	10 (15.2%)	5 (10.4%)	151 (13.8%)
n AEs	118	46	38	14	5	221
At least one SAE						
n (%) patients	12 (1.1%)	2 (0.8%)	1 (0.2%)	0	0	15 (1.4%)
n AEs	17	2	1	0	0	20
At least one SAE related to study product						
n (%) patients	1 (<0.1%)	1 (0.4%)	0	0	0	2 (0.2%)
n AEs	1	1	0	0	0	2
At least one AE resulting in death						
n (%) patients	1 (<0.1%)	0	1 (0.2%)	0	0	2 (0.2%)
n AEs	1	0	1	0	0	2
At least one AE leading to study product interruption/ discont.						
n (%) patients	7 (0.7%)	2 (0.8%)	1 (0.2%)	0	0	10 (0.9%)
n AEs	7	4	1	0	0	12

When analysed by dose of gadopiclenol, the frequency of patients experiencing at least one AE related to gadopiclenol was higher with high doses (Table 104). A higher frequency of headache and gastrointestinal disorders related to gadopiclenol was reported among subjects receiving a dose of 0.2 or 0.3 mmol/kg and a higher frequency of injection site pain was also reported among patients receiving gadopiclenol at 0.2 mmol/kg.

Table 104. Overview of Adverse Events by Dose of Gadopiclenol – All Subjects Exposed to Gadopiclenol (N= 1047)

	Gadopiclenol dose (mmol/kg)					
	0.025 (N=62)	**0.05 (N=708)**	**0.075 (N=9)**	**0.1 (N=197)**	**0.2 (N=65)**	**0.3 (N=54)**
At least one AE						
n (%) patients	16 (25.8%)	119 (16.8%)	3 (33.3%)	71 (36.0%)	25 (38.5%)	25 (46.3%)
n AEs	22	188	4	96	43	37
At least one AE related to IMP (ADR)						
n (%) patients	4 (6.5%)	33 (4.7%)	0	26 (13.2%)	17 (26.2%)	10 (18.5%)
n AEs	8	40	0	33	26	11
At least one SAE						
n (%) patients	0	7 (1.0%)	1 (11.1%)	3 (1.5%)	1 (1.5%)	0
n AEs	0	12	1	3	1	0
At least one SAE related to IMP						
n (%) patients	0	0	0	1 (0.5%)	0	0
n AEs	0	0	0	1	0	0
At least one AE resulting in death						
n (%) patients	0	0	0	1 (0.5%)	0	0
n AEs	0	0	0	1	0	0
At least one AE leading to IMP interruption/ discontinuation						
n (%) patients	0	4 (0.6%)	0	1 (0.5%)	2 (3.1%)	0
n AEs	0	4	0	1	2	0

Common adverse events

Most post-injection AEs related to gadopiclenol were reported in the System Organ Class (SOC) "General disorders and administration site conditions" (49 AEs in 42 patients, 4.0%), followed by "Nervous system disorders" (21 AEs in 19 patients, 1.8%) and "Gastrointestinal disorders" (18 AEs in 15 patients, 1.4%). These results were similar for the comparators (gadobenate dimeglumine and gadobutrol).

The most common AEs with gadopiclenol (reported in at least 10 subjects) are presented by decreasing frequency in Table 105. Headache and injection site pain were the most frequent AEs overall as well as in each individual study. Overall, the most frequently reported AEs considered related to gadopiclenol by the investigators were reactions at injection site (pain, coldness, oedema, warmth, haematoma, erythema and inflammation), gastrointestinal disorders (nausea, diarrhea, vomiting, abdominal pain) and other nervous or general disorders such as headache, fatigue, dizziness. Diarrhea and abdominal pain were reported only after gadopiclenol and not after exposure to gadobutrol or gadobenate meglumine, however these events can be expected with GBCAs and frequency was low (0.2% to 0.4%).

Table 105. Most frequent adverse events (occurring in at least 10 subjects with gadopiclenol)

	Gadopiclenol (N=1047)		**Gadobenate dimeglumine (N=256)**		**Gadobutrol (N=535)**	
	All	related	All	related	All	related
Headache	41 (3.9%)	14 (1.3%)	6 (2.3%)	4 (1.6%)	9 (1.7%)	1 (0.2%)
Injection site pain	31 (3.0%)	20 (1.9%)	9 (3.5%)	6 (2.3%)	12 (2.2%)	9 (1.7%)
Dermatitis contact	13 (1.2%)	-	-	-	2 (0.4%)	-

Nausea	15 (1.4%)	7 (0.7%)	9 (3.5%)	9 (3.5%)	5 (0.9%)	2 (0.4%)
Injection site haematoma	11 (1.1%)	1 (0.1%)	-	-	1 (0.2%)	-
Dizziness	10 (1.0%)	3 (0.3%)	4 (1.6%)	2 (0.8%)	2 (0.4%)	-

Most reported AEs (84.8%) were of mild intensity, 12.3% were of moderate intensity and 2.7% were of severe intensity. Three severe AEs were considered related to gadopiclenol: injection site pain in two patients and upper abdominal pain in one of these patients, all occurring within one hour after injection and all resolved within 1 day.

Overall, 96.1% of AEs resolved. AEs not resolved at the end of the study (3.4%) were mostly abnormal laboratory values, worsening of pre-existing diseases or local reactions. Two of these AEs were considered related to the contrast agent: electrocardiogram QT prolonged related to gadopiclenol and Cystatin C increase related to gadobutrol.

Adverse Events of Special Interest (AESI)

AESIs were defined in the studies as:

- Suspected NSF or symptoms suspected to be related to NSF in all studies except GDX-44-003. No suspected NSF or NSF-related symptoms were reported in any study, including during the follow-up periods of 3 months in GDX-44-007 study and 6 months in GDX-44-005 study.

- 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 study. No AESI was reported in this study.

- Decrease in kidney function characterised by an increase in serum creatinine by more than 25% or 0.5 mg/dl (44 µmol/l) compared to the value measured at inclusion, occurring between inclusion and discharge in GDX-44-005 study. In this study, during the follow-up period, one AESI was reported in a patient with severe renal impairment: 7 days after gadopiclenol administration, the subject experienced an increase in creatinine of more than 0.5 mg/dL compared to the value at inclusion (from 2.68 at baseline to 3.21 mg/dL). This AESI was of mild intensity, assessed as not serious, not related to gadopiclenol, and resolved within 28 days. This patient also experienced an SAE "congestive heart failure" 20 days after gadopiclenol exposure.

Tabulated list of adverse reactions

Among the 390 AEs (related or not) reported after exposure to gadopiclenol (all doses included) in 247 subjects (23.6%), a total of 118 AEs in 89 subjects (8.5%) were assessed by the investigator as related to the administration of gadopiclenol. Only one related AE (blood creatinine increased) met a seriousness criterion. This SAE was considered as a SUSAR and reported as such to regulatory authorities. After the investigator's causality assessment, a Pharmacovigilance expert from the sponsor carried out a second assessment of the AEs (i.e. of those assessed as related to gadopiclenol and those assessed as unrelated by the investigator but expected with the class of GBCAs). The analysis was based on the prior knowledge of the safety profile of the product as determined by the preclinical studies, and on the review of each subject medical history (concomitant disease and treatment were considered), the delay of appearance and resolution of the events, and their severity.

The below table summarise adverse reactions based on clinical trials including 1047 subjects exposed to gadopiclenol ranging from 0.05 mL/kg BW (equivalent to 0.025 mmol/kg BW) to 0.6 mL/kg BW (equivalent

to 0.3 mmol/kg BW). The adverse reactions are listed below by SOC (System Organ Class) and by frequency with the following guidelines: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000).

Table 106. Adverse reactions reported following gadopiclenol administration

System Organ Class	Frequency	
	Common	Uncommon
Immune system disorders	-	Hypersensitivity*
Nervous System Disorders	Headache	Dysgeusia
Gastrointestinal Disorders	-	Diarrhoea, Nausea, Abdominal pain, Vomiting
General Disorders and Administration Site Conditions	Injection site reaction**	Fatigue, Feeling hot

* Including immediate (dermatitis allergic, erythema, dyspnoea, dysphonia, throat tightness, throat irritation, paraesthesia oral and flushing) and delayed (periorbital oedema, swelling, rash and pruritus) reactions.
** Injection site reaction includes the following terms: injection site pain, injection site oedema, injection site coldness, injection site warmth, injection site haematoma and injection site erythema.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Two deaths post-contrast injection were reported in the clinical studies. None of these deaths was considered related to the contrast agent.

Other Serious Adverse Events

No non-fatal SAEs were reported after placebo or Moxifloxacin or gadobutrol.

SAEs were reported after gadobenate dimeglumine in two patients (0.8%) in GDX-44-004 study (seizure considered related to the contrast agent and meningioma surgery not related to the contrast agent).

Eleven patients experienced non-fatal SAEs after gadopiclenol administration, out of which only one (blood creatinine increase) was considered related to gadopiclenol (Table 107).

Table 107. All Serious Adverse Events (overall and those related to gadopiclenol) by System Organ Class and Preferred Term – All Subjects Exposed to Gadopiclenol (N= 1047)

	Gadopiclenol All doses (N=1047)			
	All SAEs n(%) patients	n AEs	Related n(%) patients	n AEs
At least one SAE	**12 (1.1%)**	**17**	**1 (0.1%)**	**1**
General disorders and administration site conditions	**3 (0.3%)**	**3**	**-**	**-**
Condition aggravated	3 (0.3%)	3	-	-
Injury, poisoning and procedural complications	3 (0.3%)	3	-	-
Femoral neck fracture	1 (0.1%)	1	-	-
Head injury	1 (0.1%)	1	-	-
Procedural complication	1 (0.1%)	1	-	-
Cardiac disorders	**2 (0.2%)**	**2**	**-**	**-**
Cardiac failure congestive	1 (0.1%)	1	-	-
*Cardiopulmonary failure**	*1 (0.1%)*	*1*	-	-
Infections and infestations	**2 (0.2%)**	**2**	**-**	**-**
COVID-19	1 (0.1%)	1	-	-
Tonsillitis	1 (0.1%)	1	-	-

	Gadopiclenol All doses (N=1047)			
	All SAEs n(%) patients	n AEs	Related n(%) patients	n AEs
Nervous system disorders	**2 (0.2%)**	**3**	**-**	**-**
Coma	1 (0.1%)	1	-	-
Depressed level of consciousness	1 (0.1%)	1	-	-
Epilepsy	1 (0.1%)	1	-	-
Gastrointestinal disorders	**1 (0.1%)**	**1**	**-**	**-**
Gastric perforation	1 (0.1%)	1	-	-
Investigations	**1 (0.1%)**	**1**	**1 (0.1%)**	**1**
Blood creatinine increased	1 (0.1%)	1	1 (0.1%)	1
Renal and urinary disorders	**1 (0.1%)**	**1**	**-**	**-**
Hydronephrosis	1 (0.1%)	1	-	-
Surgical and medical procedures	**1 (0.1%)**	**1**	**-**	**-**
Abortion induced	1 (0.1%)	1	-	-

MedDRA dictionary version 23.1
*Fatal SAE

Non-fatal SAEs occurred after gadopiclenol at 0.05 mmol/kg in 7 patients, after gadopiclenol 0.075 mmol/kg in 1 patient, after gadopiclenol 0.1 mmol/kg in 2 patients and after gadopiclenol 0.2 mmol/kg in 1 patient.

All non-fatal SAEs are presented in Table 108.

