NDA Multidisciplinary Review and Evaluation

Application Type	PRIOR APPROVAL SUPPLEMENT: Efficacy
Application Number(s)	NDA 020131/S-035 and NDA 021489/S-014
Priority or Standard	Standard
Submit Date(s)	2/26/2020
Received Date(s)	2/26/2020
PDUFA Goal Date	12/26/2020
Division/Office	Division of Imaging and Radiation Medicine/Office of Specialty Medicine
Review Completion Date	11/15/2020
Established/Proper Name	Gadoteridol
(Proposed) Trade Name	ProHance
Pharmacologic Class	Gadolinium-based paramagnetic MRI contrast agent
Applicant	Bracco Diagnostics Inc.
Dosage form	279.3 mg/mL
Applicant Proposed Dosing Regimen	Recommended dose in adults and pediatric patients including terms neonates is 0.1 mmol/kg (0.2 mL/kg) administered as rapid intravenous infusion or bolus.
Applicant Proposed Indication/Populations	For intravenous use to visualize: • lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues in adult and pediatric patients including term neonates • lesions in the head and neck in adults
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	440450002
Recommendation on Regulatory Action	Approval
Recommended Indication/Populations	MRI of the Central Nervous System (CNS) For magnetic resonance imaging (MRI) in adults and pediatric patients including term neonates to visualize lesions with disrupted blood brain barrier and/or abnormal vascularity in the brain (intracranial lesions), spine and associated tissues.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Not applicable

Recommended Dosing Regimen	The recommended dose for adult and pediatric patients, including term neonates, is 0.2 mL/kg (0.1 mmol/kg) administered as a rapid intravenous infusion (10 mL/min to 60 mL/min) or bolus (greater than 60 mL/min).

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Abbreviations: OB, Office of Biostatistics; OCP, Office of Combination Products

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Abbreviations: DMEPA, Division of Medication Error Prevention and Analysis; DPV, Division of Pharmacovigilance; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology;

Glossary

ADME	absorption, distribution, metabolism, excretion
AR	adverse reaction
AUC	area under the plasma drug concentration-time curve
BLA	biologics license application
BP	blood pressure
BW	body weight
CDER	Center for Drug Evaluation and Research
CNR	contrast-to-noise ratio
CNS	central nervous system
CRCL	creatinine clearance
DIRM	Division of Imaging and Radiation Medicine
DPV	Division of Pharmacovigilance
ECG	electrocardiogram
EMA	European Medicines Agency
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
GBCA	gadolinium-based contrast agent
GDD	gadolinium deposition disease
GFR	glomerular filtration rate
ICC	intraclass correlation coefficient
ITD	intent-to-diagnose
LBR	lesion-to-brain ratio
LL	lower limit
MRI	magnetic resonance imaging
NDA	new drug application
NSF	nephrogenic systemic fibrosis
PDSS	Postmarket Drug Safety Surveillance
PK	pharmacokinetic
sNDA	supplemental new drug application

1. Executive Summary

1.1. Product Introduction

ProHance is the trade name for Gadoteridol injection. ProHance belongs to the gadolinium-based contrast agent (GBCA) pharmaceutical class. Molecules of this class incorporate the paramagnetic metal gadolinium (Gd^{3+}) that reduces local relaxation times and produces enhancement on T1-weighted magnetic resonance imaging (MRI). GBCAs are classified as ionic or nonionic; linear or macrocyclic; non-, weakly, or strongly protein-binding; and FDA-labeled as relatively higher or lower risk of nephrogenic systemic fibrosis (NSF). ProHance is a macrocyclic, ionic, nonprotein-binding, relatively lower NSF-risk GBCA.

There are currently 6 marketed FDA approved GBCAs listed here in order of their approval: ProHance (1992), Omniscan (1993), MultiHance (2004), Eovist (2008), , Gadavist (2011), and Dotarem (2013). ProHance was first approved in the United States in December 1992 for use in MRI of the central nervous system (CNS) in adult patients. In August 1994, ProHance was approved for use in MRI of the CNS in pediatric patients older than 2 years of age and MRI of head and neck in adult patients. ProHance is now approved in 29 countries worldwide. Among the three FDA approved macrocyclic GBCAs, Gadavist (Gadobutrol) has also been approved for use in pediatric patients under 2 years of age in 2014, followed by Dotarem (Gadoterate meglumine) in 2016.

In the current FDA labeling, ProHance is indicated for use in magnetic resonance imaging (MRI) in adults and pediatric patients over 2 years of age to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues, and for use in MRI in adults to visualize lesions in the head and neck. The current recommended dose in adult patients and pediatric patients older than 2 years of age for MRI of the CNS is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion (10 mL/min-60 mL/min) or bolus (>60 mL/min). In adults only, a supplementary dose of 0.2 mmol/kg (0.4 mL/kg) may be given up to 30 minutes after the first dose in patients with normal renal function suspected of having poorly enhancing lesions, in the presence of negative or equivocal scans.

Through this supplemental new drug application (sNDA), the Applicant seeks to expand the use of ProHance to include CNS MRI in pediatric patients younger than 2 years of age, including term neonates at a dose of 0.1 mmol/kg (0.2 mL/kg).

ProHance (Gadoteridol) Injection is available as a 0.5M sterile clear colorless to slightly yellow aqueous solution in vials and syringes for intravenous injection. Each mL of ProHance contains 279.3 mg gadoteridol, 0.23 mg calteridol calcium, 1.21 mg tromethamine and water for injection. ProHance contains no antimicrobial preservative.

An additional sNDA application cross-referencing this application has been submitted in parallel for NDA 021-489 (ProHance® Multipack™ (gadoteridol) injection, 279.3 mg/mL.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness for the use of ProHance administered at a dose of 0.1 mmol/Kg in CNS MRI in pediatric patients younger than 2 years of age has been provided by the Applicant to adequately support approval of this sNDA through Study PH-108. Study PH-108 involved a prospective blinded read of retrospectively collected MR images collected from 5 sites (4 within the United States and one Italian site). While there were some issues related to power estimation and gains in visualization scores that could potentially be driven by large gains in a small subset of lesions (see Section 8.3 "Statistical Issues") as described by the Applicant, further analysis of the submitted data by the FDA statistical reviewer supports the Applicant's conclusions that paired visualization (pre plus postcontrast visualization) of MRI images is superior to visualization of non-contrast images alone and this finding supports the success of Study PH-108. Overall, the results of study PH-108 show that a dose of 0.1 mmol/kg ProHance provides significantly improved contrast enhancement and morphologic assessment of CNS lesions in pediatric patients less than 2 years of age. The improved visualization of CNS lesions with 0.1 mmol/kg ProHance supports extending the indication for use from adults and older pediatric patients (greater than 2 years of age) to younger pediatric patients (less than 2 years of age).

The population pharmacokinetic (PK) modeling and simulation of gadoteridol plasma exposures in pediatric patents less than 2 years of age, from existing PK data in patients greater than 2 years old and adults supported the efficacy findings of study PH-108. The simulations demonstrated that gadoteridol exposures in patients less than 2 years old were predicted to be within the range of the exposure in adults and pediatric patients greater than 2 years of age. Based on these data no dose adjustment is deemed necessary for the pediatric population less than 2 years of age.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment:

For the proposed indication to extend the use of ProHance in MRI of the CNS to neonates and infants (pediatric patients less than 2 years of age, including term neonates), ProHance is administered intravenously at the dose of 0.1 mmol/kg body weight (BW), the same dose as that recommended for CNS MRI in adult and pediatric patients 2 year of age and older. In this supplemental new drug application (sNDA), data supporting the safety of ProHance for use in MRI of the CNS in the pediatric population less than 2 years of age are derived from Applicant sponsored clinical study data, Bracco postmarketing surveillance database, and from the peer-reviewed literature. Clinical study data for ProHance in patients less than 18 years of age are few relative to the wider experience provided by studies in the adult population. To date the safety profiles for both the youngest patient population (less than 2 years of age) and for children 2 to less than 18 years of age are comparable to the profile in adults and are acceptable. Overall, the pediatric population included in the clinical study database comprises 278 children less than 18 years of age; 138 of these are less than 2 years of age including 17 younger than 1 month and 41 between 1 and 6 months of age. These patients were enrolled in three sponsored clinical studies, 32,521-6, 32,521-15P, and PH-108. In study PH-108, ProHance administered at the dose of 0.1 mmol/kg for CNS MR imaging was safe and showed a clinically meaningful improvement in the visualization of CNS lesions in a population of very young patients ranging in age from 1 day postnatal to 24 months. The benefit risk profile of ProHance for MRI of the CNS in neonates and infants is favorable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Safe and efficacious diagnostic tools are needed for the diagnosis and monitoring of CNS disease in pediatric patients including term neonates and infants. • Computed tomography scans, while helpful, are limited by concerns related to radiation exposure to the developing brain. MRI has gained recognition as an optimal technique to assess the structure and function of the CNS without exposure to	• Contrast MRI is an important diagnostic procedure in neonates and infants (Hedlund and Boyer 1999; Dorsett and Liang 2016). Improved visualization of CNS lesions in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	radiation(Brant and Helms 2012; American College of Radiology 2019). • In pediatric patients the conditions that can be assessed with MRI include congenital malformations, inflammatory disease, infection, epilepsy, stroke, and neoplastic disease (Saunders et al. 2007; Paldino et al. 2011)	pediatric patients is clinically meaningful.
Current Treatment Options	• There are currently two macrocyclic GBCAs approved for the proposed indication of intravenous use to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues in adults and pediatric patients less than 2 years old including term neonates. These agents include 1) Gadavist (approved 2014), 2) and Dotarem (approved 2017).	ProHance will be the third GBCA for use in neonates and infants for visualization of lesion with abnormal vascularity in the CNS.
Benefit	• The Applicant conducted study PH-108, a prospective blinded read of retrospectively collected MR images in pediatric patients ≤2 years of age who underwent CNS MRI with and without intravenous administration of 0.1 mmol/kg ProHance. • Study PH-108 met prespecified success criteria for performance and demonstrated ProHance administered at a dose of 0.1 mmol/kg provides MR images with significantly improved overall CNS lesion visualization when compared with noncontrast MR images in young children less than 2 years of age with CNS disease.	While there were some issues related to power estimation and gains in visualization scores being potentially driven by large gains in a small subset of lesions (see "Statistical Issues"), analyses of the submitted data by the FDA statistical reviewer supports the conclusion that paired visualization (pre plus postcontrast visualization) of MR images is superior to visualization of noncontrast images alone and support the success of Study PH-108.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Population pharmacokinetic (PK) modeling and simulation of gadoteridol plasma exposures in pediatric patients less than 2 years of age was used to support the proposed dosing regimen and extrapolation of efficacy. The simulations demonstrated that gadoteridol exposures in pediatric patients less than 2 years old were predicted to be within the range of exposures in adults and patients greater than 2 years of age.	No dose adjustment is deemed necessary for the pediatric population less than 2 years of age and a dose of ProHance 0.1 mmol/kg is recommended.
Risk and Risk Management	• The safety profile of ProHance in adults, in children from 2 to less than 18 years of age, and in children less than 2 years of age was comparable. • Most reported adverse events were mild or moderate in intensity and resolved without sequelae. • No new or unexpected events have been reported. • Based on available clinical and preclinical data, the risk for gadolinium retention does not seem to be different in pediatric patients less than 2 years of age when compared to adults and older pediatric patients.	The review team identified no major safety issue in the use of ProHance at a dose of 0.1 mmol/kg for CNS MRI in pediatric patients less than 2 years of age.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

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

	□	Patient-focused drug development or other stakeholder meeting summary reports	
	□	Observational survey studies designed to capture patient experience data	
	□	Other: (Please specify):	
X	**Patient experience data was not submitted as part of this application.**		

2. Therapeutic Context

2.1. Analysis of Condition

MRI has gained recognition as an optimal imaging technique to assess the structure and function of the CNS adults as well as pediatric patients without exposure to ionizing radiation (Brant and Helms 2012; American College of Radiology 2019). GBCAs are used in as many as 30% of MRIs that are performed in the United States (Harvey et al. 2020). In general, evidence shows that GBCAs enable better visualization of lesions that are either not easily visible or not visible at all without contrast (Runge et al. 2001; Kastrup et al. 2008; Tanenbaum 2015; Rozenfeld and Podberesky 2018). GBCAs with MRI also aid in the differentiation of CNS lesions.