Table 108. Listing of Non-Fatal Serious Adverse Events Reported in Clinical Studies

Study, Subject	Last IMP before the AE	AE duration (days) / Time since last IMP (hr:min)	Preferred Term (Description)	Seriousness criteria	Relationship to contrast agent	Intensity Outcome Action with study product (if any)
GDX-44-003						
1	Gadopiclenol 0.075	1/ 2088:00	Abortion Induced (Therapeutic Abortion)	Congenital Anomaly or Birth Defect	Not Related	Severe Resolved
GDX-44-004						
2	Gadobenate dimeglumine (MRI 2)	1/ 4:13	Seizure (Acute Seizure)	Hospitalisation /Other	Related	Severe Resolved
3	Gadobenate dimeglumine	1/ 65:03	Meningioma Surgery (Surgery For Meningioma Excision)	Hospitalisation	Not related	Moderate Resolved Drug Withdrawn
4	Gadopiclenol 0.1	21/ 22:28	Blood Creatinine Increased (Creatinine Increase Critical)	Other	Related	Mild Resolved Drug Withdrawn
5	Gadopiclenol 0.2	3/ 267:09	Femoral Neck Fracture (Right Femoral Neck Fracture)	Hospitalisation	Not Related	Severe Resolved Drug Withdrawn
GDX-44-005						
6	Gadopiclenol 0.1	7/ 480:00	Cardiac Failure Congestive (Congestive Heart Failure)	Hospitalisation	Not Related	Mild Resolved
GDX-44-007						
7	Gadopiclenol 0.05	10/ 553:16	Tonsillitis (Undefined Acute Tonsilliti)s	Hospitalisation	Not Related	Mild Resolved
8	Gadopiclenol 0.05	15/ 162:51	Hydronephrosis (Worsening Of Right Hydronephrosis)	Hospitalisation	Not Related	Moderate Resolved
			Condition Aggravated (Worsening Of Right Hydronephrosis)	Hospitalisation	Not Related	Moderate Resolved
9	Gadopiclenol 0.05	./ 1560:00	Epilepsy (Epilepsy)	Hospitalisation/ Other	Not Related	Moderate Not resolved
		./ 1560:00	Condition Aggravated (Worsening Of Neurodegenerative Disease)	Hospitalisation/ Other	Not Related	Moderate Not resolved
		1/ 1560:00	Head Injury (Head Injury)	Hospitalisation	Not Related	Mild Resolved
		15/ 1560:00	Coma (Coma)	Hospitalisation/ Life Threatening/ Other	Not Related	Moderate Resolved
GDX-44-008						
10	Gadopiclenol 0.05	1/ 336:00	Procedural Complication (Complicated Biopsy)	Hospitalisation	Not Related	Severe Resolved
		7/ 336:02	Gastric Perforation (Gastric Perforation)	Hospitalisation	Not Related	Severe Resolved
GDX-44-011						
11	Gadopiclenol 0.05 (MRI 1)	./ 62:30	Condition Aggravated (Worsening of Pre-Existing Condition of Liver Tumour)	Hospitalisation	Not Related	Moderate Not resolved
12	Gadopiclenol 0.05 (MRI 1)	./ 96:00	Depressed Level Of Consciousness (Deterioration Of Consciousness)	Hospitalisation	Not Related	Severe Not resolved Drug Interrupted
13	Gadopiclenol 0.05 (MRI 1)	16/ 177:11	Covid-19 (Covid-19 Infection)	Hospitalisation	Not Related	Mild Resolved Drug Interrupted

Seriousness criteria: Hospitalisation: Requires or Prolongs Hospitalisation; Other: Other Medically Important Serious Event

2.6.8.4. Laboratory findings

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

Few laboratory results were clinically significant and reported as AEs. They are presented in Table 109.

Table 109. Adverse Events related to Clinically Significant Abnormal Laboratory Results

	Gadopiclenol All doses (N=1047)		Gadobenate dimeglumine (N=256)		Gadobutrol (N=535)	
	All n(%)	Related n(%)	All n(%)	Related n(%)	All n(%)	Related n(%)
Investigations						
Blood creatinine increased	4 (0.4%)	3 (0.3%)	2 (0.8%)	2 (0.8%)	6 (1.1%)	2 (0.4%)
Cystatin C increased	1 (0.1%)	1 (0.1%)	-	-	1 (0.2%)	1 (0.2%)
Blood urea increased	-	-	1 (0.4%)	1 (0.4%)	-	-
Glomerular filtration rate decreased	-	-	-	-	1 (0.2%)	1 (0.2%)
Hepatic enzyme increased	1 (0.1%)	-	2 (0.8%)	-	-	-
Alanine aminotransferase increased	1 (0.1%)	-	-	-	-	-
Blood phosphorus decreased	1 (0.1%)	-	-	-	-	-
White blood cell count increased	-	-	-	-	1 (0.2%)	-
Eosinophil count increased	1 (0.1%)	-	-	-	-	-
Neutrophil count decreased	1 (0.1%)	-	-	-	-	-
Neutrophil count increased	1 (0.1%)	-	-	-	1 (0.2%)	-
Urobilinogen urine	1 (0.1%)	-	-	-	-	-
Renal and urinary disorders						
Leukocyturia	5 (0.5%)	-	4 (1.6%)	-	-	-
Proteinuria	3 (0.3%)	-	-	-	-	-
Bilirubinuria	2 (0.2%)	-	2 (0.8%)	-	-	-
Glycosuria	1 (0.1%)	-	2 (0.8%)	-	-	-
Haematuria	1 (0.1%)	-	2 (0.8%)	-	-	-
Haemoglobinuria	1 (0.1%)	-	2 (0.8%)	-	-	-
Nephropathy	1 (0.1%)	-	-	-	1 (0.2%)	-
Renal failure	1 (0.1%)	1 (0.1%)	-	-	-	-
Acute kidney injury	-	-	-	-	1 (0.2%)	1 (0.2%)
Ketonuria	-	-	1 (0.4%)	-	-	-
Nitrituria	-	-	1 (0.4%)	-	-	-
Renal impairment	-	-	-	-	2 (0.4%)	1 (0.2%)
Metabolism and nutrition disorders						
Hypertriglyceridaemia	2 (0.2%)	-	1 (0.4%)	-	-	-
Hyperglycaemia	1 (0.1%)	-	-	-	-	-
Hyperkalaemia	1 (0.1%)	1 (0.1%)	-	-	1 (0.2%)	1 (0.2%)
Hypoglycaemia	1 (0.1%)	-	-	-	-	-
Hypokalaemia	1 (0.1%)	-	-	-	-	-

The shift table by dose of gadopiclenol did not show any dose effect.

Table 110. Shift Table of Creatinine, eGFR, BUN and Cystatin C between Baseline Measurement and Post-Injection Measurement – SI units – by Study Product – All Subjects Exposed (N= 1097)

	Post-injection measurement: Relative change from Baseline									
	≤ -50%	>-50% and ≤-25%	>-25% and ≤-15%	>-15% and <0%	≥ 0% and <15%	≥15% and <25%	≥25% and <50%	≥50%	Not applicable	Missing
Creatinine (µmol/L)										
Gadopiclenol All doses	0	9(0.8%)	32(2.9%)	449(41.0%)	512(46.8%)	58(5.3%)	24(2.2%)	3(0.3%)	0	15(1.4%)
Gadobenate dimeglumine	0	1(0.4%)	7(2.7%)	99(38.7%)	120(46.9%)	18(7.0%)	5(2.0%)	0	0	6(2.3%)
Gadobutrol	0	4(0.7%)	26(4.9%)	205(38.3%)	240(44.9%)	34(6.4%)	15(2.8%)	4(0.7%)	0	9(1.7%)
Placebo	0	0	0	25(37.9%)	36(54.5%)	4(6.1%)	1(1.5%)	0	0	0
Moxifloxacin	0	0	2(4.2%)	13(27.1%)	32(66.7%)	1(2.1%)	0	0	0	0

	Post-injection measurement: Relative change from Baseline									
	≤ -50%	>-50% and ≤-25%	>-25% and ≤-15%	>-15% and <0%	≥ 0% and <15%	≥15% and <25%	≥25% and <50%	≥50%	Not applicable	Missing
Total	0	14(0.7%)	67(3.4%)	791(39.6%)	940(47.0%)	115(5.8%)	45(2.3%)	7(0.4%)	0	30(1.5%)
eGFR (mL/min/1.73m²)										
Gadopiclenol All doses	1(0.1%)	14(1.3%)	53(4.8%)	384(35.1%)	521(47.6%)	50(4.6%)	20(1.8%)	2(0.2%)	0	57(5.2%)
Gadobenate dimeglumine	0	4(1.6%)	19(7.4%)	106(41.4%)	102(39.8%)	15(5.9%)	4(1.6%)	0	0	6(2.3%)
Gadobutrol	0	11(2.1%)	33(6.2%)	184(34.4%)	264(49.3%)	24(4.5%)	11(2.1%)	1(0.2%)	0	9(1.7%)
Placebo	0	0	2(3.0%)	23(34.8%)	26(39.4%)	0	0	0	0	15(22.7%)
Moxifloxacin	0	0	0	28(58.3%)	18(37.5%)	1(2.1%)	1(2.1%)	0	0	0
Total	1(0.1%)	29(1.5%)	107(5.4%)	725(36.3%)	931(46.6%)	90(4.5%)	36(1.8%)	3(0.2%)	0	87(4.4%)
BUN (mmol/L)										
Gadopiclenol All doses	7(0.6%)	90(8.2%)	122(11.1%)	266(24.3%)	302(27.6%)	112(10.2%)	104(9.5%)	26(2.4%)	48(4.4%)	18(1.6%)
Gadobenate dimeglumine	0	20(7.8%)	34(13.3%)	63(24.6%)	70(27.3%)	30(11.7%)	23(9.0%)	7(2.7%)	0	9(3.5%)
Gadobutrol	1(0.2%)	42(7.9%)	72(13.5%)	136(25.4%)	151(28.2%)	64(12.0%)	50(9.3%)	14(2.6%)	0	5(0.9%)
Placebo	0	3(4.5%)	13(19.7%)	15(22.7%)	11(16.7%)	2(3.0%)	4(6.1%)	0	18(27.3%)	0
Moxifloxacin	0	3(6.3%)	4(8.3%)	16(33.3%)	18(37.5%)	3(6.3%)	3(6.3%)	1(2.1%)	0	0
Total	8(0.4%)	158(7.9%)	245(12.3%)	496(24.8%)	552(27.6%)	211(10.6%)	184(9.2%)	48(2.4%)	66(3.3%)	32(1.6%)
Cystatin C (mg/L)										
Gadopiclenol All doses	0	8(0.7%)	17(1.6%)	317(28.9%)	360(32.9%)	33(3.0%)	7(0.6%)	4(0.4%)	184(16.8%)	165(15.1%)
Gadobenate dimeglumine	1(0.4%)	1(0.4%)	5(2.0%)	56(21.9%)	102(39.8%)	7(2.7%)	5(2.0%)	0	0	79(30.9%)
Gadobutrol	0	4(0.7%)	21(3.9%)	242(45.2%)	222(41.5%)	27(5.0%)	10(1.9%)	4(0.7%)	0	5(0.9%)
Placebo	0	0	0	0	0	0	0	0	66(100.0%)	0
Moxifloxacin	0	0	0	0	0	0	0	0	48(100.0%)	0
Total	1(0.1%)	13(0.7%)	43(2.2%)	615(30.8%)	684(34.2%)	67(3.4%)	22(1.1%)	8(0.4%)	298(14.9%)	249(12.5%)

%: (n row / N column ALL) * 100. SI: Standard International; BUN: Blood Urea Nitrogen; eGFR: estimated Glomerular Filtration Rate
After injection : 24h after administration or 48h after administration if no value measured at 24h
Not applicable : Urea Nitrogen not measured in GDX-44-003 study ; Cystatin C not measured in GDX-44-003, GDX-44-005 and GDX-44-006 studies
Because of cross-over studies, one patient could receive multiple products and have several measurements

Blood Pressure, Heart Rate and body temperature

No relevant or consistent changes in median values of blood pressure and heart rate were observed in any clinical study. Overall results are presented in Table 111.

Table 111. Overall Values and Changes in Blood Pressure and Pulse Rate

	Gadopiclenol All doses (N=1047)		Gadobenate dimeglumine (N=256)		Gadobutrol (N=535)	
	Raw data	Change from Baseline	Raw data	Change from Baseline	Raw data	Change from Baseline
Systolic Blood Pressure (mmHg)						
Baseline						
n	1047		256		535	
Mean (SD)	124.6 (17.1)		122.5 (15.8)		127.9 (16.0)	
Median	123.0		121.0		127.0	
Min. ; Max.	77 ; 197		80 ; 176		80 ; 197	

	Gadopiclenol All doses (N=1047)		Gadobenate dimeglumine (N=256)		Gadobutrol (N=535)	
	Raw data	Change from Baseline	Raw data	Change from Baseline	Raw data	Change from Baseline
At 45-60 minutes						
n	1045	1044	256	256	534	534
Mean (SD)	123.1 (16.4)	-0.4 (11.9)	121.6 (14.6)	-0.9 (12.9)	127.3 (15.8)	-0.7 (13.4)
Median	121.0	0.0	120.0	0.0	126.0	0.0
Min. ; Max.	70 ; 199	-47 ; 48	90 ; 190	-40 ; 51	73 ; 188	-47 ; 74
Missing data	10	11	0	0	1	1
Not applicable	40 (3.7%)	40 (3.7%)	0	0	0	0
One day after						
n	1077	1077	256	256	532	532
Mean (SD)	122.5 (16.3)	-1.8 (12.7)	120.8 (14.6)	-1.7 (14.6)	125.7 (15.5)	-2.3 (13.0)
Median	120.0	0.0	120.0	0.0	125.0	-2.0
Min. ; Max.	80 ; 202	-49 ; 47	80 ; 174	-56 ; 46	80 ; 181	-64 ; 42
Missing data	18	18	0	0	3	3
Diastolic Blood Pressure (mmHg)						
Baseline						
n	1047		256		535	
Mean (SD)	76.1 (11.0)		75.8 (10.3)		78.6 (10.1)	
Median	77.0		78.0		80.0	
Min. ; Max.	45 ; 113		48 ; 99		45 ; 113	
At 45-60 minutes						
n	1045	1044	256	256	534	534
Mean (SD)	74.9 (11.0)	-0.6 (9.0)	76.2 (9.3)	0.4 (9.8)	78.5 (10.3)	-0.1 (9.4)
Median	75.0	0.0	76.0	0.0	78.5	0.0
Min. ; Max.	43 ; 119	-40 ; 36	52 ; 108	-29 ; 39	42 ; 115	-38 ; 37
Missing data	10	11	0	0	1	1
Not applicable	40 (3.7%)	40 (3.7%)	0	0	0	0
One day after						
n	1077	1077	256	256	532	532
Mean (SD)	74.4 (10.7)	-1.3 (9.2)	75.0 (10.4)	-0.8 (9.7)	77.5 (10.1)	-1.1 (9.3)
Median	75.0	0.0	75.0	0.0	78.5	-1.0
Min. ; Max.	45 ; 119	-45 ; 39	50 ; 108	-40 ; 47	50 ; 110	-40 ; 38
Missing data	18	18	0	0	3	3
Pulse Rate (beats/min)						
Baseline						
n	1047		256		535	
Mean (SD)	73.4 (13.2)		71.7 (11.3)		74.5 (11.8)	
Median	72.0		72.0		73.0	
Min. ; Max.	40 ; 125		40 ; 103		44 ; 125	
At 45-60 minutes						
n	1045	1044	256	256	534	534
Mean (SD)	72.1 (13.6)	-1.1 (9.8)	69.8 (11.7)	-1.9 (9.6)	74.8 (12.2)	0.3 (9.4)
Median	71.0	-1.0	69.0	-1.0	74.0	0.0
Min. ; Max.	40 ; 142	-56 ; 54	38 ; 108	-32 ; 28	43 ; 124	-32 ; 46
Missing data	10	11	0	0	1	1
Not applicable	40 (3.7%)	40 (3.7%)	0	0	0	0
One day after						
n	1077	1077	256	256	532	532
Mean (SD)	73.1 (12.9)	0.1 (9.9)	72.0 (11.1)	0.3 (10.2)	74.9 (11.5)	0.4 (9.2)
Median	72.0	0.0	71.0	0.0	74.0	0.0
Min. ; Max.	40 ; 154	-48 ; 49	36 ; 105	-30 ; 29	43 ; 125	-39 ; 37
Missing data	18	18	0	0	3	3

Few abnormal values related to blood pressure and heart rate were reported as AEs:

Blood pressure increase was reported as an AE in 9 patients (0.9%) after gadopiclenol, 2 patients (0.8%) after gadobenate dimeglumine and 2 patients (0.4%) after gadobutrol. All these AEs were of mild to moderate intensity, did not lead to any change in IMP administration and resolved. None was serious. AEs were considered related to the contrast agent for one patient after gadopiclenol and both patients after gadobenate dimeglumine. Regarding the case related to gadopiclenol, it concerned a 39-year-old male patient who experienced an increase in systolic blood pressure (SBP) from 108 mmHg at baseline to 142 mmHg one hour after gadopiclenol injection. He had a medical history of neurofibromatosis type II, which could increase the risk of hypertension and therefore be a confounding factor.

Hypertension was reported for one patient after gadopiclenol and one patient after gadobenate dimeglumine while hypotension was reported for one patient after gadobenate dimeglumine. None of these AEs was considered related to the contrast agent.

Tachycardia/sinus tachycardia was reported as an AE in one patient (0.1%) after gadopiclenol, one patient (0.2%) after gadobutrol, both not related to the contrast agent, and two patients (0.8%) after gadobenate dimeglumine, considered related to the contrast agent for both patients.

Body temperature increase was reported as an AE for one subject, considered related to gadopiclenol.

ECG Evaluations

No pooling of data has been performed for ECG data. All ECG changes considered as abnormal and clinically significant had to be reported as AEs.

No relevant or consistent changes in median values for ECG intervals were observed after contrast agent administration in GDX-44-003 study (Phase I and Phase IIa) and in GDX-44-005 study (including patients with renal impairment). No ECG findings were reported as AEs. No treatment-emergent QTcB or QTcF values >500 ms or increases in QTcB or QTcF interval from baseline >60 ms were observed during the studies.

In the Phase IIb dose-finding study (GDX-44-004), two cases of abnormal QT interval on ECG were reported as AEs and considered related to gadopiclenol. One case of QTc Bazett's interval >500 ms was reported between 2 and 4 hours after a first injection of gadopiclenol 0.2 mmol/kg (value of 500.3 ms while baseline value was 482.3 ms) and led to the patient’s premature discontinuation from the study. The other case was a QTc value >500ms reported 48 min after gadopiclenol injection at 0.1 mmol/kg. This AE was considered of mild intensity and resolved within one day. No other cases of QTc Bazett's or Fridericia's interval >500 ms was reported and no change from baseline >60 ms was reported for mean of triplicate ECG at the different time points of measurement after gadopiclenol administration.

In the paediatric study (GDX-44-007), the median values of change from baseline in QTc values were negligible and not reported as clinically significant, except in two patients from the CNS cohort, for whom changes in QT interval were reported as AEs: long QT syndrome in a 17-year-old female patient, considered not related to gadopiclenol, and a QT prolongation of mild intensity reported in a 5-year-old male patient, considered related to gadopiclenol. For this latter case, QTcF [QTcB] was 397 ms [465 ms] before injection, increasing to 454 ms [537 ms] 34 minutes after injection and to 467 ms [517 ms] one day after injection. The event was assessed as clinically significant by the investigator but not serious. Of note, this patient experienced strong anxiety during the ECG, that started one hour before gadopiclenol injection (heart rate at 154 bpm) and recovered one day after. The patient was not discontinued from the study after occurrence of

this AE and no corrective treatment was administered. According to the investigator, a possible explanation could be the strong anxiety leading to tachycardia.

The thorough QT/QTc study (GDX-44-006) demonstrated that gadopiclenol did not prolong the QT interval at clinical and supraclinical doses and was well tolerated in healthy volunteers. The upper limit of the 90% CI of the baseline- and placebo-corrected values did not exceed the threshold of regulatory concern of 10 ms for QT and QTc according to population specific correction formula (QTcPOP) at the 11 timepoints tested for the 2 doses of 0.1 and 0.3 mmol/kg, indicating a lack of effect of gadopiclenol on these intervals. No abnormal absolute values or changes from baseline of QTcF, QTcPOP, QRS and PR intervals were noted.

The number of subjects with at least one treatment-emergent ECG abnormality was similar with gadopiclenol 0.1 mmol/kg, gadopiclenol 0.3 mmol/kg and placebo (10.4%, 12.5% and 14.6%, respectively) whereas this number was slightly higher (20.8%) with the positive control. Most of the recorded abnormalities were related to the rhythm and were non-clinically significant.

Tolerance at Injection Site

Overall, 5.7% of the subjects who received gadopiclenol reported at least one reaction at injection site through the specific questionnaire. In studies testing different doses, these AEs were more frequent at higher doses. The rate of patients with at least one intolerance at injection site was similar with gadobutrol (6.4%) and gadobenate dimeglumine (6.6%). In studies where subjects were also injected with placebo, the rate of patients with at least one reaction at injection site was similar for contrast agent and placebo.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Age

- Elderly

The safety of gadopiclenol was assessed in 80 paediatric patients, 697 adult patients aged less than 65 years, 208 patients between 65 and 75 years old, and 62 patients aged 75 years or older (including 2 patients older than 85 years).

The incidence of AEs according to age classes is summarised in:

Table 112. Overview of Adverse Events According to Age Classes – Gadopiclenol All doses (N= 1047)

	≥2 and <7 years (N=26)		≥7 and <12 years (N=23)		≥12 and <18 years (N=31)		≥18 and <65 years (N=697)		≥65 and <75 years (N=208)		≥75 years (N=62)	
	n(%) patients	n AEs	n(%) patients	n AEs	n(%) patients	n AEs	n(%) patients	n AEs	n(%) patients	n AEs	n(%) patients	n AEs
At least one AE	5 (19.2%)	8	6 (26.1%)	11	3 (9.7%)	12	192 (27.5%)	301	33 (15.9%)	50	8 (12.9%)	8
At least one related AE	1 (3.8%)	1	1 (4.3%)	1	-	-	74 (10.6%)	100	11 (5.3%)	14	2 (3.2%)	2
At least one SAE	1 (3.8%)	4	-	-	2 (6.5%)	3	6 (0.9%)	6	3 (1.4%)	4	-	-
At least one related SAE	-	-	-	-	-	-	1 (0.1%)	1	-	-	-	-

In the paediatric population, AEs considered related to the contrast agent were reported for one patient (3.8%) in the age class ≥2 and <7 years (electrocardiogram QT prolonged), one patient (4.3%) in the age class ≥7 and <12 years (rash maculo-papular) and no patient aged 12 to 17 years.

In the adult population aged <65 years, AEs related to gadopiclenol were reported for 74 patients (10.6%), the most frequent being injection site pain, headache and nausea.

In the adult population aged ≥65 years, AEs related to gadopiclenol were reported for 11 patients (5.3%) less than 75 years and 2 patients (3.2%) aged 75 years and more, none older than 85 years. The frequency of AEs was lower than in younger adults and the most frequent related AEs were injection site pain and headache.

The table below details the frequency of AEs that may be of special concern in the older population, by age category. No AEs appear with a higher frequency in older patients (>65 years) compared to younger patients (<65 years).

Table 113. Overall characteristics of AEs in the older population - All subjects exposed to gadopiclenol (N=1047)

	Age < 65 years (N=777)		Age 65-74 years (N=208)		Age 75-84 years (N=60)		Age 85+ years (N=2)	
	Patients	AE	Patients	AE	Patients	AE	Patients	AE
Total AEs	206 (26.5%)	332	33 (15.9%)	50	8 (13.3%)	8	0	0
Serious AEs - Total	9 (1.2%)	13	3 (1.4%)	4	0	0	0	0
Fatal	1 (0.1%)	1	0	0	0	0	0	0
Hospitalization/prolong existing hospitalization	6 (0.8%)	10	3 (1.4%)	4	0	0	0	0
Life-threatening	1 (0.1%)	1	0	0	0	0	0	0
Disability / incapacity	0	0	0	0	0	0	0	0
Congenital abnormality or birth defect	1 (0.1%)	1	0	0	0	0	0	0
Other (medically significant)	2 (0.3%)	4	0	0	0	0	0	0
AE leading to drop-out	4 (0.5%)	4	2 (1.0%)	2	1 (1.7%)	1	0	0
Psychiatric disorders	1 (0.1%)	1	2 (1.0%)	2	0	0	0	0
Nervous system disorders	52 (6.7%)	59	5 (2.4%)	5	2 (3.3%)	2	0	0
Accidents and injuries	2 (0.3%)	2	0	0	0	0	0	0
Cardiac disorders	4 (0.5%)	7	1 (0.5%)	1	0	0	0	0
Vascular disorders	3 (0.4%)	4	1 (0.5%)	1	0	0	0	0
Cerebrovascular disorders	0	0	0	0	0	0	0	0
Infections and infestations	14 (1.8%)	15	2 (1.0%)	2	0	0	0	0
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fracture	7 (0.9%)	7	2 (1.0%)	2	0	0	0	0
Other AEs appearing for at least 2 patients >65 years	94 (12.1)	110	14 (6.7%)	20	6 (10.0%)	6	0	0
Anaemia	0	0	1 (0.5%)	1	1 (1.7%)	1	0	0
Blood creatinine increased	2 (0.3%)	2	2 (1.0%)	2	0	0	0	0
Blood pressure increased	6 (0.8%)	6	2 (1.0%)	2	0	0	0	0
Dizziness	8 (1.0%)	8	2 (1.0%)	2	0	0	0	0
Headache	38 (4.9%)	43	1 (0.5%)	1	2 (3.3%)	2	0	0
Injection site bruising	5 (0.6%)	5	1 (0.5%)	1	1 (1.7%)	1	0	0
Injection site pain	26 (3.3%)	28	5 (2.4%)	6	0	0	0	0
Leukocyturia	3 (0.4%)	3	0	0	2 (3.3%)	2	0	0
Nausea	12 (1.5%)	12	3 (1.4%)	3	0	0	0	0
Vomiting	3 (0.4%)	3	2 (1.0%)	2	0	0	0	0

Only AEs occurring after injection are considered in the analysis
Results are presented as n (%) patients with at least one AE and number of AEs in each category
*%: (n row / N column) *100*

- Paediatric population (2 years and older)

A total of 80 paediatric patients aged 2 years and older were included in the clinical trial. As compared to adults, the safety profile of gadopiclenol in this population did not show any specific safety concern (see 2.6.5.3. and SmPC sections 4.8 and 5.1). A total of 31 Treatment Emergent Adverse Events (TEAEs) occurred

during and/or after gadopiclenol administration for 14 patients (17.5%). Twelve TEAEs were reported in the CNS cohort and 2 in the Body cohort. Among these TEAEs, 1 event in 1 patient (1.25%) from the CNS cohort was considered related to gadopiclenol.