While there is growing evidence in support of the efficacy and safety of GBCAs in children older than 2 years of age, evidence in patients less than 2 years of age is more limited. To date, only two of the macrocyclic GBCAs (Gadavist and Dotarem) and one linear GBCA (MultiHance) have been approved for use in patients less than 2 years of age. Thus far, ProHance has been used off-label in this vulnerable patient population. Through this sNDA the Applicant proposes to expand its use to pediatric patients less than 2 years of age including term neonates to visualize lesions in the CNS.

2.2. Analysis of Current Treatment Options

Of the nine GBCAs that are currently approved for intravenous use in the United States, eight are approved for use in pediatric patients. Three GBCAs (Gadavist, Dotarem and MultiHance) are approved for use in pediatric patients less than 2 years of age. Gadavist (nonionic) and Dotarem (ionic) are macrocyclic GBCAs that were approved for use in pediatric patients less than 2 years of age in December 2014 and August 2017, respectively. MultiHance, a linear ionic GBCA, was approved for use in pediatric patients less than 2 years of age in January 2018. Thus far, ProHance, has only been approved for pediatric patients older than 2 years of age and is being used off-label in patients less than 2 years of age. Table 1 shows the currently approved GBCAs and their approval status for CNS MRI in pediatric patients.

Table 1. Reviewer's Tabulation of FDA Approved GBCAs, Their Characteristics and Current Pediatric Approval Status for CNS MRI

Proprietary Name	Chemical Name	Structure	Date of Approval (New Molecular Entity)	FDA Approval for Pediatric CNS MRI	ACR Risk Category*	Osmolality (mOsm/kg)
Dotarem	Gadoterate	macrocyclic ionic	3/20/2013	Yes, including term neonates	2	1,350
Gadavist	Gadobutrol	macrocyclic nonionic	3/14/2011	Yes, including term neonates	2	1,603
ProHance	Gadoteridol	macrocyclic nonionic	11/16/1992	Yes, 2 years of age and older	2	630
Eovist	Gadoxetate	linear ionic	7/3/2008	Yes, ages greater than 2 months	3	688
MultiHance	Gadobenate	linear ionic	11/23/2004	Yes, including term neonates	2	1,970
Magnevist	Gadopentetate	linear ionic	6/2/1988	Yes, 2 years of age and older	1	1,960
Optimark	Gadoversetamide	linear nonionic	12/8/1999	No	1	1,110
Omniscan	Gadodiamide	linear nonionic	1/8/1993	Yes, 2 years of age and older	1	789

Source: ACR Manual on Contrast Media, 2020, ISBN: 978-1-55903-012-0 – https://www.acr.org/-/media/ACR/files/clinical-resources/contrast_media.pdf

* American College of Radiology risk category for NSF[1] -

Note: Category 1: agents associated with the greatest number of NSF cases; Category 2: agents associated with few, if any, unconfounded cases of NSF; Category 3: agents for which data remains limited regarding NSF risk,

Abbreviation: CNS, central nervous system; FDA, Food and Drug Administration; GBCA, gadolinium-based contrast agent; MRI, magnetic resonance imaging; NSF, nephrogenic systemic f brosis

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Gadoteridol injection (Trade name – ProHance) was approved in the United States in December 1992 for use in MRI of the CNS in adult patients. In August 1994, ProHance was approved for use in MRI of the CNS in pediatric patients older than 2 years of age and MRI of head and neck in adult patients. ProHance is approved in 29 countries worldwide. Among the total number of patients receiving MultiHance 14,033,053 (45.4%) were from North America (U.S. and Canada), 9,897,353 (32%) from the EU and other European countries, 4,758,965 (15.4%) from Japan, and 2,224,485 (7.3%) from other countries of the world.

Per language in the FDA label, ProHance is currently indicated for use in magnetic resonance imaging (MRI) in adults and pediatric patients greater than 2 years of age to visualize lesions with abnormal vascularity in the brain (intracranial lesions), spine and associated tissues, and for use in MRI in adults to visualize lesions in the head and neck. The current recommended dose in adult patients and pediatric patients greater than 2 years of age for MRI of the CNS is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion (10 mL/min-60 mL/min) or bolus (>60 mL/min). In adults only, a supplementary dose of 0.2 mmol/kg (0.4 mL/kg) may be given up to 30 minutes after the first dose in patients with normal renal function suspected of having poorly enhancing lesions, in the presence of negative or equivocal scans.

3.2. Summary of Presubmission/Submission Regulatory Activity

Bracco submitted this sNDA to include the administration of ProHance in pediatric patients less than 2 years of age. To support this sNDA, Bracco submitted the following:

- Report of a clinical study titled PH-108
- Report of a population PK and PK simulations analysis.
- Postmarketing safety data from patients less than 2 years of age exposed to ProHance.
- Summary of studies from peer-reviewed literature – in which patients below the age of 2 years were exposed to ProHance

The Applicant submitted a pre-sNDA meeting package in May 2018.

The Division had specific feedback points to the Applicant on Study PH-108 which included the following – 1) randomize the patient order within each of the two big blocks, 2) ensure that the demographics of enrolled patients represent the range of patients for which approval was being sought , and 3) submit the final statistical analysis plan for the study .

The Division, in principle, also agreed to the Applicant's proposed population PK simulation to support the proposed dose regimen in pediatric patients less than 2 years of age. On July 1, 2018 – the Applicant followed the Division's advice and submitted the following:

- The final protocol for study PH-108
- Case report forms for study PH-108 incorporating all of the Division's comments,
- A copy of the final Statistical Analysis Plan for the study.

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

4.1. Office of Scientific Investigations (OSI)

A site inspection was not needed for this sNDA.

4.2. Product Quality

This section is not applicable to this sNDA.

4.3. Clinical Microbiology

This section is not applicable to this product.

4.4. Devices and Companion Diagnostic Issues

This section is not applicable to this product.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The purpose of this review is to provide a nonclinical assessment of gadoteridol based on findings from a class perspective (linear and macrocyclic GBCA), to support inclusion of an additional patient population to the current indication, specifically inclusion of pediatric patients less than 2 years of age (including term neonates).

The proposed indication statement is "ProHance is indicated for (b) (4) magnetic resonance imaging (MRI) in adults and pediatric patients including term neonates to visualize lesions with (b) (4) blood-brain barrier and/or abnormal vascularity in the brain (intracranial lesions), spine and associated tissues. An additional sNDA application cross-referencing this application is being submitted in parallel to NDA 021-489 (ProHance® Multipack™ (gadoteridol) injection, 279.3 mg/Ml.

No new findings were identified from juvenile animal studies for structurally similar macrocyclic GBCAs (i.e., gadoterate meglumine; (Giorgi et al. 2015)) or linear agents (i.e., gadobenate; (Bussi et al. 2018c)) when evaluated against findings in adult animal studies. More importantly, the risk to the pediatric population may be more directly related to PK/ADME properties of GBCAs which can affect Gd retention. Repeat administration of gadoteridol resulted in significantly less Gd retention in the kidney, liver, and skin and comparable levels in the brain and bone when compared to other structurally similar GBCAs (McDonald et al. 2017a; Bussi et al. 2018b; Bussi et al. 2020).

There are ongoing nonclinical safety studies in juvenile mice and nonhuman primates as part of postmarketing requirements for approved GBCAs to evaluate Gd retention (McDonald et al. 2018); the results of these studies will inform future labeling. There is also clinical experience with gadoteridol in the intended pediatric population to inform on safety. From a nonclinical perspective, there is adequate data from macrocyclic GBCAs as a class to support the conclusion that a dedicated juvenile toxicity study is not needed for this application.

It is recommended that this supplemental NDA (s-35/s-14) for the proposed use of ProHance (Gadoteridol) in pediatric patients under 2 years of age (including term neonates) be approved from a nonclinical perspective.

5.2. Referenced NDAs, BLAs, DMFs

NDA 020-131 and NDA 021-489

5.3. Pharmacology

ProHance (0.5 M gadoteridol) is a MRI agent to visualize lesions with abnormal vascularity in the brain, spine and associated tissues. Gadoteridol (Gd-HP-DO3A) is a thermodynamically stable octadentate chelate of the paramagnetic gadolinium ion, Gd^{3+}, which based on PK/ADME properties, is intended for use as an intravascular MRI contrast agent. Following intravenous administration, gadoteridol distributes rapidly to the extracellular space. Based on the NDA review by Dr. John Melograna and published studies (Eakins et al. 1995; Lancelot 2016), gadoteridol is excreted unchanged, primarily by the renal route with an elimination half-life of less than 2 hours (94.2±4.8 min) and greater than 94% (94.4±4.8%) of the injected dose eliminated within 24 hours. The primary pharmacology of gadoteridol was previously reviewed in NDA 020-131 and is comparable to other macrocyclic GBCAs, i.e., gadobutrol and gadoterate.

5.4. ADME/PK

The Applicant did not conduct dedicated PK or toxicokinetic studies in juvenile animals to support the efficacy supplement. Pharmacokinetic/toxicokinetic properties of structurally similar macrocyclic GBCAs (i.e., gadoterate) have been evaluated in juvenile animals following single and repeat dosing and a treatment-free recovery period (Giorgi et al. 2015; Fretellier et al. 2019) and demonstrated dose-dependent retention with ongoing Gd elimination during recovery. Systemic exposure to GBCAs following a single dose decreased with age, likely due to maturation of kidney function and improved clearance. Comparative PK/ADME studies have been performed in adult animals, evaluating gadolinium retention for gadoteridol and other GBCAs (McDonald et al. 2017a; Bussi et al. 2018b; Bussi et al. 2020). Tissue gadolinium levels in rats following repeat dosing and recovery were greatest in kidney > bone >> liver and skin > brain for all GBCAs. Gadoteridol demonstrated comparable or greater elimination when compared to other to other macrocyclic GBCA (i.e., gadobutrol and gadoterate).

The PK/ADME properties of gadoteridol were previously reviewed in NDA 020-131 and are comparable to other macrocyclic GBCAs.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant did not submit general toxicology study reports to support the efficacy supplement.

General toxicology study reports were not submitted and are not needed. No new toxicity findings were observed for structurally similar GBCAs (i.e., gadoterate meglumine and gadobutrol) in dedicated juvenile animal studies conducted in rats. Class-related toxicity findings are directly related to the PK/ADME properties of GBCAs, rapid distribution following

intravenous administration and elimination from the intravascular space primarily by the kidneys.