Sex

The incidence of AEs was 21.2% in male patients and 25.7% in female patients for all AEs and 7.9% and 9.0%, respectively, for AEs related to gadopiclenol.

The type of AEs was in majority similar for female and male patients and no specific risks were identified as related to sex. However, a few differences were observed, particularly for gadopiclenol-related injection site reactions with injection site coldness only reported in male patients (6 patients) while injection site warmth was reported only in female patients (3 patients).

Patients with Impaired Renal Function

The overall incidence of AEs was higher in patients with severe renal impairment. However, the incidence of AEs related to gadopiclenol was similar for patients with moderate to severe renal impairment and patients with no or mild renal impairment. Among the AEs related to gadopiclenol reported only in patients with moderate or severe renal impairment, renal failure was reported in one patient with moderate impairment, and hyperkalaemia in one patient with severe impairment. Both were assessed as non-serious. Given the underlying diseases of these patients, there is no clear evidence for a causal role of gadopiclenol. Blood creatinine increase was reported as an AE related to gadopiclenol in one patient with moderate renal impairment (1.8%) and in 2 patients with no or mild renal impairment (0.2%). Therefore, no increased risk was identified in patients with renal impairment.

Table 114. Overview of Adverse Events According to Renal Impairment– Gadopiclenol All doses (N=1047)

ga	Patients with no or mild renal impairment (N=974)		Patients with moderate renal impairment (N=57)		Patients with severe renal impairment (N=16)	
	n(%) patients	n AEs	n(%) patients	n AEs	n(%) patients	n AEs
At least one AE	227 (23.3%)	362	11 (19.3%)	15	9 (56.3%)	13
At least one related AE	83 (8.5%)	110	5 (8.8%)	6	1 (6.3%)	2
At least one SAE	9 (0.9%)	13	1 (1.8%)	2	2 (12.5%)	2
At least one related SAE	1 (0.1%)	1	-	-	-	-

Among the AEs related to gadopiclenol reported in patients with moderate or severe renal impairment, renal failure and blood creatinine increased were reported in one patient with moderate impairment each, and hyperkalaemia in one patient with severe impairment (Table 115).

Table 115. AEs Related to Gadopiclenol according to Renal Impairment - System Organ Class and Preferred Term

	Patients with no or mild renal impairment (N=974)		Patients with moderate renal impairment (N=57)		Patients with severe renal impairment (N=16)	
	n(%) patients	n AEs	n(%) patients	n AEs	n(%) patients	n AEs
At least one AE	83 (8.5%)	110	5 (8.8%)	6	1 (6.3%)	2
General disorders and administration site conditions	**38 (3.9%)**	**44**	**2 (3.5%)**	**3**	**-**	**-**
Injection site pain	19 (2.0%)	19	1 (1.8%)	2	-	-

	Patients with no or mild renal impairment (N=974)		Patients with moderate renal impairment (N=57)		Patients with severe renal impairment (N=16)	
	n(%) patients	n AEs	n(%) patients	n AEs	n(%) patients	n AEs
Injection site warmth	2 (0.2%)	2	1 (1.8%)	1	-	-
Nervous system disorders	**18 (1.8%)**	**20**	**1 (1.8%)**	**1**	**-**	**-**
Headache	13 (1.3%)	14	1 (1.8%)	1	-	-
Investigations	**8 (0.8%)**	**8**	**1 (1.8%)**	**1**	**-**	**-**
Blood creatinine increased	2 (0.2%)	2	1 (1.8%)	1	-	-
Renal and urinary disorders	**-**	**-**	**1 (1.8%)**	**1**	**-**	**-**
Renal failure	-	-	1 (1.8%)	1	-	-
Metabolism and nutrition disorders	**1 (0.1%)**	**1**	**-**	**-**	**1 (6.3%)**	**2**
Hyperkalaemia	-	-	-	-	1 (6.3%)	2

Patients with Hepatic Diseases

The incidence of adverse events was similar for patients with or without hepatic diseases, not showing any specific profile in patients with hepatic diseases. Serious AEs were reported in 3 patients (4.5%) with hepatic diseases, none considered related to gadopiclenol. Gastrointestinal disorders related to gadopiclenol were reported in 2 patients (3.0%) among the 67 patients with hepatic diseases and in 13 patients (1.3%) out of 980 patients without hepatic diseases.

Patients with Cardiac Diseases

No difference in the proportion of patients with at least one AE was observed in patients with cardiac diseases compared to those without cardiac diseases. Among the AEs related to gadopiclenol, abnormal QT interval and blood pressure increase were reported in patients with cardiac diseases. Serious AEs were reported for 2 patients with cardiac diseases (congestive cardiac failure and cardiopulmonary failure), none assessed as related to gadopiclenol.

Patients with Allergic Diseases

There was no difference in incidence of AEs between patients with and without allergic diseases. The AEs related to gadopiclenol reported in patients with allergic diseases only were injection site inflammation, pyrexia, malaise, abdominal discomfort, oral paraesthesia, blood pressure increase, cystatin C increase, erythema and eye irritation.

Patients with History of Convulsions

There was no difference between patients with and without history of convulsions in terms of incidence of AEs overall and related to gadopiclenol. Three patients with history of convulsions experienced AEs related to convulsions (seizures, partial seizures, and epilepsy) after gadopiclenol. None of these AEs was considered related to gadopiclenol.

Indication

The rate of patients with at least one AE was slightly lower in Body indication compared to CNS indication: 18.1% versus 20.3%. The most frequent AEs related to gadopiclenol were similar for both populations with study diseases leading to either MRI of the CNS or MRI of another body region.

2.6.8.7. Immunological events

Overall, 5.7% of the subjects who received gadopiclenol reported at least one reaction at injection site through the specific questionnaire. In studies testing different doses, these AEs were more frequent at higher doses. The rate of patients with at least one intolerance at injection site was similar with gadobutrol (6.4%) and gadobenate dimeglumine (6.6%) (Table 116). In studies where subjects were also injected with placebo, the rate of patients with at least one reaction at injection site was similar for contrast agent and placebo.

Table 116. Tolerance at Injection Site –All Subjects Exposed to IMP (N= 1097)

	N	n (%) with at least one intolerance
Gadopiclenol 0.025 mmol/kg	62	3 (4.8%)
Gadopiclenol 0.05 mmol/kg	708	26 (3.7%)
Gadopiclenol 0.075 mmol/kg	9	0
Gadopiclenol 0.1 mmol/kg	197	20 (10.2%)
Gadopiclenol 0.2 mmol/kg	65	7 (10.8%)
Gadopiclenol 0.3 mmol/kg	54	4 (7.4%)
Gadopiclenol all doses	1047	60 (5.7%)
Gadobenate dimeglumine 0.1 mmol/kg	256	17 (6.6%)
Gadobutrol 0.1 mmol/kg	535	34 (6.4%)
Placebo	66	8 (12.1%)

To be noted, no hypersensitivity reactions were diagnosed and reported as such, however some events could be regarded as signs of allergic reactions such as periorbital oedema, dyspnoea, throat tightness, pruritus, rash, dermatitis allergic and erythema.

2.6.8.8. Safety related to drug-drug interactions and other interactions

No interactions with other medicinal products have been observed. However, formal drug interaction studies have not been carried out; therefore, gadopiclenol should not be mixed with other compounds.

2.6.8.9. Discontinuation due to adverse events

Overall, a total of 10 patients experienced AEs (SAEs in 5 cases) that led to interruption or discontinuation of IMP: 7 (0.7%) after gadopiclenol, 2 (0.8%) after gadobenate dimeglumine and 1 (0.2%) after gadobutrol (**Table 117**). IMP discontinuation meant that additional IMP administrations were not performed in the cross-over studies with a planned administration of two contrast agents.

The AEs leading to IMP discontinuation were assessed as related to the contrast agent by the investigators for 4 patients:

- Three patients in GDX-44-004 study (AEs corresponding to stopping rules):
  - o blood creatinine increase >25% compared to baseline for 2 patients: one after gadopiclenol and one after gadobenate dimeglumine,
  - o QTc Bazett or QTc Fridericia >500 ms or an increase of >60 ms over baseline for one patient after gadopiclenol (non-serious electrocardiogram QT interval abnormal).
- One patient in GDX-44-011 study: Cystatin C increase considered related to gadobutrol.

Stopping rules in GDX-44-004 study related to creatinine variation or ECG results led to study discontinuation of another 9 patients (5 after gadopiclenol and 4 after gadobenate dimeglumine), despite not always being reported as AEs.

Table 117. Adverse Events Leading to IMP interruption/discontinuation by System Organ Class and Preferred Term – All Subjects Exposed to IMP/AMP (N= 1097)

	Gadopiclenol All doses (N=1047)		**Gadobenate dimeglumine (N=256)**		**Gadobutrol (N=535)**	
	n(%) patients	n AEs	n(%) patients	n AEs	n(%) patients	n AEs
At least one AE leading to IMP int/disc	**7 (0.7%)**	**7**	**2 (0.8%)**	**4**	**1 (0.2%)**	**1**
Infections and infestations	**2 (0.2%)**	**2**	**-**	**-**	**-**	**-**
COVID-19	1 (0.1%)	1	-	-	-	-
Upper respiratory tract infection	1 (0.1%)	1	-	-	-	-
Investigations	**2 (0.2%)**	**2**	**1 (0.4%)**	**3**	**1 (0.2%)**	**1**
Blood creatinine increased	1 (0.1%)	1	1 (0.4%)	1	-	-
Electrocardiogram QT interval abnormal	1 (0.1%)	1	-	-	-	-
Blood urea increased	-	-	1 (0.4%)	2	-	-
Cystatin C increased	-	-	-	-	1 (0.2%)	1
Injury, poisoning and procedural complications	**1 (0.1%)**	**1**	**-**	**-**	**-**	**-**
Femoral neck fracture	1 (0.1%)	1	-	-	-	-
Nervous system disorders	**1 (0.1%)**	**1**	**-**	**-**	**-**	**-**
Depressed level of consciousness	1 (0.1%)	1	-	-	-	-
Psychiatric disorders	**1 (0.1%)**	**1**	**-**	**-**	**-**	**-**
Claustrophobia	1 (0.1%)	1	-	-	-	-
Surgical and medical procedures	**-**	**-**	**1 (0.4%)**	**1**	**-**	**-**
Meningioma surgery	-	-	1 (0.4%)	1	-	-

MedDRA dictionary version 23.1
int/disc: interruption/discontinuation

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

In total, 1047 subjects were exposed to gadopiclenol. In the guideline on clinical evaluation of diagnostic agents (CPMP/EWP/1119/98/Rev. 1), including Appendix 1 to this guideline, no advice is included on the minimum number needed of exposed subjects for the safety evaluation. In the ICH E1: population exposure guideline (CPMP/ICH/375/95) is described that "It is anticipated that the total number of individuals treated with the investigational drug, including short-term exposure, will be about 1500". However, this is intended as a guideline to access clinical safety for drugs intended for long-term treatment and is not applicable to the current application. Information and (post-marketing) data are available for other gadolinium-based contrast agents, and information on class-effect-related ADRs is therefore available. Therefore, a different safety profile is not anticipated. Considering these arguments, the number of 1047 subjects that were exposed is acceptable for the short-term safety evaluation. The safety data submitted by the applicant and the data available in particular for other macrocyclic gadolinium contrast media are adequate to evaluate the short safety of gadopiclenol as an MR contrast agent for the evaluation of the CNS and Body in adults and paediatric patients > 2 years of age. However, this product may potentially be used on an intermittent repeat basis on multiple occasions. Patients who receive repeated dosing of gadolinium-based contrast media, especially when closely spaced, are at higher risk for gadolinium accumulation. This is a particular concern for the paediatric population (see discussion on paediatric population). The long-term impact of gadolinium

deposition on developing structures, i.e. brain and bones, liver and skin, is currently unknown. This uncertainty is addressed by the inclusion of adverse effects of accumulation and retention of gadolinium in the brain and organs and tissues other than the brain as important potential risks in the RMP.