5.5.2. Genetic Toxicology

Genetic toxicology studies were not submitted with the efficacy supplement and were previously reviewed as part of the original NDA review.

5.5.3. Carcinogenicity

Carcinogenicity studies were not submitted with the efficacy supplement and are not required.

5.5.4. Reproductive and Developmental Toxicology

Reproductive and developmental toxicology studies were not submitted with the efficacy supplement and were previously reviewed as part of the original NDA review.

5.5.5. Other Toxicology Studies

None.

6. Clinical Pharmacology

6.1. Executive Summary

In this submission, the Applicant is seeking to extend the CNS indication to neonates and infants less than two years of age. The proposed dose for the additional population targeted is the same as the approved dose in adults and pediatrics greater than 2 years old, 0.1 mmol/kg administered as an intravenous bolus injection.

The Applicant submitted population PK modeling and simulation of gadoteridol plasma exposures in pediatrics less than 2 years of age, based on existing PK data in pediatrics greater than 2 years old and adults, to support the proposed dosing regimen and extrapolation of efficacy. The simulations demonstrated that gadoteridol exposures in pediatrics less than 2 years old were predicted to be within the range of that in adults and pediatrics greater than 2 years of age.

The key points supporting use of PK simulations are that gadoteridol is cleared almost entirely by renal elimination (>95%) and that for products cleared by this mechanism, maturation of renal function has been established previously by (Anderson and Holford 2008). Additionally, the proposed dose has been evaluated for safety in 125 pediatric patients less than 2 years of age in Study PH-108. Therefore, the proposed weight-based dose (0.1 mmol/kg) in pediatrics less than 2 years old is acceptable.

The review issues with specific recommendations and comments are summarized below.

6.1.1. Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness for MRI of the CNS in pediatrics less than 2 years of age is demonstrated in a retrospective trial PH-108. Population PK modeling and simulation provides supportive evidence of efficacy by supporting extrapolation of efficacy from adults and pediatrics over 2 years of age with an exposure-matching approach.
General dosing instructions	The recommended dose for MRI of the CNS is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion (10 mL/min to 60 mL/min) or bolus (greater than 60 mL/min) in pediatric patients less than 2 years of age and weighing at least 2.5 kg.
Labeling	**Section 2 Dosage and Administration** The proposed dose of 0.1 mmol/kg is acceptable. **Section 8.4 Pediatric Use** Pharmacokinetic studies suggest that weight normalized clearance of ProHance is similar in pediatric patients and adults, including pediatric patients age less than 2 years of age. **Section 12.3 Pharmacokinetics** The population PK analysis results were summarized in the Pediatric subsection. PK simulations indicate similar half-life, AUC, and C_{max} values for ProHance in pediatric patients less than 2 years of age when compared to those reported for adults; no age-based dose adjustment is necessary for this pediatric population.

There are no postmarketing requirements and commitments.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

A population pharmacokinetic analysis was conducted in 79 subjects, including 51 adult subjects and 28 pediatric subjects between 5 years and 15 years of age, from Study 32,521-29 (Study 29), Study 32,521-27 (Study 27), and Study 32,521-12 (Study 12). The pediatric patients received a single intravenous dose of 0.1 mmol/kg of ProHance. Refer to Section 6.3.1 for detailed PK parameters obtained from the population PK analysis. There was no significant gender-related difference in the PK parameters in the pediatric patients. Over 80% of the dose was recovered in urine for pediatric patients after 10 hours. PK simulations indicate similar half-life, area under the plasma drug concentration-time curve (AUC), and C_{max} values for ProHance in pediatric subjects less than 2 years of age when compared to those reported for adults; no age-based dose adjustment is necessary for this pediatric population.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

- The recommended dose for MRI of the CNS is 0.1 mmol/kg (0.2 mL/kg) administered as a rapid intravenous infusion (10 mL/min to 60 mL/min) or bolus (greater than 60 mL/min) in pediatric patients less than 2 years of age and weighing at least 2.5 kg.
- Safety and efficacy of doses greater than 0.1 mmol/kg, and sequential and/or repeat procedures have not been studied
- Follow injection by at least a 5 mL normal saline flush

Therapeutic Individualization

Dose adjustment is not recommended for factors other than body weight (BW) in pediatrics less than 2 years of age. Dose adjustment in adults and pediatrics greater than 2 years of age should follow the recommendations in the current approved labeling.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Gadoteridol is a paramagnetic agent and, as such, develops a magnetic moment when placed in a magnetic field.
Active Moieties	Gadoteridol is the pharmacological active moiety.
QT Prolongation	Unknown.

General Information	
Bioanalysis	Gadoteridol blood and urine samples from Studies 27 and 29 were analyzed using inductively coupled plasma-atomic emission spectroscopy (ICP-AES), with a range of 0.2 to 40 µg/mL and a lower limit of quantification of 0.2 µg/mL. Gadoteridol serum and urine samples from Study 12 were determined by radioimmunoassay with a range of 0 to 25 µg/mL and a lower limit of detection of 0.05 µg/mL.
Drug exposure after first dose	The mean ± SD $AUC_{0\text{-}24hr}$, C_{max}, C20 and C30 of gadoteridol in each age group were listed below:

Age Group	$AUC_{0\text{-}24hr}$ (mmol/L·h)	C_{max} (mmol/L)	C_{20} (mmol/L)	C_{30} (mmol/L)
0-1 months	1.66±0.46	0.43±0.10	0.30±0.07	0.27±0.06
1-6 months	1.23±0.39	0.46±0.11	0.30±0.07	0.27±0.06
6-12 months	0.98±0.30	0.49±0.11	0.31±0.07	0.28±0.06
12-24 months	0.94±0.28	0.53±0.12	0.34±0.08	0.29±0.07
2-4 years	0.95±0.28	0.55±0.13	0.35±0.08	0.30±0.07
4-6 years	1.02±0.31	0.59±0.14	0.37±0.09	0.32±0.07
6-12 years	1.13±0.34	0.64±0.14	0.41±0.10	0.35±0.08
12-18 years	1.31±0.40	0.72±0.17	0.46±0.11	0.40±0.09
Adults	1.39±0.42	0.76±0.18	0.49±0.11	0.42±0.10

Abbreviations: $AUC_{0\text{-}24hr}$, area under the plasma concentration time curve from dosing to 24 hours postdose; C_{20}, simulated ProHance concentration at 20 minutes; C_{30}, simulated ProHance concentration at 30 minutes; C_{max}, maximum concentration

Drug total exposure at steady state following the therapeutic dosing regimen	Not applicable as gadoteridol is a product for single administration.
Minimal effective dose or exposure	The minimum effective dose is 0.1 mmol/kg in adults and pediatrics greater than 2 years old.
Maximal tolerated dose or exposure	No increase in the occurrence of laboratory abnormalities or clinical adverse events accompanied the increasing doses from 0.05 mmol/kg to 0.3 mmol/kg.
Dose Proportionality	Gadoteridol exposure increased approximately dose-proportionally from 0.05 to 0.3 mmol/kg.
Accumulation	Not applicable as gadoteridol is a product for single administration.
Variability	The observed inter-subject variability (CV%) for AUC_{inf} was 29% in pediatric subjects 2 years to 6 years of age, 12% in pediatric subjects 6 years to 12 years of age, 9% in adolescent subjects older than 12 years of age, and 27% in adult subjects.
Distribution	
Volume of Distribution	The mean ± SD V_{SS} was 371±84 mL/kg in pediatrics 0-1 month, 347±80 mL/kg in pediatrics 1-6 months, 320±72 mL/kg in pediatrics 6-12 months, 297±68 mL/kg in pediatrics 12-24 months, 285±66 mL/kg in pediatrics 2-4 years, 269±62 mL/kg in pediatrics 4-6 years, 247±57 mL/kg in pediatrics 6-12 years, 222±51 mL/kg in adolescents 12-18 years, and 212±48 mL/kg in adult subjects, which is generally equal to that of extracellular water.
Plasma Protein Binding	It is unknown if protein binding of gadoteridol occurs in vivo.
Blood to Plasma Ratio	Unknown.

Elimination	
Clearance	The mean ± SD CL was 64±20 mL/h/kg in pediatrics 0-1 month, 90±29 mL/h/kg in pediatrics 1-6 months, 111±33 mL/h/kg in pediatrics 6-12 months, 115±33 mL/h/kg in pediatrics 12-24 months, 114±34 mL/h/kg in pediatrics 2-4 years, 107±31 mL/h/kg in pediatrics in pediatrics 4-6 years, 96±29 mL/h/kg in pediatrics 6-12 years, 84±25 mL/h/kg in adolescents 12-18 years, and 79±23 mL/h/kg in adult subjects.
Mean terminal elimination half-life	The mean ± SD terminal elimination half-life was 4.4±1.3 h in pediatrics 0-1 month, 3.0±1.0 h in pediatrics 1-6 months, 2.3±0.67 h in pediatrics 6-12 months, 2.0±0.59 h in pediatrics 12-24 months, 2.0±0.58 h in pediatrics 2-4 years, 2.0±0.58 h in pediatrics 4-6 years, 2.1±0.60 h in pediatrics 6-12 years, 2.1±0.61 h in adolescents 12-18 years, and 2.2±0.63 h in adult subjects.
Metabolism	
Primary metabolic pathway(s)	Gadoteridol is eliminated unchanged via the kidneys. There was no detectable biotransformation or in vivo degradation of this substance.
Inhibitor/Inducer	No human drug interaction studies have been performed.
Excretion	
Primary excretion pathways (% dose)	Within 24 hours postinjection 94.4±4.8% (mean ± SD) of the dose is excreted in the urine.

6.3.2. Clinical Pharmacology Questions

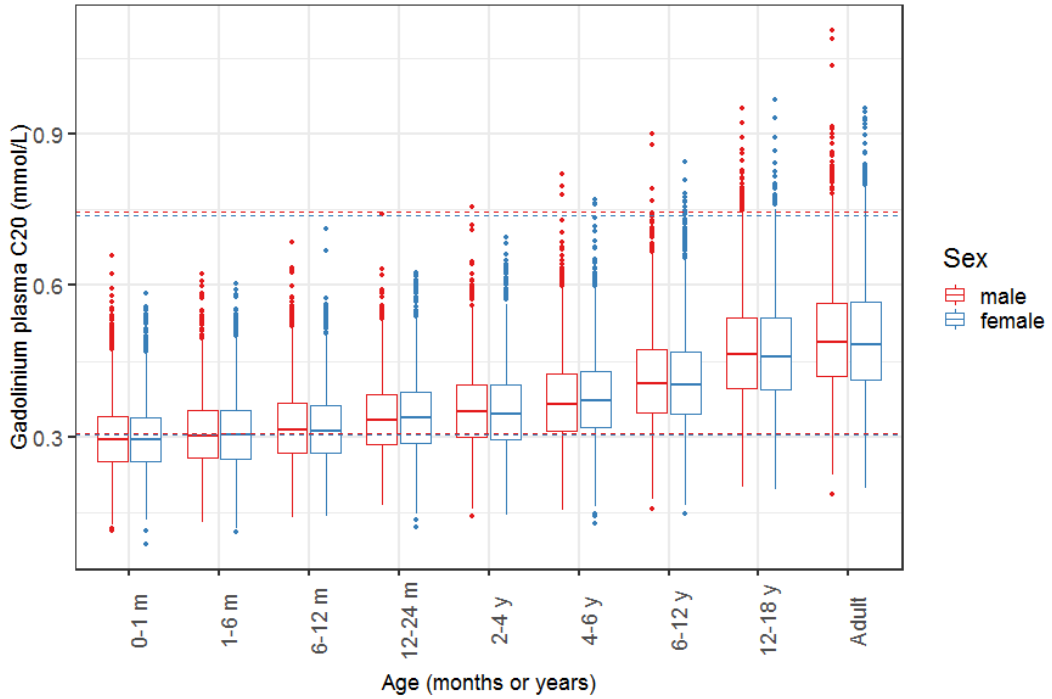
Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Agency had agreed to utilize exposure matching for extrapolation of efficacy from adults and pediatrics greater than 2 years of age. Therefore, the population PK modeling and simulation provides supportive evidence of effectiveness for use of the proposed 0.1 mmol/kg dosing regimen in pediatrics less than 2 year of age.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

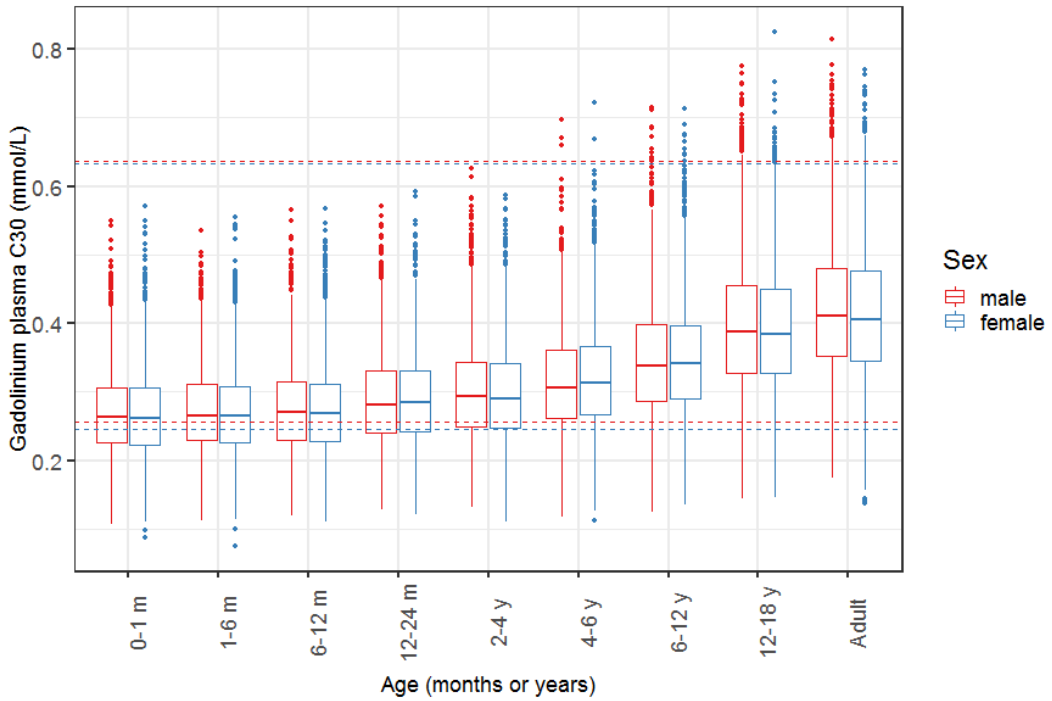
Yes, the Reviewer's independent population PK modeling and simulation show that the simulated concentrations at 20 min (Figure 1) and at 30 min (Figure 2) post injection, $AUC_{0\text{-}24h}$ (Figure 3), and C_{max} (Figure 4) in pediatric patients less than 2 years of age appear to fall within the range of those in adults and children over the age of 2 years at the same dose of 0.1 mmol/kg. Refer to Appendix 16.4 for details.

Figure 1. Simulated ProHance Concentration at 20 Minutes (C20) by Age (0.1 Mmol/Kg)



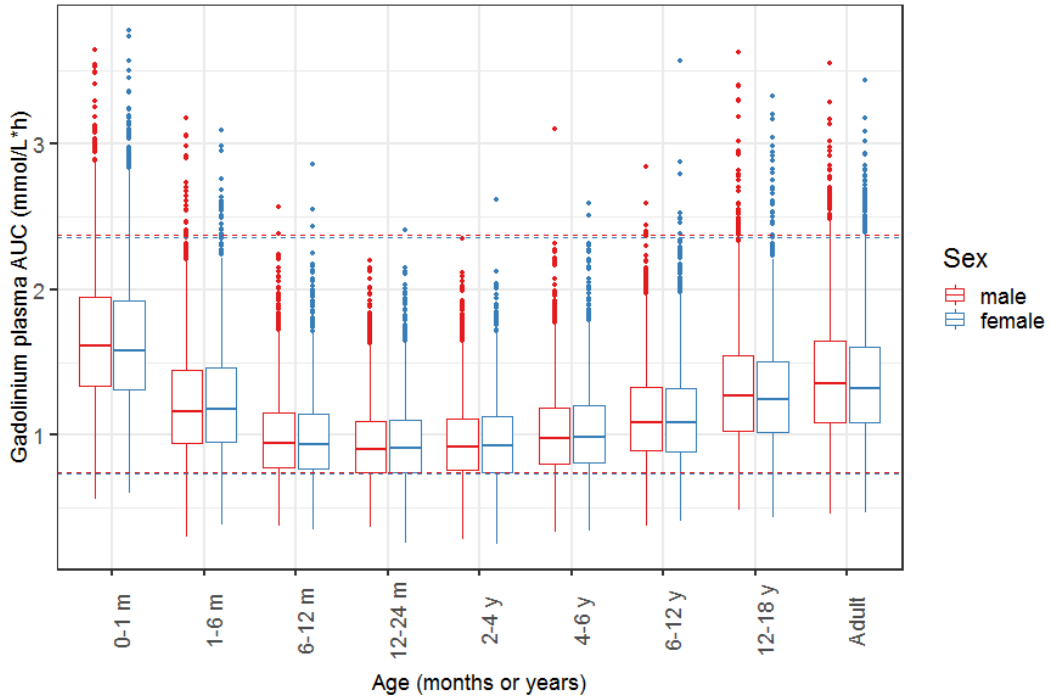
Source: Reviewer's analysis.
Abbreviations: m, month; y, year

Figure 2. Simulated ProHance Concentration at 30 Minutes (C30) by Age (0.1 Mmol/Kg)



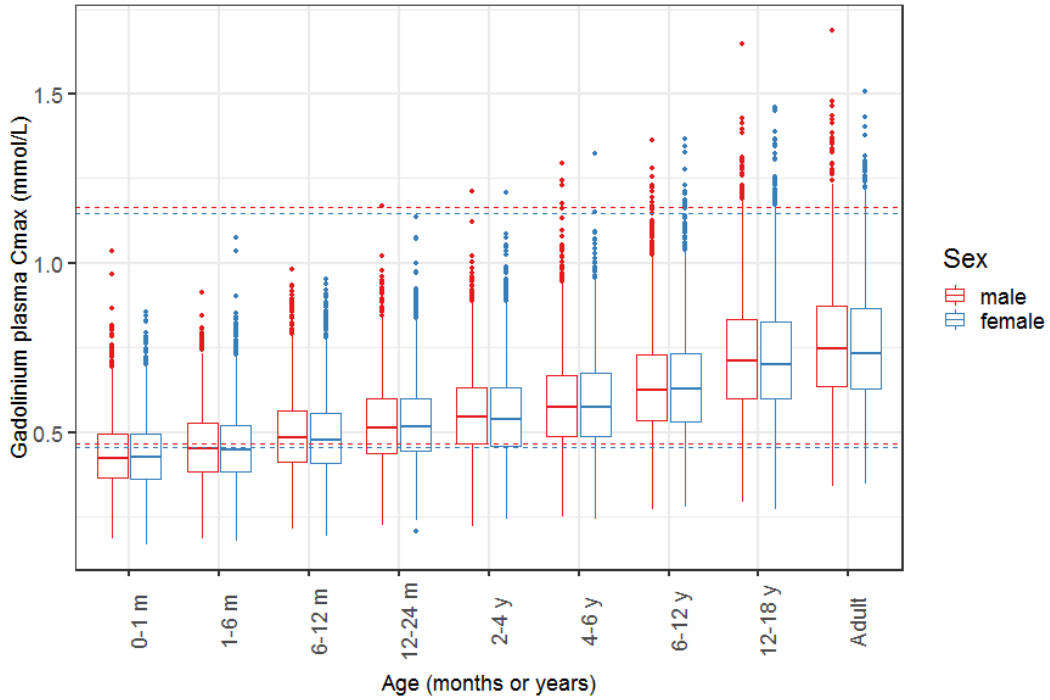
Source: Reviewer's analysis.
Abbreviations: m, month; y, year

Figure 3. Simulated ProHance Exposure (AUC) by Age (0.1 Mmol/Kg)



Source: Reviewer's analysis.
Abbreviations: m, month; y, year

Figure 4. Simulated ProHance Maximum Concentration (C_{max}) by Age (0.1 Mmol/Kg)



Source: Reviewer's analysis.
Abbreviations: m, month; y, year

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

No, alternate dosing regimens are not required for intrinsic or extrinsic PK factors in adult and pediatric patients from birth, including term neonates, given gadoteridol is a product for single administration with a very short half-life.

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

No. It is not expected that food interactions will influence the PK of gadoteridol, as it is a product given as a single intravenous bolus administration. No human drug interaction studies have been performed.

7. Sources of Clinical Data and Review Strategy

7.1. Clinical Studies

To support this sNDA, Bracco submitted the following:

- Results from a clinical study titled PH-108
- Results from a population PK analysis.
- Postmarketing safety data from patients less than 2 years of age exposed to ProHance.
- Summary of studies from peer-reviewed literature - in which patients below the age of 2 years were exposed to ProHance

The efficacy evaluation for use of ProHance in patients less than 2 years of age in this application is based on the results of Study PH-108. This study involved a prospective blinded read of retrospectively collected MR images from pediatric patients less than 2 years of age (N =120), who received ProHance at a dose of 0.1 mmol/kg. The Images were collected from 5 sites (4 within the United States and one Italian site). Overall, there were 3 image sets for each patient - predose, postdose, and predose plus postdose images. And, these were read by 3 independent neuroradiologists who were blinded to all patient information. In addition, lesion tracking was performed by an independent neuroradiologist adjudicator who was also blinded to all patient information.

Table 2. Listing of Clinical Trials Relevant to This NDA/BLA

Trial Identity	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Ph-108-	NCT03750188	A prospective blinded read of retrospectively collected MR images	Intravenous administration of ProHance at a dose of 0.1 mmol/kg	By-lesion changes from Predose to Pre plus Postdose for: border delineation, visualization of internal morphology, and contrast enhancement.	125	Pediatric patients less than 2 years of age with documented disease of CNS (brain/spine)	5 sites (4 US and one Italian)

7.2. Review Strategy

The review of clinical study (PH-108) included data verification, evaluation of the trial design, primary and secondary endpoints and inferred conclusions.