The majority was exposed in the intended dose, i.e. 0.05 mg/kg of gadopiclenol. A dedicated paediatric study was also performed, including in total 80 paediatric patients (i.e. 7.6% of the study population) between the age of 2 to 17 years old. This is considered compliant with the PIP. Also, elderly subjects were included, nearly 20% were aged 65 to 74 years, and 6% were at least 75 years old. Only a small percentage of patients had moderate (5.5%) or severe (1.5%) renal impairment. Therefore, a good safety evaluation in this specific patient group will not be possible.

The maximum daily single dose tested in humans was 0.6 mL/kg BW (equivalent to 0.3 mmol/kg BW), which corresponds to 6 times the recommended dose. No signs of intoxication from an overdose have so far been reported. Gadopiclenol can be removed by haemodialysis. However, there is no evidence that haemodialysis is suitable for prevention of nephrogenic systemic fibrosis (NSF).

In the two large phase 3 trials and therefore in most cases, gadopiclenol 0.05 ml/kg was compared to gadobutrol 0.1 mmol/kg (in 535 patients, in the GDX-44-010 and GDX-44-011 studies). In gadopiclenol and gadobutrol, gadolinium is bound in a macrocyclic complex with high stability. However, in GDX-44-004 the active comparator gadobenate dimeglumine was used (in 256 patients). This is a linear-bound gadolinium complex with less stability compared to a macrocyclic complex. For safety evaluation it would have been more appropriate to compare gadopiclenol with only macrocyclic complex agents. However, as the adverse events (AEs) are presented separately for the different agents, and in most subjects, the active comparator gadobutrol was used, this is not considered a large issue.

In total 376 (33.5%) of the subjects experienced at least one AE. The proportion of subjects was similar for gadopiclenol compared to gadobutrol and was not larger with gadopiclenol compared to placebo. The applicant described the most commonly reported AEs. For most of the reported AEs, the frequency was similar for gadopiclenol and the active comparators. However, headache and contact dermatitis were more frequent with gadopiclenol, but the total proportion was not large (headache: gadopiclenol 3.9%, gadobutrol 1.7%, gadobenate dimeglumine 2.3%; contact dermatitis: gadopiclenol 1.2%, gadobutrol 0.4%, gadobenate dimeglumine 0%). Contact dermatitis is not included in section 4.8 of the SmPC, since none of these events were reported as related to the IMP but were either related to the adhesive plaster of the patches used for ECG or to the elastic bandage/adhesive used for IV administration or blood sampling.

There were 6 reports of incorrect dose administered. The applicant has provided brief details in relation to these cases. Incorrect dose administration was caused in these cases by human error. No ADRs were reported for these patients. Injection site reactions captured using the special questionnaire accounted for approximately 6% of AEs. Injection site pain (3%) was the most common effect, of which 1.9% were reported as related to study medication. Time to onset and duration of effect was reported for two severe ISRs. In section 4.2 of the SmPC, it is specified that this medicinal product should only be administered by trained healthcare professionals with technical expertise in performing gadolinium enhanced MRI. The product is indicated for intravenous use only. The recommended dose is administered intravenously as a bolus injection at approximatively 2 mL/sec followed by a flush of sodium chloride 9 mg/ml (0.9%), solution for injection via manual injection or power injector. Intravenous administration of contrast agent should, if possible, be done with the patient lying down. Since experience shows that most undesirable effects occurs within minutes after administration, the patient should be kept under observation during and following

administration for at least half an hour (see SmPC section 4.2 and 4.4). Instructions on the medicinal product before administration have been detailed in SmPC section 6.6.

Injection site reactions occurred more frequently at doses > 0.05 mmol/kg and were 3 times commoner with the power injector compared to manual injection. The majority of reactions were mild. Fifty percent resolved within 24hrs however, the remaining 50% took up to 10 days to resolve.

Caution during administration is necessary to avoid any extravasation. In case of extravasation, the injection must be stopped immediately. In case of local reactions, evaluation and treatment should be carried out as necessary.

Hypersensitivity reaction to gadolinium has been well described. Known hypersensitivity is included as a contraindication in the SmPC (see section 4.3) and section 4.4 includes a detailed warning regarding the potential for hypersensitivity reactions, including life-threatening reactions. Hypersensitivity reactions may be either allergic (described as anaphylactic reactions when serious) or non-allergic. They can occur either immediately (less than 60 minutes) after injection or delayed (up to 7 days). Anaphylactic reactions occur immediately and can be fatal. They are independent of the dose, can occur after even the first dose of the product, and are often unpredictable. During the examination, supervision by a physician is necessary. If hypersensitivity reactions occur, administration of the contrast agent must be discontinued immediately and – if necessary – a specific therapy must be instituted. A venous access should thus be kept during the entire examination. To permit immediate emergency countermeasures, appropriate drugs (e.g. epinephrine and antihistamines), an endotracheal tube and a respirator should be ready at hand. The risk of hypersensitivity reaction may be higher in patients with a history of previous reaction to gadolinium-containing contrast agents, bronchial asthma or allergy. SmPC section 4.8 includes hypersensitivity as an ADR and defines hypersensitivity as an immediate reactions including one or more effects, which appear simultaneously or sequentially, which are most often cutaneous, respiratory and/or vascular reactions. Each sign may be a warning sign of a starting shock and go very rarely to death. Kounis Syndrome has been described following the administration of gadolinium-based contrast agents with both linear and macrocyclic carrier ligands. (Wang et al Feb 2022 AmJ Emerg Med).

Although the risk of serious hypersensitivity reactions complicated by vascular events resulting in fatal outcome with gadopiclenol use is already documented in section 4.8 of the SmPC for Elucirem in line with the wording of the Core SmPc for gadoteric acid, it is agreed at this point that there is insufficient data to support inclusion of the specific term Kounis syndrome as a class effect for the GBCAs. However, Kounis Syndrome and hypersensitivity/anaphylactic reactions with cardiovascular events will be monitored as a topic of special interest in future PSURs.

The applicant has outlined the methodology for identifying ADRs for inclusion in section 4.8. The selection process and methodology for causality assessment determination is reasonable and accepted. The applicant has provided a comprehensive justification for all of the proposed ADRs. Three subjects had a Se Creatinine increase > 50%, however, all three AEs were reported as non-serious AE of mild intensity. Moreover, two cases were confounded by underlying medical conditions and concomitant medications. Overall, there is no clear evidence of gadolinium induced nephropathy. The subsection of section 4.8 entitled ‘Description of selected adverse reactions’ has been updated to include a reference to NSF.

Several AESIs were defined, i.e. suspected NSF or related symptoms, sudden death or serious ECG arrhythmias, and decrease in kidney function. Of these events, only one was observed, i.e. decrease in kidney function, in study GDX-44-005 in one patient with severe renal impairment. The applicant describes

that this event was not related to the administration of gadopiclenol, but this cannot be excluded. However, as the event was of mild intensity and resolved within 28 days, this is not considered a large safety issue.

NSF is an AESI because the development of NSF is associated with the administration of a gadolinium-based contrast agent (Kanal E, et al. 2007[3].; Kuo PH, et al. 2007[4]). The first symptoms present weeks to months after the administration of a gadolinium-based contrast agent. The applicant describes that no events of suspected NSF or symptoms suspected to be related to NSF were reported in any study, including during the follow-up periods of 3 months in GDX-44-007 study (paediatric study, n=80) and 6 months in GDX-44-005 (renal impairment study, n=40). However, most subjects were included in study GDX-44-010 and GDX-44-011, which had a safety follow-up visit only one day after the last administration of the contrast agent and no long-term follow-up visit. The cross-over design is also not suitable for evaluating the risk of developing NSF with gadopiclenol compared to gadobutrol or placebo. Patients with renal impairment are at larger risk for developing NSF after the administration of gadolinium-based contrast agents. In study GDX-44-005, no symptoms of NSF were observed after 6 months. However, this study included a small number of subjects and is therefore not considered sufficient to evaluate the risk of NSF. In addition, this study did not compare the administration of gadopiclenol vs other gadolinium-based contrast agents. The risk of developing NSF with gadopiclenol compared to other gadolinium-based contrast agents has not been fully evaluated and included in the RMP. Improvement in safety aspects has, therefore, not been demonstrated. However, as gadopiclenol is a macrocyclic chelate, has high kinetic stability, and the concentration of the administered gadolinium with gadopiclenol is lower compared to the currently used gadolinium-based contrast agents such as gadobutrol, it is not considered likely that this risk is larger with gadopiclenol. On 6 November 2008, Denmark asked the CHMP, under Article 31 of Directive 2001/83/EC, to give its opinion on whether the marketing authorisations for GBCAs should be varied in relation to its use in special patient's population more at risk to develop NSF. The CHMP recognised that there are different categories of NSF-risk for GBCA: medium/high risk (linear non-ionic chelates and linear ionic chelates and low risk (macrocyclic chelates). Since gadopiclenol is a macrocyclic GBCA with a high kinetic stability, it can be considered a low risk GBCA, although risk of developing NSF with gadopiclenol has not fully been evaluated. In line with the recommendations to be included in the SmPC for low risk gadolinium-containing contrast agents following the EMA referral EMEA/727399/2009 Annex, section 4.2 includes the information that "gadopiclenol should only be used in patients with severe renal impairment (GFR < 30 ml/min/1.73m2) and in patients in the perioperative liver transplantation period after careful risk/benefit assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI (see section 4.4). If it is necessary to use gadopiclenol, the dose should not exceed mmol/kg body weight". Also, the other recommendations following the EMA referral have been included. Therefore, the recommendations for gadopiclenol are in line with other low-risk GBCA like gadobutrol, which is considered acceptable. In SmPC section 4.4, it is moreover mentioned that prior to administration of gadopiclenol, it is recommended that all patients are screened for renal dysfunction by obtaining laboratory tests. There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with acute or chronic severe renal impairment (GFR < 30 mL/min/1.73 m2). Patients undergoing liver transplantation are at particular risk since the incidence of acute renal failure is high in this group. As there is a possibility that NSF may occur with gadopiclenol, it should only be used in patients with severe renal impairment and in patients in the perioperative liver transplantation period after careful benefit/risk assessment and if the diagnostic information is essential and not available with non-contrast enhanced MRI. Haemodialysis shortly after gadopiclenol administration may be useful at removing it from the body. There is no evidence to support the

[3] Kanal E, et al. ACR guidance document for safe MR practices: 2007. AJR Am J Roentgenol. 2007.
[4] Kuo PH, et al. Gadolinium-based MR contrast agents and nephrogenic systemic fibrosis. Radiology. 2007;242(3):647-649

initiation of haemodialysis for prevention or treatment of NSF in patients not already undergoing haemodialysis.

The number of deaths was similar in the gadopiclenol group (n=1) compared to gadobutrol (n=1). Based on the narratives of both events, these deaths appear not related to the administration of the drug.

The number of non-fatal SAEs was larger with gadopiclenol (all doses combined, n=11, 1.1%) vs. gadobutrol (n=0, 0.0%) or gadobenate dimeglumine (n=2, 0.8%). The SAEs after gadopiclenol administration were distributed between different SOCs and PTs without a clear pattern. Based on the listing, most of the SAE appear not related to the administration of gadopiclenol. The time between the administration and the SAEs is in general long. One SAE classified as related was the creatinine increase. This was 21 days after administration but resolved afterwards. This observation is not considered an important safety issue.

In 10 subjects, AEs (SAEs in 5 cases) led to interruption or discontinuation of IMP: 7 (0.7%) after gadopiclenol, 2 (0.8%) after gadobenate dimeglumine and 1 (0.2%) after gadobutrol. In 4 cases the AE was considered related to the administration of the contrast agent and the AEs were often related to the stopping rules of the study. The number of AEs related to discontinuation is considered small.

No relevant changes were reported for haematology and biochemistry values in general. There is a special interest in the effects on creatinine values, and kidney function and an increase in blood creatinine was the most frequent abnormal laboratory result reported as an AE related to the contrast agent. This was similar for gadopiclenol (3 patients, 0.3%), gadobenate dimeglumine (2 patients, 0.4%), and for gadobutrol (2 patients, 0.4%). The number of patients that shifted with an increase of >50% of their creatinine values was similar for gadopiclenol (all doses combined) (0.3%) vs gadobutrol (0.7%) or gadobenate dimeglumine (0%)). For a shift between 25% and 50% increase in creatinine values, the numbers were also similar for gadopiclenol (2.2%) vs gadobutrol (2.8%) or gadobenate dimeglumine (2.0%). For cystatin C, BUN and eGFR the numbers were also similar for gadopiclenol vs. gadobutrol or gadobenate dimeglumine. No new safety issue is therefore observed with gadopiclenol compared to the authorised gadolinium agents. Compared to placebo, the numbers are larger, but this is not unexpected.

Seizures are a known adverse effect of GBCAs. Therefore, it is mentioned in the SmPC that as with other gadolinium-containing contrast agents, special caution is necessary in patients with a lowered threshold for seizures. All equipment and drugs necessary to counter convulsions occurring during the MRI examination must be made ready for use beforehand.