The assessment of safety consisted of:

- Safety results from study PH-108
- Summary of studies from peer-reviewed literature
- Safety data submitted by the Applicant from studies in the ProHance clinical study safety database

(b) (4)

[redacted]

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8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. The Safety and Efficacy of ProHance® at the Dose of 0.10 mmol/kg in Magnetic Resonance Imaging of the Central Nervous System in Pediatric Patients Who are Younger Than 2 Years of Age (Study PH-108)

Trial Design

Prospective blinded read of retrospectively collected MR images

Study Objectives and Endpoints

The primary efficacy outcome was by-lesion changes from predose to pre plus postdose image sets on the following three coprimary visualization endpoints:

- Delineation of borders
- Visualization of the internal morphology
- Contrast enhancement

Each lesion was assigned a grade on a 5-point scale from 0 to 4 for each endpoint where a score of 0 means no visualization, 1 is poor, 2 is moderate, 3 is good and 4 is excellent visualization.

The secondary objectives of this study included:

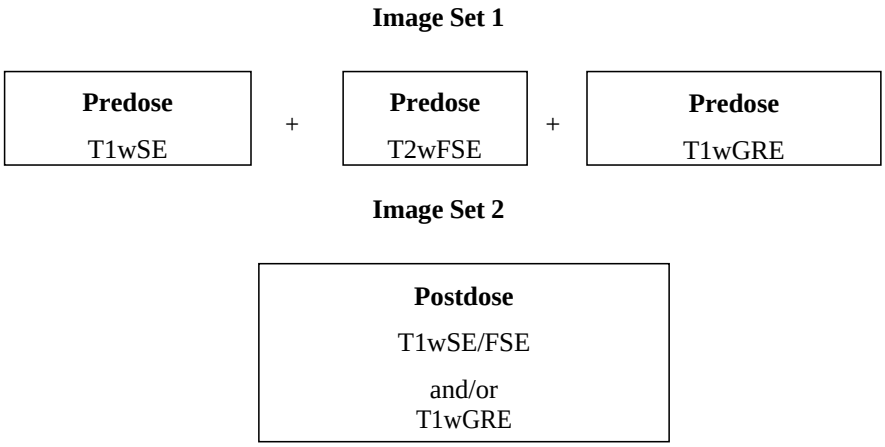
- Common Lesion Analysis, and Patient Level Analysis for changes from Predose to Predose plus Postdose. A common lesion analysis means analysis of changes in lesions that are present on both image sets
- Common Lesion Analysis and Patient Level Analysis for changes from predose to postdose images only
- By-lesion changes comparing predose to postdose for up to the three of the largest lesions in a) lesion-to-brain ratio (LBR), and b) contrast-to-noise ratio (CNR)

Statistical Analysis Plan

The efficacy assessment included two reading sessions separated by at least 14 days to minimize recall bias by the three independent readers. The first reading session (Figure 5) involved unpaired assessment and all Predose images and Postdose images were evaluated individually in randomized order by each reader; for this purpose, each of the two image sets for each patient (i.e., Predose or Postdose) had a unique randomization number. The second reading session (Figure 6) involved a paired assessment for which the Predose plus Postdose images for each patient were presented to each reader independently in a randomized order

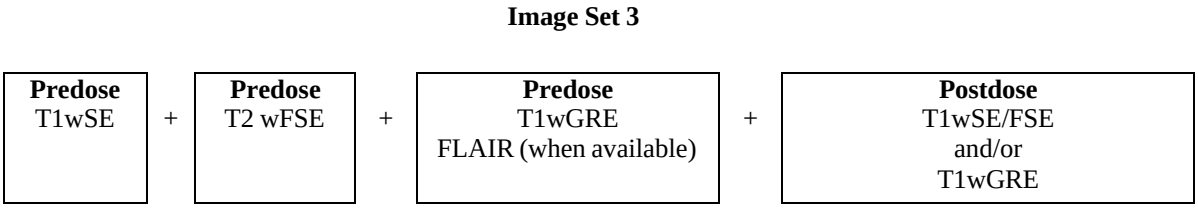
and evaluated in a paired fashion. After the blinded readings by the three independent readers, a fourth independent neuroradiologist blinded to all patient data performed lesion tracking to ensure that the visualization endpoints were evaluated for the same lesion across the various image sets and assessments.

Figure 5. Reading Session 1, Unpaired Predose and Postdose Images Alone



Source: Figure 8, Clinical Overview

Figure 6. Reading Session 2, Paired Predose Plus Postdose Images Together



Source: Figure 9, Clinical Overview)

Table 3 summarizes the statistical analyses conducted by the Applicant. The primary hypothesis was that noncontrast MRI plus contrast MRI is superior to the noncontrast MRI alone for the three coprimary endpoints. The mean changes and 95% CI for the three coprimary endpoints were calculated and a paired t-test was used to evaluate the significance.

To be considered a success in the primary test, all three coprimary endpoints for at least two of the three readers had to succeed in the hypothesis test.

Table 3. Statistical Analysis, Study PH-108

Image Set	Unit of Analysis	Primary/Secondary Analysis
Pre vs Pre + Postdose	All Lesions[a]	Primary
	Sensitivity – All Lesions[a]	Supportive to primary
	Common Lesions[a]	Secondary
	Patient Level[a]	Secondary
Pre vs Postdose	All Lesions[a]	Secondary
	Common Lesions[a]	Secondary
	Patient Level[a]	Secondary
	Number of Lesions and Lesion Tracking	Secondary
	Additional Information from Postdose Images	Secondary
	Lesion Level Quantitative (LBR and CNR)	Secondary
Pre, Post, Pre+Postdose	Inter-reader Agreement[a]	Secondary

LBR, lesion-to-brain ration; CNR, contrast-to-noise ratio
[a] Three co-primary endpoints (lesion border delineation, internal morphology, and contrast enhancement).

Source: Clinical Overview – Section 2.5.4.1.6

The secondary efficacy analyses included:

- A paired t-test of the 3 qualitative endpoints (lesion border delineation, visualization of internal lesion morphology, and contrast enhancement of lesions) for
  - "Lesion-Level, Common-Lesion Analysis": compared predose versus predose plus postdose and included all lesions detected on both image sets.
  - "Patient-Level Analysis": compared predose to predose plus postdose. To perform this analysis, the score of each of the three endpoints was calculated as an average of the lesion scores for each image set of the patient. The average scores of the three endpoints for an image set of a given patients were calculated as the sum of all the individual lesion scores divided by the total number of lesions in that image set. Patients with no lesions detected at both image sets were excluded from this analysis.
  - Predose to Postdose Analyses: compared predose to postdose alone for all lesions, common lesions and patient-level scores.

The Applicant also conducted subgroup analyses by age, gender, and race (white and nonwhite) using the same analysis methods as they used for the primary analysis (All Lesions Analysis, intent-to-diagnose (ITD) population).

Other secondary endpoint analysis included inter-reader agreement, number of lesions and lesion tracking and quantitative assessments including the lesion to brain ration and contrast to brain ratio as follows.

- Inter-reader agreement: The inter-reader agreement analysis was performed using intraclass correlation coefficient (ICC) analysis for the coprimary variables based on the patient-level averaged results of separate assessments (Predose, Postdose, and Predose plus Postdose) after consideration of lesion tracking and data handling

rules. Two sources of variance were considered in the calculation of inter-reader agreement: patient (treated as a random effect) and reader plus residual. The ICC was computed from the MIXED model as the ratio of the variance attributable to the patient effect to the total variance (subject plus residual).

- Number of lesions and lesion tracking: The number of lesions detected for each image set was assessed to provide a patient-level distribution of changes in the number of lesions from predose to pre plus postdose, and from predose to postdose. The Wilcoxon Signed-Rank test was used to examine changes from predose.

- Quantitative Assessments: Predose to postdose changes in LBR and CNR for predose and postdose assessments were analyzed using paired t-tests. The differences between means were presented together with the 2-sided 95% CIs.

Additional information from postdose images were summarized in frequency distribution tables; this included enhancement patterns and/or lack of enhancement for patients with lesions, and the value of postdose images in excluding lesions for patients without lesions.

Sample size calculation for the PH-108 study was based on the estimation from paired t-test with assumptions from the results of Study MH-150, a similar study of MultiHance in the same patient population. Assuming, on average, the expected mean change from Predose of 0.6 points (on a 5-point scale), and the standard deviation of the change in the range of 1.9 points, with a 2-sided alpha level of 0.05, 108 evaluable patients could be expected to provide 90% power. Considering a maximum of 10% unevaluable patient studies (patients with images not evaluable or patients without lesions), it was determined that 120 patients would be needed for the study.

Protocol Amendments

Following the pre-sNDA meeting on June 4, 2018, the Applicant amended the protocol for study PH-108 in response to the Agency's feedback. These amendments included 1) randomizing patient order within each of the two "big blocks", and 2) steps to ensure reasonable balance among the age groups (0 to less than 1 month, 1 to less than 6 months, 6 to less than 12 months, 12 to less than 24 months).

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant reports no deviation from the ethical principles detailed in the Declaration of Helsinki or specific ethical considerations and provisions for pediatric patients, as detailed in

the International Conference on Harmonization document on clinical investigation of medicinal products in pediatric population (E11).

Financial Disclosure

The Applicant reports adequate collection of financial disclosure forms and no disclosable information from all study principal investigators and subinvestigators

Patient Disposition

A total of 125 patients with documented known or highly suspecting enhancing disease of the CNS (brain/spine) and who underwent ProHance MRI were studied. All patients with the exception of one 24-month old patient were less than 24 months of age. All 125 patients were included in the Safety Population, the ITD Efficacy Population the Per Protocol Population. The 24-month old patient was excluded from all analyses based on age group.

Protocol Violations/Deviations

There was a total of 12 protocol violations in 12 patients:

- One patient was 24 months of age and outside the protocol-specified age range of less than 24 months.
- 11 patients received a volume of ProHance that deviated by greater than the volume of 0.1 mmol/kg plus 25% specified in the protocol. Among these 11 patients, 6 patients received higher than the protocol-specified dose and 5 received lower than the protocol-specified dose.

The above violations were deemed minor.

Demographic Characteristics (Table 4)

A total of 56% of patients were male. The majority of patients (86; 69%) were between 0 and less than 12 months of age (17 (13.6%) were less than 1 month, 40 (32.0%) were between 1 and less than 6 months, 29 (23.2%) were between 6 and less than 12 months of age), and 38 patients (30.4%) were between 12 and less than 24 months of age.

Table 4. Demographic Characteristics, Study PH108 Participants

Characteristic	Total N=125[a]	0-<1 month N=17[a]	1-<6 months N=40[a]	6-<12 months N=29[a]	12-<24 months N=38[a]
Gender, n (%)					
Male	70 (56.0)	12 (70.6)	15 (37.5)	19 (65.5)	23 (60.5)
Female	55 (44.0)	5 (29.4)	25 (62.5)	10 (34.5)	15 (39.5)
Age (months)					
N	125	17	40	29	38
Mean ± SD	8.1 ± 6.98	0.0 ± 0.00	2.7 ± 1.64	8.3 ± 1.89	16.9 ± 2.97
Median	6.0	0.0	2.0	8.0	16.5
Range (min – max)	(0 – 24)	(0 – 0)	(0 – 5)	(6 – 11)	(12 – 22)
Race, n (%)					
Caucasian	70 (56.0)	10 (58.8)	21 (52.5)	15 (51.7)	23 (60.5)
Black	31 (24.8)	4 (23.5)	16 (40.0)	7 (24.1)	4 (10.5)
Asian	6 (4.8)	1 (5.9)	1 (2.5)	0	4 (10.5)
Other	18 (14.4)	2 (11.8)	2 (5.0)	7 (24.1)	7 (18.4)

[a] Denominator for percent calculation.
Patient (b) (6) was 24 months of age at the time of his MRI and is summarized only under Total.
Source: *Module 5, Section 5.3.5.2 – PH-108 Clinical Study Report, End-of-Text Table 14.2.1.1*

The final diagnosis (Table 5) in these 125 patients was nontumor in 72 patients (57.6%) and tumor in 51 patients (40.8%). Among the 51 patients with tumors, intra-axial tumors were diagnosed in 19 patients, and extra-axial tumors in 32 patients; benign tumors were diagnosed in 22, and malignant tumors were diagnosed in 27 patients. The nontumor diagnosis generally included inflammatory disease, demyelinating disease, infections, meningitis, abscesses and vasculitis.