Elucirem has negligeable influence on the ability to drive and use machines.

The number of AEs related to changes in vital signs (heart rate, body temperature, blood pressure) was low, were mild to moderate in intensity and were similar for gadopiclenol vs gadobutrol or gadobenate dimeglumine. No new safety issues are observed. The reaction at the injection site was also similar for gadopiclenol (5.7%) vs gadobutrol (6.4%) or gadobenate dimeglumine (6.6%).

The ECG data were not pooled due to the heterogeneity in data collection between the studies. In study GDX-44-003 and GDX-44-005 no relevant or consistent changes in median values for ECG intervals were observed after contrast agent administration. In study GDX-44-004, two cases of an abnormal QT interval on ECG were reported as AEs and considered related to gadopiclenol, of which one led to premature discontinuation. However, a dedicated study was performed to evaluate the effects of gadopiclenol on QT/QTc (GDX-44-006). This study did not indicate that administration of gadopiclenol in the clinical or supra-clinical dose prolonged QT interval, and the upper limit of the 90% CI of the baseline- and placebo-corrected values did not exceed the threshold of regulatory concern. In the paediatric study (GDX-44-007), there were two cases of clinically

significant changes in QTc. One was explained by long QT syndrome and not related to the contrast agent. The other was most likely explained by tachycardia related to anxiety. Taken together, no large safety issues are observed in ECG changes related to the administration of the contrast agent.

In patients with severe cardiovascular disease gadopiclenol should only be administrated after careful risk benefit assessment because no data are available so far.

As no interaction studies have been performed, concomitant medicinal products should be taken into account (see SmPC section 4.5). Beta-blockers, vasoactive substances, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists decrease the efficacy of the mechanisms of cardiovascular compensation for blood pressure disorders. The physician must obtain information before injection of gadopiclenol about the concomitant intake of those medicinal products.

In the pooled studies, a total number op 208 subjects with age 65 to <75 years were included and 62 subjects of ≥ 75 years. The number of AEs was not larger in elderly subjects compared to subjects of 18 to <65 years. The most frequently reported AE type was similar for the different ages, i.e. injection site pain and headache. These findings support a similar safety profile for the elderly. However, as renal impairment is more frequent in the elderly, the renal clearance of gadopiclenol could be more frequently impaired in the elderly. A warning to screen patients aged 65 years and older for renal dysfunction is warranted. This is included in section 4.4 of the SmPC.

No differences in AEs were identified between male and female patients, except for injection site reactions, with injection site coldness only reported in male patients (6 patients) while injection site warmth was reported only in female patients (3 patients). This is, however, not considered a safety issue.

It has been acknowledged that gadopiclenol may be regarded to have a lower potential of accumulation in the body than other GBCAs. Nonetheless, this potential exists. The number of subjects included with severe renal impairment is very small (n=16), and the number of patients with moderate renal impairment is not large (n=57). The incidence of AEs was higher in patients with severe renal impairment compared to patients with no or mild renal impairment. This is not unexpected, but a safety evaluation cannot be performed with this small number of subjects. The number of AEs (19.3%) for patients with moderate renal impairment is similar to that for patients with no or mild renal impairment (23.3%). As discussed in section 3.4.1.1 (Special populations, Pharmacokinetics) in patients with renal impairment, the elimination of gadopiclenol is prolonged proportionally to the degree of renal impairment. Nevertheless, considering that gadopiclenol is at low risk for NSF due to its macrocyclic chelate and high kinetic stability, it can be used at a lower dose compared with other approved GBCAs and that there is no evidence that lowering the dose would provide adequate MRI images, it can be acceptable that no dose adjustments for patients with renal impairment are recommended in the SmPC, even though it would have been preferred to conduct an adequate efficacy clinical study in patients with severe renal impairment using lower doses instead of simulation approaches.

No differences of specific profile were identified in incidence or type of AEs between patients based on the presence of hepatic disease, cardiac disease, allergic disease, history of convulsions or based on the indication of the MRI.

The usual precautions for MRI examination should be applied, such as exclusion of patients with pacemakers, ferromagnetic vascular clips, infusion pumps, nerve stimulators, cochlear implants, or suspected intracorporal metallic foreign bodies, particularly in the eye.

MRI images produced with this medicinal product should only be analysed and interpreted by the healthcare professionals trained in interpretation of gadolinium enhanced MRI.

There are no data from the use of gadopiclenol in pregnant women. Animal studies showed little placental transfer and do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see under 2.5.6.). Elucirem should not be used during pregnancy unless the clinical condition of the woman requires use of gadopiclenol. Gadolinium-containing contrast agents are excreted into breast milk in very small amounts (see under 2.5.6.). At clinical doses, no effects on the infant are anticipated due to the small amount excreted in milk and poor absorption from the gut. Continuing or discontinuing breast feeding for a period of 24 hours after administration of Elucirem, should be at the discretion of the doctor and lactating mother. Animals studies do not indicate impairment of fertility (see under 2.5.6.).

Assessment of paediatric data on clinical safety

A dedicated paediatric trial was performed (GDX-44-007) with in total 80 patients, ranging in age between 2 and 17 years old (≥2 and <7 years: n=26; ≥7 and <12 years: n=23;≥12 and <18 years: n=31). The paediatric study was confirmed compliant with the PIP. The trial included more than 60 paediatric subjects and had a follow-up period of at least 3 months. The number of total AEs is similar or not increased compared to the adult population in the paediatric population. The type of AEs reported are not clearly different compared to the adult population. The number of AEs within one SOC or PT is low, and a pattern in observed AEs is therefore, difficult to observe. However, no new or other safety issues have been observed in the paediatric population.

The 3-month follow-up period is insufficient to characterise delayed reactions or longer-term effects after administration of gadopiclenol, i.e. NSF or gadolinium brain retention. The risk of long-term deposition of gadolinium in the brain in children has been linked primarily but not exclusively to linear rather than macrocyclic chelates. The consequences of accumulated gadolinium, other than NSF, are unknown, particularly on developing brain structures. Adverse effects of accumulation and retention of gadolinium in the brain along with organs and tissues other than the brain (i.e. bones and skin) is included as an important potential risk in the safety specification of the RMP (for children and adults). NSF will be monitored with a specific questionnaire and the clinical significance of gadolinium accumulation and retention in the brain and in other organs and tissues with a standardised reporting form for ADRs that have lasted over 4 weeks. The adequacy of this approach to gather information on GBCA long-term effects has been further justified and is accepted. The proposal to further evaluate the long-term effects of Elucirem either through a participation in the on-going Odyssey study or by conducting another study with a similar design is supported. In line with other macrocyclic GBCAs (Ref EMEA/H/A-31/1437/Annex III dated 23/11/2017), it is agreed that no specific information regarding gadolinium retention needs to be added in section 4.4 of the SmPC for gadopiclenol.

2.6.10. Conclusions on the clinical safety

The safety profile of gadopiclenol appears similar to other authorised gadolinium-based contrast agents, i.e. gadobutrol (or gadobenate dimeglumine). No new large safety issues have been identified. However, due to the limited long-term follow-up, differences in the risk for NSF cannot be evaluated and has been included in the RMP.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 118. Summary of safety concerns

Summary of concerns	
Important identified risks	• Nephrogenic Systemic Fibrosis
Important potential risks	• Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues • Adverse clinical effects of accumulation and retention of gadolinium in the brain
Missing information	• Safety in pregnancy and lactation • Clinical significance of gadolinium accumulation and retention in organs and tissues other than brain tissues • Clinical significance of gadolinium accumulation and retention in the brain

2.7.2. Pharmacovigilance plan

Table 119. (Part III.3:) On-going and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concern(s) addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit risk)				
None				
Category 3 - Required additional pharmacovigilance activities (EMA)				
GMRA-105 **Title:** Prospective Evaluation of Potential Effects of Repeated Gadolinium-based contrast	To evaluate the potential effect on motor and cognitive function	Effects of gadolinium retention	Protocol amendment finalised	July 2023
			Interim Reports	Annual for EMA

Study Status	Summary of objectives	Safety concern(s) addressed	Milestones	Due dates
agent (GBCA) Administrations of the Same GBCA on Motor and Cognitive Functions in Neurologically Normal Adults in Comparison to a Non-GBCA Exposed Control Group - ODYSSEY **Planned**			Final report	6 months after completion

Four non-clinical studies are currently ongoing in the context of Gd accumulation and retention in the body

Study Status	***Summary of objectives***	***Safety concerns addressed***	***Milestones***	***Due dates***
Investigation of Small Fiber Neuropathy (SFN) after single administration of gadolinium based-contrasts agents (GBCAs) in mice (ER-21-00003) *On going*	The aim of the study is to investigate a potential occurrence of small fiber neuropathy following single intravenous injection of gadopiclenol *versus* other GBCAs (at the human equivalent dose) in mice.	- Clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain - Clinical effects of accumulation and retention of gadolinium in the brain	In-life completion Determination of total Gd concentrations in the selected tissues Behavioral assessment Histopathology Final report	June 2021 Dec 2021 Oct 2021 Expected July 2023 Expected Dec 2023
Investigation of Small Fiber Neuropathy (SFN) after repeated administrations of gadolinium based-contrasts agents (GBCAs) in mice (ER-21-00007) *On going*	The aim of the study is to investigate a potential occurrence of small fiber neuropathy following repeated intravenous injections of gadopiclenol *versus* other GBCAs (at the human equivalent dose) in mice.	- Clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain - Clinical effects of accumulation and retention of gadolinium in the brain	In-life completion Behavioral assessment Histopathology Determination of total Gd concentrations in the selected tissues Final report	May 2022 Expected Dec 2022 Expected Dec 2023 Expected Dec 2023 Expected July 2024
Early (W1, M1) and long-term (M5) gadolinium retention after a dose of 0.05 mmol/kg of gadopiclenol vs 0.1 mmol/kg dose of already marketed macrocyclic GBCAs in rat (ER-21-00015) *On going*	The main aim of the study is to provide information about Gd retention and wash-out after single administration of 0.05 mmol/kg of gadopiclenol, to better apprehend the behaviour of this GBCA at the human equivalent dose and to compare with the other marketed macrocyclic GBCAs.	- Clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain - Clinical effects of accumulation and retention of gadolinium in the brain	In-life completion Determination of Gd concentrations in the selected tissues Final report	Aug 2021 Expected July 2023 Expected Dec 2023
Exhaustive speciation of Gd retained after repeated	The main aim of this study is to document Gd	- Clinical effects of accumulation and	In-life completion	Mar 2022

Study Status	*Summary of objectives*	*Safety concerns addressed*	*Milestones*	*Due dates*
injections of 0.05 mmol/kg of gadopiclenol vs 0.1 mmol/kg of gadobutrol in rat (ER-21-00011) *On-going*	retention until 12 months after repeated administrations by providing exhaustive speciation data of gadolinium to understand in which form(s) it is present in different organs.	retention of gadolinium in organs and tissues other than brain - Clinical effects of accumulation and retention of gadolinium in the brain	Determination of Gd concentrations in the selected tissues Gd spatial distribution with LA-ICP-MS in selected tissues Speciation analysis in different organs Final report	Expected Dec 2023 Expected July 2024 Expected July 2024 Expected Dec 2024

2.7.3. Risk minimisation measures

Table 120. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Nephrogenic Systemic Fibrosis (NSF)	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 SmPC section 4.4 SmPC section 4.8 SmPC section 4.9 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up form for collection of additional information.
Important potential risks		
Adverse clinical effects of accumulation and retention of gadolinium in organs and tissues other than brain tissues	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up form for adverse events lasting over 4 weeks. Additional pharmacovigilance activities: None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None	
Adverse clinical effects of accumulation and retention of gadolinium in the brain	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up form for adverse events lasting over 4 weeks. Additional pharmacovigilance activities: ODYSSEY clinical study (post-authorisation safety study): Prospective evaluation of potential effects of repeated gadolinium-containing contrast agent administrations of the same GBCA on motor and cognitive functions in neurologically normal adults in comparison to a non-GBCA exposed control group.
Missing information		
Safety in pregnancy and lactation	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 SmPC section 4.6 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Pregnancy forms and follow-up forms.
Clinical significance of gadolinium accumulation and retention in other organs and tissues than brain tissues	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up form for adverse events lasting over 4 weeks. Additional pharmacovigilance activities: - Preclinical studies in mice investigating the occurence of small fiber neuropathy after single or repeated administration - Preclinical study in rats investigating early (W1, M1) and long-term (M5) gadolinium retention after a single half-dose of gadopiclenol vs full-dose of already marketed macrocyclic GBCAs - Preclinical study in rats investigating speciation of Gd retained after repeated injections of a half-dose of gadopiclenol vs gadobutrol

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Clinical significance of gadolinium accumulation and retention in the brain	Routine risk minimisation measures: SmPC section 4.1 SmPC section 4.2 Peel-off tracking labels Other routine risk minimisation measures beyond the Product Information: Prescription only medicine Additional risk minimisation measures: None	Routine pharmacovigilance activities with signal detection and adverse reactions reporting including: Adverse event follow-up form for adverse events lasting over 4 weeks. Additional pharmacovigilance activities: - Preclinical studies in mice investigating the occurence of small fiber neuropathy after single or repeated administration - Preclinical study in rats investigating early (W1, M1) and long-term (M5) gadolinium retention after a single half-dose of gadopiclenol vs full-dose of already marketed macrocyclic GBCAs - Preclinical study in rats investigating speciation of Gd retained after repeated injections of a half-dose of gadopiclenol vs gadobutrol - ODYSSEY clinical study (post-authorisation safety study): Prospective evaluation of potential effects of repeated gadolinium-containing contrast agent administrations of the same GBCA on motor and cognitive functions in neurologically normal adults in comparison to a non-GBCA exposed control group.