Table 5. Final Subject Diagnosis, Study PH-108

	N (%)
Condition	
Normal Parenchyma	1 (0.8)
Non-tumor	72 (57.6)
Tumor	51 (40.8)
Not Available	1 (0.8)
Tumor type	
Intra-axial	19 (15.2)
Extra-axial	32 (25.6)
Tumor nature	
Benign	22 (17.6)
Malignant	27 (21.6)
Not Available	2 (1.6)

Efficacy Population (N=125) is denominator for percentage calculations.
[a]Denominator for percent calculations.
Data source: *Module 5, Section 5.3.5.2 – PH-108 Clinical Study Report, End-of-Text Table 14.19.*

The inclusion criteria for enrollment of participants into this study included the following:

- Less than 2 years of age at the time of the MRI examination

- ProHance administered at a dose of 0.1 mmol/kg
- Documented, known or highly suspected, contrast enhancing disease of the brain or spine
- All the predose and postdose images acquired in the same plane
- Images necessary for blinded read assessment included: Predose T1 SE/FSE and Postdose T1 SE/FSE and/or GRE and T2 SE/FSE. T2 FLAIR images were read when available but were not deemed necessary.

The enrollment at all the sites was tracked centrally to achieve balance across the following age groups:

- Group 1 -0 to less than 1 month
- Group 2 - 1 to less than 6 months
- Group 3 - 6 to less than 12 months
- Group 4 - 12 to less than 24 months

The target recruitment was at least 20% per group.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Not Applicable

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Not Applicable

Efficacy Results – Primary Endpoint

Table 6 summarizes the Applicant's results of the primary analysis of lesion visualization changes from the Predose to Predose plus Postdose image sets for the three coprimary endpoints based on the lesion-level analyses of all lesions. The number of lesions upon which the analysis was based varied by reader, from 185 (in Reader #3) to 283 (in Reader #1). Overall, the improvement from Predose to Pre plus Postdose was highly statistically significant for all three readers ($p<0.0001$) for all three coprimary endpoints. Mean improvements ranged from 0.8 to 1.1 for lesion border delineation, from 0.9 to 1.2 for visualization of lesion internal morphology, and from 0.9 to 1.1 for lesion contrast enhancement.

Table 6. Lesion Level, Predose Versus Predose Plus Postdose Image Set, All Lesions, Primary Analysis

	Reader 1	Reader 2	Reader 3
Lesion Border Delineation			
Number of Lesions[a]	283	252	185
Mean Predose ± SD	2.3 ± 1.39	1.8 ± 1.28	2.3 ± 1.36
Mean Pre + Postdose ± SD	3.2 ± 1.39	2.6 ± 1.30	3.3 ± 1.34
Change ± SD	0.9 ± 1.98	0.8 ± 1.94	1.1 ± 1.99
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.7, 1.1)	(0.6, 1.1)	(0.8, 1.3)
Visualization of Lesion Internal Morphology			
Number of Lesions[a]	283	252	185
Mean Predose ± SD	2.3 ± 1.37	1.6 ± 1.08	2.2 ± 1.33
Mean Pre + Postdose ± SD	3.1 ± 1.41	2.5 ± 1.22	3.4 ± 1.34
Change ± SD	0.9 ± 2.01	0.9 ± 1.77	1.2 ± 2.00
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.7, 1.1)	(0.7, 1.1)	(0.9, 1.5)
Lesion Contrast Enhancement			
Number of Lesions[a]	283	252	185
Mean Predose ± SD	2.3 ± 1.38	1.6 ± 1.14	2.2 ± 1.33
Mean Pre + Postdose ± SD	3.3 ± 1.40	2.6 ± 1.24	3.3 ± 1.35
Change ± SD	1.0 ± 2.11	0.9 ± 1.81	1.1 ± 2.03
p-value[b]	<0.0001)	<0.0001	<0.0001
95% CI of Change	(0.7, 1.2)	(0.7, 1.2)	(0.8, 1.4)

SD= standard deviation; CI = confidence interval
[a] With imputations of zero scores for the lesions not detected in an image set.
[b] p-value based on paired t-test for change from Predose to Predose + Postdose.
Data source: *Module 5, Section 5.3.5.2 – PH-108 Clinical Study Report, End-of-Text Table 14.8.1*

A number of sensitivity analyses with nominal p values were generally supportive and are summarized below. The results of a sensitivity analysis comparing Predose to Predose plus Postdose are shown below (Table 7). If a lesion was not detected on one of the image sets, the average score of all lesions of all patients within that image set was assigned to that lesion. As in the primary analysis, results for all three readers show improvement for all three endpoints. In this analysis, improvement in lesion visualization scores ranged from 0.6 to 1.1 across endpoints and readers.

Table 7. Sensitivity Analysis, Comparison of the Three Coprimary Variables, Predose Versus Pre Plus Postdose, Lesion-Level, All Lesion

	Reader 1	Reader 2	Reader 3
Lesion Border Delineation			
Number of Lesions[a]	283	252	185
Mean Predose ± SD	2.9 ± 0.75	2.5 ± 0.63	2.9 ± 0.58
Mean Pre + Postdose ± SD	3.7 ± 0.50	3.1 ± 0.61	3.8 ± 0.37
Change ± SD	0.8 ± 0.79	0.6 ± 0.80	0.9 ± 0.61
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.7, 0.9)	(0.5, 0.7)	(0.8, 1.0)
Visualization of Lesion Internal Morphology			
Number of Lesions[a]	283	252	185
Mean Predose ± SD	2.9 ± 0.71	2.2 ± 0.47	2.8 ± 0.61
Mean Pre + Postdose ± SD	3.7 ± 0.56	3.0 ± 0.56	3.9 ± 0.27
Change ± SD	0.8 ± 0.81	0.8 ± 0.74	1.1 ± 0.67
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.7, 0.9)	(0.7, 0.9)	(1.0, 1.2)
Lesion Contrast Enhancement			
Number of Lesions[a]	283	252	185
Mean Predose ± SD	2.9 ± 0.70	2.2 ± 0.54	2.9 ± 0.57
Mean Pre + Postdose ± SD	3.9 ± 0.35	3.0 ± 0.56	3.8 ± 0.40
Change ± SD	0.9 ± 0.75	0.8 ± 0.76	0.9 ± 0.65
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.8, 1.0)	(0.7, 0.9)	(0.8, 1.0)

SD= standard deviation; CI = confidence interval
[a] If a lesion was not detected on one of the image sets, the average score of all lesions of all patients within that image set was assigned for that lesion.
[b] p-value based on paired t-test for change from Predose to Predose + Postdose.
Data source: *Module 5, Section 5.3.5.2 – PH-108 Clinical Study Report, End-of-Text Table 14.13.1*

To further support the primary lesion-level analysis comparing Predose to Predose plus Postdose, the Applicant conducted analysis for common lesions, i.e., only lesions detected in both image sets were included for this analysis (Table 8). In this analysis, improvements in lesion visualization scores ranged from 0.7 to 1.0 across endpoints and readers.

Table 8. Lesion Level: Comparison of Lesion Visualization in Predose Versus Predose Plus Postdose Images, Common Lesions Only

	Reader 1	Reader 2	Reader 3
Lesion Border Delineation			
Number of Lesions[a]	182	142	120
Mean Predose ± SD	2.9 ± 0.83	2.5 ± 0.76	3.0 ± 0.64
Mean Pre + Postdose ± SD	3.8 ±(0.48	3.2 ± 0.67	3.8 ± 0.42
Change ± SD	0.9 ± 0.80	0.7 ± 0.90	0.8 ± 0.65
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.7, 1.0)	(0.5, 0.8)	(0.7, 0.9)
Visualization of Lesion Internal Morphology			
Number of Lesions[a]	182	142	120
Mean Predose ± SD	2.9 ± 0.79	2.2 ± 0.57	2.9 ± 0.67
Mean Pre + Postdose ± SD	3.7 ± 0.55	3.0 ± 0.60	3.9 ±(0.29
Change ± SD	0.9 ± 0.83	0.8 ± 0.83	1.0 ± 0.74
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.8, 1.0)	(0.7, 0.9)	(0.9, 1.2)
Lesion Contrast Enhancement			
Number of Lesions[a]	182	142	120
Mean Predose ± SD	2.9 ± 0.79	2.3 ± 0.64	2.9 ± 0.61
Mean Pre + Postdose ± SD	3.9 ± 0.30	3.1 ± 0.61	3.8 ± 0.47
Change ± SD	1.0 ± 0.79	0.8 ± 0.87	0.9 ± 0.70
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.9, 1.1)	(0.6, 0.9)	(0.7, 1.0)

SD= standard deviation; CI = confidence interval
[a] To be included, a lesion had to be detected in both of the image sets.
[b] p-value based on paired t-test for change from Predose to Predose + Postdose.
Data source: *Module 5, Section 5.3.5.2 – PH-108 Clinical Study Report, End-of-Text Table 14.8.2*

The results of changes from the Predose to Pre plus Postdose image sets for the three coprimary endpoints based on the patient-level analyses are summarized in Table 9. For the patient-level analyses, the average value of the lesion scores "1" to "4" assigned by the readers was used for each of the 3 variables of lesion border delineation, visualization of lesion internal morphology, lesion contrast enhancement. The results are consistent with those for the primary analysis. At the patient level, mean improvements ranged from 0.8 to 0.9 for lesion border delineation, from 0.8 to 1.0 for visualization of lesion internal morphology, and from 0.9 to 1.0 for lesion contrast enhancement.

Table 9. Patient Level: Comparison of Lesion Visualization in Predose Versus Predose Plus Postdose Images

	Reader 1	Reader 2	Reader 3
Lesion Border Delineation			
Number of Patients[a]	107	107	106
Mean Predose ± SD	2.9 ± 0.80	2.5 ± 0.78	2.9 ± 0.67
Mean Pre + Postdose ± SD	3.7 ± 0.45	3.3 ± 0.55	3.8 ± 0.38
Change ± SD	0.8 ± 0.78	0.8 ± 0.84	0.9 ± 0.67
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.7,1.0)	(0.7,1.0)	(0.8,1.0)
Visualization of Lesion Internal Morphology			
Number of Patients[a]	107	107	106
Mean Predose ± SD	2.8 ± 0.76	2.2 ± 0.58	2.9 ± 0.68
Mean Pre + Postdose ± SD	3.7 ±(0.56	3.1 ± 0.50	3.9 ± 0.28
Change ± SD	0.8 ± 0.84	0.9 ± 0.77	1.0 ± 0.75
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.7,1.0)	(0.7,1.0)	(0.9,1.2)
Lesion Contrast Enhancement			
Number of Patients[a]	107	107	106
Mean Predose ± SD	2.9 ±(0.77	2.3 ± 0.66	2.9 ± 0.66
Mean Pre + Postdose ± SD	3.9 ± 0.34	3.2 ± 0.51	3.8 ± 0.45
Change ± SD	1.0 ± 0.84	0.9 ± 0.79	0.9 ± 0.73
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.8,1.1)	(0.8,1.1)	(0.8,1.1)

SD= standard deviation; CI = confidence interval
The subject score is calculated as the sum of the scores divided by the total number of lesions for the subject.
[a] Number of patients with both Predose and Pre + Postdose scores.
[b] p-value based on paired t-test for change from Predose to Pre + Postdose.
Data source: *Module 5, Section 5.3.5.2 – PH-108 Clinical Study Report, End-of-Text Table 14.9*

The results of changes from the Predose to Postdose image sets for the three coprimary endpoints based on the lesion-level analyses of all lesions (with imputations of zero scores for the lesions not detected in an image set) are summarized in Table 10. The results are again consistent with those for the primary analysis.. Mean improvements ranged from 0.4 to 1.0 for lesion border delineation, from 0.4 to 1.1 for visualization of lesion internal morphology, and from 0.5 to 1.1 for lesion contrast enhancement.

Table 10. Lesion Level: Predose Versus Postdose Image Sets, All Lesions

	Reader 1	Reader 2	Reader 3
Lesion Border Delineation			
Number of Lesions	291	246	196
Mean Predose ± SD	2.2 ± 1.42	1.8 ± 1.27	2.2 ± 1.42
Mean Postdose ± SD	2.8 ± 1.57	2.2 ± 1.45	3.1 ± 1.46
Change ± (SD	0.6 ± 2.24	0.4 ± 2.13	1.0 ± 2.24
p-value[a]	<0.0001	0.0095	<0.0001
95% CI of Change	(0.4,0.9)	(0.1,0.6)	(0.7,1.3)
Visualization of Lesion Internal Morphology			
Number of Lesions	291	246	196
Mean Predose ± SD	2.2 ± 1.40	1.6 ± (1.07	2.1 ± 1.38
Mean Postdose ± SD	2.8 ± 1.54	2.0 ± (1.34	3.2 ± 1.47
Change ± SD	0.6 ± 2.20	0.4 ± (1.93	1.1 ± 2.23
p-value[a]	<0.0001	0.0005	<0.0001
95% CI of Change	(0.3,0.8)	(0.2,0.7)	(0.8,1.4)
Lesion Contrast Enhancement			
Number of Lesions	291	246	196
Mean Predose ± SD	2.2 ± 1.41	1.7 ± 1.13	2.1 ± 1.39
Mean Postdose ± SD	2.9 ± 1.59	2.1 ± 1.39	3.2 ± 1.47
Change ± SD	0.6 ± 2.36	0.5 ± 1.98	1.1 ± 2.26
p-value[a]	<0.0001	0.0003	<0.0001
95% CI of Change	(0.4,0.9)	(0.2,0.7)	(0.8,1.4)

SD= standard deviation; CI = confidence interval
[a] p-value based on paired t-test for change from Predose to Postdose.
Data source: *Module 5, Section 5.3.5.2 – PH-108 Clinical Study Report, End-of-Text Table 14.10.1*

Table 11 summarizes the results from the Predose to Postdose comparison for the common lesions, i.e., only lesions detected in both image sets. In this analysis, mean improvements from Predose to Postdose ranged from 0.5 to 0.7 for lesion border delineation, from 0.7 to 1.0 for visualization of lesion internal morphology, and from 0.7 to 0.9 for lesion contrast enhancement.

Table 11. Lesion Level: Predose Versus Postdose Image Sets, Common Lesions

	Reader 1	Reader 2	Reader 3
Lesion Border Delineation			
Number of Lesions[a]	161	115	112
Mean Predose ± SD	2.9 ± 0.82	2.5 ± 0.74	3.0 ± 0.64
Mean Postdose ± SD	3.6 ± 0.63	3.1 ± 0.64	3.7 ± 0.48
Change ± SD	0.7 ± 0.95	0.5 ± 0.94	0.7 ± 0.86
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.5,0.8)	(0.4,0.7)	(0.6,0.9)
Visualization of Lesion Internal Morphology			
Number of Lesions[a]	161	115	112
Mean Predose ± SD	2.9 ± 0.79	2.2 ± 0.56	2.8 ± 0.69
Mean Postdose ± SD	3.6 ± 0.59	2.9 ± 0.57	3.8 ± 0.46
Change ± SD	0.7 ± 0.86	0.7 ± 0.77	1.0 ± 0.85
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.6,0.9)	(0.6,0.8)	(0.8,1.1)
Lesion Contrast Enhancement			
Number of Lesions[a]	161	115	112
Mean Predose ± SD	2.9 ± 0.76	2.3 ± 0.64	2.9 ± 0.62
Mean Postdose ±(SD	3.7 ± 0.64	3.0 ± 0.58	3.8 ± 0.39
Change ± SD	0.7 ± 0.99	0.7 ± 0.75	0.9 ± 0.80
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.6,0.9)	(0.6, 0.8)	(0.8,1.1)

SD= standard deviation; CI = confidence interval
[a] To be included, a lesion had to be detected in both of the image sets.
[b] p-value based on paired t-test for change from Predose to Postdose.
Data source: *Module 5, Section 5.3.5.2 – PH-108 Clinical Study Report, End-of-Text Table 14.10.2*

Table 12 summarizes the results of changes from the Predose to Postdose image sets for the three coprimary endpoints based on the patient-level analyses. The results are consistent with those for the primary analysis. At the patient level, mean improvements ranged from 0.6 to 0.9 for lesion border delineation, from 0.7 to 1.0 for visualization of lesion internal morphology, and from 0.7 to 1.0 for lesion contrast enhancement.

Table 12. Patient Level: Comparison of Lesion Visualization in Predose Versus Postdose Images

	Reader 1	Reader 2	Reader 3
Lesion Border Delineation			
Number of Patients[a]	104	103	103
Mean Predose ± SD	2.9 ± 0.80	2.5 ± 0.78	2.9 ± 0.69
Mean Postdose ± SD	3.7 ± 0.47	3.0 ± 0.61	3.8 ± 0.44
Change ± SD	0.8 ± 0.86	0.6 ± 0.96	0.9 ± 0.85
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.6,0.9)	(0.4,0.8)	(0.7,1.0)
Visualization of Lesion Internal Morphology			
Number of Patients[a]	104	103	103
Mean Predose ± SD	2.8 ± 0.77	2.2 ± 0.59	2.9 ± 0.70
Mean Postdose ± SD	3.6 ± 0.52	2.9 ± 0.51	3.8 ± 0.41
Change ± SD	0.8 ± 0.80	0.7 ± 0.70	1.0 ± 0.81
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.6,0.9)	(0.6,0.8)	(0.8,1.1)
Lesion Contrast Enhancement			
Number of Patients[a]	104	103	103
Mean Predose ± SD	2.9 ± 0.76	2.3 ± 0.67	2.9 ± 0.66
Mean Postdose ± SD	3.7 ± 0.47	3.0 ± 0.52	3.9 ± 0.35
Change ± SD	0.9 ± 0.84	0.7 ± 0.76	1.0 ± 0.80
p-value[b]	<0.0001	<0.0001	<0.0001
95% CI of Change	(0.7,1.0)	(0.6,0.9)	(0.8,1.1)

SD= standard deviation; CI = confidence interval
The subject score is calculated as the sum of the scores divided by the total number of lesions for the subject.
[a] Number of patients with both Predose and Postdose scores
[b] p-value based on paired t-test for change from Predose to Postdose
Data source: *Module 5, Section 5.3.5.2 – PH-108 Clinical Study Report, End-of-Text Table 14.11*

Inter-reader agreement was evaluated separately for each coprimary endpoint using ICC for the patient-level analyses. Given that there were three coprimary variables, this analysis resulted in 9 possible values for the ICC, with 3 per image set (Predose, Postdose, and Predose plus Postdose), for assessing agreement across the three readers. The results showed that there was fair agreement (ICC values between 0.21 to 0.40) across the three readers in 4 of the 9 values and slight agreement (ICC values less than 0.20) across the three readers for the remaining 5 values (Table 13 below). The agreement across readers was higher for Predose assessments than for Postdose or Pre plus Postdose assessments. This reviewer agrees with the Applicant's assessment that these low ICC values may relate to the lack of variability among the sampled subjects possibly due to the overwhelmingly high visualization scores, especially at Pre plus Postdose, for many of the subjects. Such low variability can result in even small differences among readers to stand out.

Table 13. Analysis of Inter-Reader Agreement in Qualitative Assessments: Intraclass Correlation Coefficient, Patient Level Analysis

Characteristic	Delineation of Lesion Border	Visualization of Internal Morphology	Contrast Enhancement of Lesions
Intra-class Correlation Coefficient, all 3 readers together			
Predose	0.32	0.24	0.27
Postdose	0.19	0.20	0.21
Pre + Postdose	0.09	0.02	<0.01
The Intraclass Correlation Coefficient is the ratio of variance due to the random subject effect of total variance. Data source: *Module 5, Section 5.3.5.2 – PH-108 Clinical Study Report, End-of-Text Table 14.14.*			

In summary, the results of study PH-108 show that a dose of 0.1 mmol/kg ProHance provides a significantly improved contrast enhancement and morphologic assessment of CNS lesions in pediatric patients less than 2 years of age. Specifically, the primary analysis of changes in the three coprimary endpoints based on the lesion-level analyses show significant improvement from Predose to the Predose plus Postdose images (p<0.0001) for all three readers. These results were also confirmed in the sensitivity analyses.

Data Quality and Integrity

The quality and integrity of the data related to this study were found to be sufficiently adequate to permit substantive review.

8.1.3. Integrated Assessment of Effectiveness

This section is not applicable to this application.

8.2. Review of Safety

8.2.1. Safety Review Approach

Safety evaluation for this sNDA included:

- A review of the following information submitted by the Applicant:
  - Safety results from study PH-108
  - Summary of studies from peer-reviewed literature
  - Safety data from studies in the ProHance Integrated Clinical Study Safety Database.. This Database included safety findings for 2,896 adults and 278 children less than 18 years of age; 138 of these children were less than 2 years of age and included 125 patients from study PH-108.

(b) (4)

8.2.2. Review of the Safety Database

Overall Exposure

Safety findings included data from 29 clinical studies (see Table 14, source Table A, iss.pdf) which includes 2,896 adults and 278 children less than 18 years of age; 138 of these 278 children are less than 2 years of age and include 125 patients from clinical study PH-108. Of the 278 pediatric subjects who received ProHance, 250 were pediatric patients between the age of 1 day postnatal to less than 18 years with medical conditions referred for MRI, and 28 were healthy pediatric subjects from 5 years through 15 years of age participating in a pharmacokinetic study.