Routine risk minimisation activities are sufficient to manage the safety concerns of gadopiclenol.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

Of note, in the finalised version of the RMP the QPPV's actual signature or the evidence that the RMP was reviewed and approved by the QPPV as well as the sign-off date should be provided. Duplicate queries in the targeted follow-up questionnaire regarding long-term symptoms should be removed when finalising the RMP.

The applicant is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in the updated RMP submitted with the responses.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the

requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21.09.2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Elucirem (gadopiclenol) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Gadopiclenol is a non-ionic macrocyclic gadolinium (Gd) complex intended to be used in humans as a contrast agent for Magnetic Resonance Imaging (MRI).

The applicant was proposing the following indication:

This medicinal product is for diagnostic use only.

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

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

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

3.1.2. Available therapies and unmet medical need

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

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

GBCAs are classified as linear or macrocyclic agents based on the chemical structure of their ligand. Macrocyclic agents have shown a better safety profile due to higher stability, less risk of dissociation, and less release of free Gd. Associations between GBCAs and nephrogenic systemic fibrosis (NSF) and gadolinium deposition in the brain and other organs have been reported. In this context, regulatory bodies recommend using the minimum GBCA dose that provides sufficient contrast enhancement for diagnosis in routine practice. (EMEA/H/A-31/1437 ; EMEA/H/A-31/1097). Thus, the development of high-relaxivity GBCAs meets a true medical need. Such agents would allow a reduction of the injected dose with the same efficacy as the other available GBCAs.

3.1.3. Main clinical studies

The main evidence of efficacy submitted were the two confirmatory (phase 3) studies GDX-44-010 for CNS imaging (n=256) and GDX-44-011 for body imaging (n=304), which were conducted with the same study design. Both studies were prospective, multi-centre, randomised, double-blind, controlled cross-over studies to evaluate the safety and efficacy of gadopiclenol at 0.05 mmol/kg compared with gadobutrol at 0.1 mmol/kg for CNS and body MRI in female or male adults presented at the time of inclusion with known or highly suspected CNS lesion(s) with focal areas of disrupted BBB or with known or suspected enhancing abnormality(ies) and/or lesion(s) in at least one body region among head & neck, thorax, abdomen, pelvis and musculoskeletal, respectively, based on a previous imaging procedure performed within 12 months for the body study. Two MRI examinations were performed at visit 2 and visit 4 for each patient, which was randomised in a 1:1 ratio for the order of receiving the contrast agents to avoid bias. The pivotal studies included two co-primary objectives, i.e., the superiority of combined unenhanced/enhanced imaging with gadopiclenol vs. unenhanced imaging and non-inferiority of gadopiclenol (0.05 mmol/kg) vs. gadobutrol (0.1 mmol/kg) enhanced imaging in terms of 3 qualitative lesion visualisation criteria (border delineation, internal morphology, and degree of contrast enhancement) as judged by 3 independent blinded readers. The secondary endpoints included improvement in lesion visualisation scores at patient-level, technical adequacy of images, number, size and location of lesions, diagnostic confidence, impact on the patient treatment plan, quantitative criteria, and overall diagnostic preference.

An exploratory (phase 2) open-label, uncontrolled multi-centre, international study GDX-44-007 evaluated the PK, safety and efficacy of gadopiclenol-enhanced MRI (0.05 mmol/kg) in CNS and body in paediatric patients from 2 to 17 years of age to support the proposed paediatric indication. Supportive data were obtained from the double-centre, non-randomised, open-label exploratory study (GDX-44-008) in female or male adult patients with liver cirrhosis or chronic liver disease. In this proof-of-concept study, small numbers of patients and nodules were analysed using a standard of reference based on previous imaging and/ or histology to evaluate the diagnostic performance of gadopiclenol for hepatocellular carcinoma.

An image evaluation study has been conducted to assess concordance in lesion detectability with 0.05 mmol/kg gadopiclenol and 0.1 mmol/kg of comparator gadobutrol in MRI in the CNS and other body regions.

3.2. Favourable effects

Primary objectives. In both confirmatory studies GDX-44-010 and GDX-44-011, the two co-primary objectives, i.e., the superiority of combined unenhanced/contrast-enhanced MRI with gadopiclenol vs unenhanced imaging and non-inferiority of gadopiclenol (0.05 mmol/kg) vs gadobutrol (0.1 mmol/kg) enhanced imaging in terms of 3 qualitative lesion visualisation criteria (border delineation, internal morphology, and degree of contrast enhancement), were achieved for all three blinded readers. Similar results were observed with lesion visualisation criteria at lesion level.

These findings were confirmed in the supportive analyses performed on the PSS1 for criterion 1 and FAS 2 for criterion 2. Additionally, the investigator observed similar results with on-site reading for the two primary objectives. Furthermore, the analysis of the difference "Paired - Pre" for each of 3 co-primary criteria for MRI with gadobutrol showed similar results to those obtained with gadopiclenol, confirming the assay sensitivity.

Subgroups. In both confirmatory studies GDX-44-010 and GDX-44-011, subgroup analyses concerning demographic parameters and magnetic field strength showed consistent results in terms of both primary objectives. Moreover, assessments based on lesion size for MRI with gadopiclenol compared with MRI with

gadobutrol showed that the differences in mean of scores for each criterion was close to 0 in all cases, indicating that also for smaller lesions (≤1 cm) gadopiclenol is non-inferior to gadobutrol.

Other secondary criteria. In the CNS study GDX-44-010, regarding *quantitative (objective) parameters,* LBR and percentage of lesion enhancement were significantly higher with gadopiclenol than with gadobutrol for all three blinded readers (p<0.0001). For CNR, the difference was statistically significant for the two readers. In the body study GDX-44-011, a significant higher percentage of lesion enhancement was observed for two readers, whereas there was no difference in LBR for all readers. The level of *diagnostic confidence* was improved with paired images compared to pre-contrast images, with a slightly higher percentage of excellent level for paired images with gadopiclenol compared to paired images with gadobutrol for all three readers in the CNS study (67.4% vs 64.6% 66.0% vs 63.1% and 93.0% vs 89.1% for reader 1,2, and 3 respectively) and a similar percentage of excellent level for all three readers (80.4% vs 75.2%, 64.0% vs 68.3%, and 20.8% vs 23.4% for reader 1,2, and 3 respectively) in the body study. The *percentage of treatment plan changes* based on paired images compared with pre-contrast images was similar between both contrast agents (23.3% of the patients for gadopiclenol and 23.7% for gadobutrol in the CNS study and 30.1% vs 29.3% in the body study). There was also no difference between both contrast agents for the change on treatment plan according to tumour classification. Assessment for *overall diagnostic preference* by 3 additional independent blinded radiologists showed that images with gadopiclenol were in majority preferred to images with gadobutrol in the CNS study (44.8%, 54.4% and 57.3% for readers 4, 5, and 6, respectively; p< 0.0001), whereas in the body study, in the majority, no preference was reported (78.3%, 74.6%, and 82.6% for reader 4, 5, and 6, respectively; p< 0.0001). Additionally, similar or better results for paired images with gadopiclenol compared with paired images of gadobutrol were observed for the other secondary endpoints, including *improvement in lesion visualization scores at patient-level* and *technical adequacy of images.*

Paediatric population. Administration of gadopiclenol at 0.05 mmol/kg in paediatric subjects 2-17 years old resulted in enhancement of the CNS and body images in terms of the quantitative parameters (signal intensity, percentage of lesion enhancement and LBR (only for body)) and the qualitative parameters (lesion visualisation score). Despite improvements in technical performance appearing much less pronounced compared with the adult population, particularly concerning CNS imaging, which could be explained by the different histology of paediatric lesions included in the study compared to the adult population, the investigator's confidence in diagnosis was improved for most examinations (52.9% for CNS and 63.6% for body MRI).

3.3. Uncertainties and limitations about favourable effects

Both confirmatory studies

Selection bias. Lesion visualisation parameters (e.g., co-primary endpoints and quantitative assessments, such as, Contrast to Noise Ratio, Lesion to Brain (background) Ratio and percentage of lesion enhancement) were assessed in all the lesions identified by the blinded readers, independently of their size, in more than 86% of patients in CNS study and in more than 81% of patients in Body study, who had no more than 3 lesions. In the remaining patients with more than 3 lesions visible, a subset of 3 most representative lesions were selected for assessment of the co-primary endpoints. Therefore, in those patients, the additional lesions were not assessed. Consequently, the technical capability of lesion visualisation for both contrast agents cannot be extrapolated for those non-selected lesions. This limitation is reflected accordingly in SmPC section 5.1.

CNS imaging, GDX-44-010

Specific conditions. There are no or limited clinical data investigating the performance of gadopiclenol for CNS imaging in patients with inflammatory, infectious, autoimmune or demyelinating disorders (such as multiple sclerosis), patients with acute or chronic infarct, or patients with intramedullary spine lesions. This limitation is reflected in the SmPC section 4.4..

Body imaging, GDX-44-011

Specific conditions. There are also no or limited clinical data investigating the performance of gadopiclenol for body imaging in patients with inflammatory, infectious and autoimmune conditions, including acute/chronic pancreatitis, inflammatory bowel disease, inflammatory diseases of head and neck region and endometriosis. Section 4.4 of the SmPC reflects this limitation.

3.4. Unfavourable effects

In total, 1047 subjects were exposed to gadopiclenol. The majority was exposed in the intended dose, i.e., 0.05mg/kg of gadopiclenol. In the two large phase 3 trials and therefore, in most subjects, gadopiclenol 0.05 ml/kg was compared to gadobutrol 0.1 mmol/kg (in 535 patients, in GDX-44-010 and GDX-44-011 studies).

In total 376 (33.5%) of the subjects experienced at least one AE. The proportion of subjects was similar for gadopiclenol compared to gadobutrol and was not larger with gadopiclenol compared to placebo. Most post-injection AEs related to gadopiclenol were reported in the System Organ Class (SOC) "General disorders and administration site conditions" (49 AEs in 42 patients, 4.0%), followed by "Nervous system disorders" (21 AEs in 19 patients, 1.8%) and "Gastrointestinal disorders" (18 AEs in 15 patients, 1.4%). These results were similar for the comparators (gadobenate dimeglumine and gadobutrol). The most common AEs with gadopiclenol (reported in at least 10 subjects) were headache (3.9%), injection site pain (3.0%), contact dermatitis (1.2%), nausea (1.4%), injection site hematoma (1.1%) and dizziness (1.0%).

The number of non-fatal SAEs was larger with gadopiclenol (all doses combined, n=11, 1.1%) vs gadobutrol (n=0, 0.0%) or gadobenate dimeglumine (n=2, 0.8%). Non-fatal SAEs occurred after gadopiclenol at 0.05 mmol/kg in 7 patients, after gadopiclenol 0.075 mmol/kg in 1 patient, after gadopiclenol 0.1 mmol/kg in 2 patients, and after gadopiclenol 0.2 mmol/kg in 1 patient.

Adverse events of special interest

No events of suspected NSF or symptoms suspected to be related to NSF were reported in any study, including during the follow-up periods of 3 months in GDX-44-007 study (paediatric study, n=80) and 6 months in GDX-44-005 study (renal impairment study, n=40).

An increase in blood creatinine was the most frequent abnormal laboratory result reported as an AE related to the contrast agent. This was similar for gadopiclenol (3 patients, 0.3%), gadobenate dimeglumine (2 patients, 0.4%), and gadobutrol (2 patients, 0.4%). The number of patients that shifted with an increase of >50% of their creatinine values was similar for gadopiclenol (all doses combined) (0.3%) vs gadobutrol (0.7%) or gadobenate dimeglumine (0%)). For a shift between 25% and 50% increase in creatinine values, the numbers were also similar for gadopiclenol (2.2%) vs gadobutrol (2.8%) or gadobenate dimeglumine (2.0%). The numbers for cystatin C, BUN and eGFR were also similar for gadopiclenol vs gadobutrol or gadobenate dimeglumine.

In a dedicated paediatric trial, the number of patients with at least one AEs was similar for the paediatric age subgroup (age ≥2 - <7 years, n=5 (19.2%); ≥7 - <12 years, n=6 (26.1%); ≥12 - <18 years, n=3 (9.7%)) compared to the adult population (age 18 - < 65 years, n=192 (27.5%). The type of AEs reported are not clearly different compared to the adult population.

3.5. Uncertainties and limitations about unfavourable effects

No events of suspected NSF or symptoms suspected to be related to NSF were reported. However, the largest number of subjects were included in studies GDX-44-010 and GDX-44-011, but these studies had a safety follow-up visit one day after the last administration of the contrast agent but no long-term follow-up visit. The cross-over design is also not suitable to evaluate the risk of developing NSF with gadopiclenol compared to gadobutrol or placebo. Patients with renal impairment are at larger risk for developing NSF after the administration of gadolinium-based contrast agents. In study GDX-44-005, no symptoms of NSF were observed after 6 months. However, this study included a small number of subjects and is therefore not considered sufficient to evaluate the risk of NSF. In addition, this study did not compare the administration of gadopiclenol vs other GBCA. The risk of developing NSF with gadopiclenol compared to other gadolinium-based contrast agents has not been fully evaluated and NSF was included as an important identified risk in the RMP.

The number of subjects included with severe renal impairment is very small (n=16) and the number of patients with moderate renal impairment is not large (n=57). The incidence of AEs was higher in patients with severe renal impairment compared to patients with no or mild renal impairment. This is not unexpected, but with this small number of subjects, a safety evaluation cannot be performed. Gadopiclenol should only be used in patients with severe renal impairment (GFR < 30 ml/min/1.73m2) and in patients in the perioperative liver transplantation period after careful risk/benefit assessment (see section 4.2 of the SmPC). In patients with renal impairment, the elimination of gadopiclenol is prolonged proportionally to the degree of renal impairment. Renal insufficiency (decreased elimination) is identified as a risk factor for the important potential risks in the RMP, (accumulation and retention of gadolinium).

Due to the intermittent method of administration, no long-term safety data is available. No repeat dose data is available with the intended dose and target population. Gadolinium retention in the skin, bone, liver and other organs has been reported with macrocyclic GBCAs. No AEs were reported in this application that were attributed to gadolinium retention. The safety implications of gadolinium retention are unknown. The risk of gadolinium retention with gadopiclenol specifically compared to other gadolinium-based contrast agents has not been evaluated. Gadolinium retention is therefore included in the RMP as an important potential identified risk. As such, gadopiclenol is to be included in a category 3 PASS (Prospective Evaluation of Potential Effects of Repeated gadolinium-based contrast agent (GBCA) Administrations of the Same GBCA on Motor and Cognitive Functions in Neurologically Normal Adults in Comparison to a Non-GBCA Exposed Control Group – ODYSSEY) to evaluate the potential effect on motor and cognitive function.

3.6. Effects Table

Table 121. Effects table for gadopiclenol for CNS and other body regions MRI

Effect	Short Description	Unit	Gadopiclenol	Gadobutrol	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint Lesion visualisation criteria **CNS**	Border delineation	LSM (SE)	3.83 (0.02)	3.82 (0.02)	**SoE:** LSM difference (95%CI) 0.01 (-0.02; 0.05); p=0.50; Demonstration of non-inferiority for all 3 readers; lower limit 95%CI largely above non-inferiority margin of -0.35 Consistent effect across subgroups in terms of demographic parameters and magnetic field strength; supported by all secondary endpoints **Unc:** - some disorders, different stages of the underlying diseases and lesion types are under- or not represented	44-010
	Internal Morphology	LSM (SE)	3.83 (0.02)	3.81 0.02)	**SoE:** LSM difference (95%CI) 0.02 (-0.01; 0.05); p=0.20	44-010
	Degree of contrast enhancement	LSM (SE)	3.73 (0.03)	3.68 (0.03)	**SoE**: LSM difference (95%CI) 0.05 (0.01; 0.09); p=0.017	44-010
Primary endpoint Lesion visualisation criteria **MSBR&BO**	Border delineation	LSM (SE)	3.60 (0.03)	3.60 (0.03)	**SoE**: LSM difference (95%CI) 0.00 (-0.05; 0.04); p=0.90 Demonstration of non-inferiority for all 3 readers; lower limit 95%CI largely above non-inferiority margin of -0.35. Consistent effect across subgroups in terms of demographic parameters and magnetic field strength; supported by all secondary endpoints **Unc:** - Non-inferiority not shown for the musculoskeletal body region and the body organs pancreas, kidney, and prostate. Some disorders/ organs, different stages of the underlying diseases and lesion types are under- or not represented	44-011
	Internal Morphology	LSM (SE)	3.75 (0.02	3.76 (0.02)	**SoE**: LSM difference (95%CI) - 0.01 (-0.05; 0.03); p=0.68	44-011

Effect	Short Description	Unit	Gadopiclenol	Gadobutrol	Uncertainties/ Strength of evidence	References
	Degree of contrast enhancement	LSM (SE)	3.30 (0.04)	3.29 (0.04)	**SoE**: LSM difference (95%CI) 0.01 (-0.05; 0.07); p=0.86	44-011
Secondary endpoints **CNS**	Impact on patient treatment plan (changed)	%	23.3	23.7		44-010
Secondary endpoints **MSBR&BO**	Impact on patient treatment plan (changed)	%	30.1	29.3		44-011
Unfavourable Effects						
AEs	proportion	%	23.6	18.6		Pooled (eight phase 1-3 clinical studies)
Death	number	N	1	1		
Non-fatal AEs	proportion	%	1.1	0		

Abbreviations: AE: adverse event, SAE: serious adverse event

MSBR&BO: Musculoskeletal body region and the body organs

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Associations have been reported between gadolinium-based contrast agents (GBCAs) and nephrogenic systemic fibrosis (NSF) and gadolinium deposition in the brain and other organs. In this context, regulatory bodies recommend using the minimum GBCA dose that provides sufficient contrast enhancement for diagnosis in routine practice. Thus, the development of high-relaxivity GBCAs meets a true medical need since such agents would allow a reduction of the injected dose with the same efficacy as the other available GBCAs. Due to its high relaxivity, gadopiclenol can be given at half a dose of gadolinium compared to other non-specific gadolinium-containing contrast agents while providing the same contrast enhancement.

The current application is based on the results of the two confirmatory studies GDX-44-010 for CNS imaging and GDX-44-011 for body imaging, which included two co-primary objectives, i.e. superiority of combined unenhanced/enhanced imaging with gadopiclenol vs. unenhanced imaging and non-inferiority of gadopiclenol (0.05 mmol/kg) vs. gadobutrol (0.1 mmol/kg) enhanced imaging in terms of 3 qualitative lesion visualisation criteria (border delineation, internal morphology, and degree of contrast enhancement) as judged by 3 independent readers.

In the two pivotal studies, both primary objectives were achieved for all three readers. The results of the primary objectives are supported by relevant secondary endpoints, including quantitative assessment (CNR, LBR, % of lesion enhancement), diagnostic confidence, overall diagnostic preference, technical adequacy of images, and lesion visualisation assessment by the investigator. The percentage of treatment plan changed based on paired images compared with pre-contrast images was similar between gadopiclenol and gadobutrol (23.3% vs 23.7% for CNS imaging and 30.1% vs 29.3% for body imaging, respectively).

Concordance assessment showed that, at lesion level, 88.0% to 89.8% (depending on the blinded reader) of the CNS lesions detected with gadobutrol were also detected with gadopiclenol ("perfect matching lesions") and that at patient level a relatively high perfect agreement between gadopiclenol and gadobutrol was observed (84.3% to 86.0% of the patients). For the other body regions, at lesion level, relatively high percentages of perfect matching lesions were observed in the body MRI study (89.5% to 100% for head & neck, 88.3% to 92.2% for thorax, 91.7% to 100% for pelvis, 94.6% to 95.2% for abdomen, and 100% for musculoskeletal, depending on the blinded reader). At patient level, a relatively high perfect agreement between gadopiclenol and gadobutrol was observed for pelvis (87.5% to 94.6% of the patients, depending on reader), abdomen (84.0% to 87.2%), and musculoskeletal (100%). A lower percentage of perfect agreement between gadopiclenol and gadobutrol was observed for head & neck (70.6% to 94.1%) and thorax (69.8% and 73.2%). An explanation for these lower percentages has not been provided. Nevertheless, the discordances in lesions in the thorax group were almost all attributed to the reader. Additionally, the discordances both in CNS and other body regions did not highlight any concern regarding clinical impact. Additionally, there were no large differences in the intra- and inter-reader agreement between the two contrast agents, which is reassuring.

Further, the external validity of the pivotal studies has been widely discussed since the fact that some disorders/ organs, different stages of the underlying diseases and lesion types are not represented or underrepresented in the pivotal studies. Considering that non-inferiority of gadopiclenol compared to gadobutrol was demonstrated over the total population, that gadobutrol is indicated for CNS and body

imaging without restrictions and that gadolinium is a well-established contrast agent, it is considered acceptable to extrapolate the overall results to the organs which are under- or not represented. Therefore, information on no or limited data for CNS and body imaging of patients with inflammatory, infectious, autoimmune or demyelinating disorders has been included in section 4.4 of the SmPC.

Administration of gadopiclenol at 0.05 mmol/kg in paediatric subjects 2-17 years old resulted in enhancement of the CNS and body images in terms of the quantitative parameters (signal intensity, percentage of lesion enhancement and LBR (only for body)) and the qualitative parameters (lesion visualisation score). The improvements in these technical performance parameters appeared much less pronounced compared with the adult population, particularly concerning CNS imaging, which can be explained by the different histology of paediatric lesions included in the study compared to the adult population. Moreover, the applicant has adequately substantiated that results found in the adult CNS and body MRI study can be extrapolated to the paediatric populations since the determinants of contrast enhancements in paediatric and adult diseases are the same and the PK profile of gadopiclenol in paediatric patients aged 2 to 18 years are comparable to the PK profile in adults.

Safety data are based on eight clinical studies in which 1047 subjects were exposed to gadopiclenol (majority at 0.05 mmol/kg), including 80 paediatric patients (i.e., 7.6% of the study population). The number of patients exposed is considered sufficient for short-term safety evaluation. The most common AEs with gadopiclenol (reported in at least 10 subjects) were headache, injection site pain, contact dermatitis, nausea, injection site hematoma and dizziness, which appear in line with other authorised GBCAs, i.e., gadobutrol (or gadobenate dimeglumine). Based on the efficacy results, it can be concluded that gadopiclenol at 0.05 mmol/kg, which is half the dose of other currently approved GBCAs, including gadobutrol, provided the same contrast enhancement compared with gadobutrol. However, the submitted safety data package only concerns short-term follow-up following a single dose of gadopiclenol, and, consequently, does not provide insight into the incidences of NSF or Gd deposition in the brain and other organs or the differences in risk for NSF and Gd deposition between gadopiclenol and other approved GBCAs or the impact of repeat administrations of gadopiclenol. These limitations have been reflected in the SmPC and in the RMP.

3.7.2. Balance of benefits and risks

The superiority of gadopiclenol-enhanced MRI at 0.05 mmol/kg compared to unenhanced MRI and, more importantly, non-inferiority of gadopiclenol at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg based on 3 lesion visualisation co-primary criteria (border delineation, internal morphology, degree of contrast enhancement) in CNS and body MRI has been demonstrated, which was accompanied by a safety profile in line with other authorised GBCAs, i.e., gadobutrol.

Good concordance was shown between gadopiclenol at 0.05 mmol/kg and gadobutrol at 0.1 mmol/kg, and there were no large differences in the intra- and inter-reader agreement between the two contrast agents.

Some organs, lesions types, and different stages of the underlying disease were under- or not represented. Considering that non-inferiority of gadopiclenol compared to gadobutrol was demonstrated over the total population, that gadobutrol is indicated for CNS imaging without restrictions, and that gadolinium is a well-established contrast agent, it is considered acceptable to extrapolate the overall results to these disease-specific characteristics or organs which are under- or not represented. See section 4.4 of the SmPC.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Elucirem is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Elucirem is favourable in the following indication(s):

This medicinal product is for diagnostic use only:

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

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

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product on medical prescription for renewable or non-renewable delivery.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that gadopiclenol is to be qualified as a new active substance in itself as it is a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0151/2021 and P/0152/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.