Table 14. ProHance Integrated Clinical Trial Safety Database, Populations Included in the Cumulative Summary of Clinical Safety

Type of Study	Number of Studies[a]	Number of Subjects ProHance	Control[b]	Total[c]
Adult and pediatric populations	29	3,174	349	3,314
Adult population (≥18 years of age)	25	2,896	344	3,031
Adult patient population	23	2,854	344	2,989
Patients undergoing MRI	20	2,810	344	2,945
Special population PK	3	44	–	44
Adult healthy volunteers	3	42	–	42
Pediatric population (<18 years of age)	5	278	5	283
Pediatric population 2 to <18 years	4	140	-5	145
Healthy subjects - PK patients	1	28	–	28
Undergoing MRI	3	112	5	117
Pediatric population <2 years	2	138	–	138
Patients undergoing MRI	2	138	–	138

Source: Preface A to End-of-Text Safety Tables
[a] Three studies (PH-103, 32,521-(E2), 32,521-6) enrolled both adult and pediatric subjects and are included both in the Adult Population and the Pediatric Population, but are counted only once in the overall total number of studies.
b Includes comparator from Studies PH-103 (Magnevist, N=63), PH-104 (Magnevist, N=70), and PH-107 (Gadavist, N=216) only; legacy integrated database did not include comparator (Magnevist, N=325) data from Studies 32521-7(E) (N=92), 32521-15 (N=168), 32521-15(E) (N=48), or 32521-15P (N=17).
[c] Includes subjects who have received ProHance, or comparator. Subjects who have received ProHance and comparator or placebo during crossover studies are counted once.
Abbreviations: MRI, magnetic resonance imaging; PK, pharmacokinetics

Table 15 includes the six studies with pediatric patients. All six studies included at least one subject between that age of 2 and 8 years. Three of the six studies, study PH-108, study 32,251-6 and study 232521-15P, included children less than 2 years of age. The majority of pediatric patients below 2 years of age are derived from study PH-108 (N=124).

Table 15. Studies Enrolling Pediatric Subjects by Study and Age Group

Study	Population	No. of Subjects Receiving ProHance Total	<2 Years	2 to <18 Years	≥18 Years
32,521-29	Healthy volunteers	28	0	28	0
32,521-6[a]	Patients	103	13	88	2
232,521-15P[b]	Patients	17	1	16	0
PH-103[c]	Patients	73	0	6	67

		No. of Subjects Receiving ProHance			
Study	**Population**	**Total**	**<2 Years**	**2 to <18 Years**	**≥18 Years**
PH-108[d]	Patients	125	124	1	0
32,521-(E2)[e]	Patients	173	0	1	172
Total		519	138	140	241

Source: Table C from iss.pdf
[a] Study 32,521-6 was a pediatric study in which patients ≥18 years were inadvertently enrolled.
[b] Study 32,521-15P was study in patients 2 to <18 years of age in which one patient <24 months was inadvertently enrolled.
[c] Study PH-103 was a study in which both adult and pediatric patients were enrolled.
[d] Study PH-108 was a study in patients <2 years of age in which one patient aged 24 months was inadvertently enrolled.
[e] Study 32,521-(E2) was an adult study in which one pediatric patient was inadvertently enrolled.

Table 16 summarizes the demographics and baseline characteristics in completed clinical studies in adult and pediatric populations.

Table 16. Demographics and Baseline Characteristics in Completed Clinical Studies

	Adult Patients	**Pediatric Subjects**	
Categories	**(N=2,854[a])**	**2 to <18 Yrs (N=112[a])**	**<2 Yrs (N=138[a])**
Sex, n (%)			
Male	1,332 (46.7)	60 (53.6)	74 (53.6)
Female	1,522 (53.3)	52 (46.4)	64 (46.4)
Age (years)			
Mean (SD)	51.3±15.09	9.82±4.62	0.73±0.59
Range	18-91	2.0-17.5	<0.1-1.9
Categories n (%)			
<2 years			
<1 month	-	-	17 (12.3)
1 to <6 months	-	-	41 (29.7)
6 to <12 months	-	-	32 (23.2)
12 to <24 months	-	-	48 (34.8)
2 to <18 years			
2 to 5 years	-	23 (20.5)	-
6 to 10 years	-	44 (39.3)	-
11 to 17 years	-	45 (40.2)	-
18 to 64 years	2,205 (77.3)	-	-
≥65 years	649 (22.7)	-	-
Race, n (%)			
Caucasian	2,301 (80.6)	80 (71.4)	79 (57.2)
Black	155 (5.4)	12 (10.7)	34 (24.6)
Hispanic	47 (1.6)	9 (8.0)	4 (2.9)
Asian	169 (5.9)	9 (8.0)	6 (4.3)
Other	42 (1.5)	2 (1.8)	5 (3.6)
Unknown	140 (4.9)	-	10 (7.2)
Weight (kg)			
N	2,854	112	138
Mean (SD)	72.4±15.9	40.7±23.7	7.8±3.2
Range	30.1-159.5	9.7-113.8	2.1-15.5
Height (cm)			
N	2,846	102	102
Mean (SD)	168.5±10.9	134.6±28.6	67.0±12.2
Range	62.0-216.0	70.0-193.0	45.0-92.0

Categories	Adult Patients (N=2,854[a])	Pediatric Subjects 2 to <18 Yrs (N=112[a])	Pediatric Subjects <2 Yrs (N=138[a])
Study location (n, %)			
North America	1,842 (63.6)	104 (92.9)	129 (93.5)
Europe	927 (32.0)	2 (1.8)	9 (6.5)
Asia	127 (4.4)	6 (5.4)	-

Source: Module 5, Section 5.3.5.3, Safety Update, End-of-Text Safety Tables 3.2, 5.2, and 6.2.
[a] Denominator used for calculation of percentage values.
Abbreviations: cm, centimeter; kg, kilogram; N, number of subject; n, number of subjects in subgroup; SD, standard deviation

Exposure to ProHance in the clinical studies in the Adult Patient Population (n=2,854), Pediatric Patient Population 2 to <18 Years (n=112), and Pediatric Patient Population <2 Years (n=138) are presented in Table 17 below (source Table HH- Clinical Overview).

Table 17. Exposure to ProHance in Completed Clinical Studies in Adult Patients and Pediatric Populations (2 to <18 Years of Age) and (<2 Years of Age)

	Adult Patients (≥18 Years) (N=2,854)	Pediatric Patients (2 to <18 Years) (N=112)	Pediatric Patients (<2 Years) (N=138)
Overall exposure (N)	3,106	112	138
Mean dose ± SD, mmol/kg	0.148±0.084	0.127±0.071	0.103±0.027
Range of doses, mmol/kg	0.03-0.34	0.05-0.31	0.05-0.34
Actual Dose a	n (%)	n (%)	n (%)
<0.05 mmol/kg	2 (<0.1)	0	0
0.05 mmol/kg	34 (1.2)	1 (0.9)	1 (0.7)
>0.05 - <0.1 mmol/ kg	30 (1.1)	11 (9.8)	27 (19.6)
0.1 mmol/kg	1,883 (66.0)	81 (72.3)	81 (58.7)
>0.1 - <0.2 mmol/kg	52 (1.8)	3 (2.7)	27 (19.6)
0.2 mmol/kg	126 (4.4)	0	0
>0.2 mmol/kg	702 (24.6)	16 (14.3)	2 (1.4)
Missing dose	208 (7.3)	0	0
Injection rate, n (%)	n (%)	n (%)	n (%)
<1 mL/sec	1,122 (39.3)	72 (64.3)	11 (8.0)
≥1 mL/sec	1,213 (42.5)	7 (6.3)	124 (89.9)
Unknown	531 (18.6)	33 (29.5)	3 (2.2)

Source: Module 5, Section 5.3.5.3, Safety Update, End-of-Text Safety Tables 4.2, 4.3, 5.2, 5.3, 6.2, and 6.3.
[a] For overall exposure, a patient in a repeated dose or crossover study was counted only once for a given dose level but could be counted in more than one dose level.
Abbreviations: kg, kilogram; N, number of subjects; n, number of subjects in subgroup; SD, standard deviation

The mean dose of ProHance administered across all studies in the 2,854 adult patients was 0.15±0.08 mmol/kg BW; the range was 0.03 to 0.34 mmol/kg and 66% of the injections involved the administration of 0.1 mmol/kg. At least 702 adult patients received a dose of >0.2 mmol/kg. In 40 % of the adult patient population ProHance was administered intravenously as an infusion (<1 mL/sec) and as a rapid bolus (≥1 mL/sec) in 42.5% of patients.

In the pediatric patient population 2 to less than 18-years of age, the mean administered ProHance dose was 0.14±0.07 mmol/kg, and in patients less than 2 years of age the mean dose was 0.10±0.03 mmol/kg. The majority of pediatric patients less than 18 years of age received a dose of 0.1 mmol/kg or below. In the majority of pediatric patients 2 to less than 18 years (64%)

ProHance was administered intravenously as an infusion (<1 mL/sec), while in pediatric patients less than 2 years it was administered as a rapid bolus (≥1 mL/sec) in most patients (89.9%).

Adequacy of the Safety Database:

Collectively, the safety data submitted by the Applicant (b) (4) are adequate to evaluate the safety of ProHance as an MR contrast agent for the evaluation of the brain and spine in pediatric patients less than 2 years of age.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant presents safety data from an adult population (including both healthy volunteers and patients; 18+ years) and pediatric subjects from 2 to less than 18 years of age as well as those less than 2 years of age. Collectively, these data provide a comprehensive overview of adverse events for ProHance and allow a comparison of the profiles across age groups. Descriptive statistics are used to describe demographic and baseline characteristics. Descriptive statistics for the dose of ProHance administered are also included.

Categorization of Adverse Events

The MedDRA coding system (Version 22.0) was used to code all adverse events. Adverse events reported before and after injection of ProHance are listed and a summary of the incidence of adverse events reported after injection of ProHance is included. The adverse events were tabulated by MedDRA system organ class and preferred term, by relationship to investigational product and by intensity. The serious adverse events and adverse events leading to discontinuation were tabulated and summarized. Subgroup analyses of adverse events were performed by gender, age group, race, ProHance dose, ProHance injection rate, study location, and study indication for the Adult Patient Population, and for the two Pediatric Populations (2 to less than 18 years and less than 2 years of age) as specified Table 18 below.

Table 18. Subgroup Analyses of Adverse Events by Study Population in ProHance Completed Clinical Studies Through November 30, 2019

Parameter	Details
Gender	Male, female
Age group	Adult Patient Population • 18 to 40 years, 41 to 64 years, ≥65 years Pediatric Population 2 to <18 years • 2 to 5 years, 6 to 10years 11 to 17 years Pediatric Population <2 years • 0 to <1 month, 1 to <6 months, 6 to <12 months, 12 to <24 months
Race	Caucasian, Black, Hispanic, Asian, Other, Unknown, Missing
Dose	<0.05, 0.05, >0.05-<0.1, 0.1, >0.1-<0.2, 0.2, >0.2 mmol/kg, Missing
Location of study	North America, Europe, Asia, Unknown
Injection rate	<1 mL/sec, ≥1 mL/sec, Unknown

Parameter	Details
Indication	Healthy volunteers, central nervous system, cardiac, extracranial/extraspinal, liver, breast, musculoskeletal/soft tissue, special population PK

Source: Table CC, Clinical Overview
Abbreviation: PK, pharmacokinetic

Routine Clinical Tests

Information on vital sign changes and lab results are presented from two studies, in patients between the ages of 2 and 17 years from clinical study 32-521-6 and in patients below the age of 2 years from clinical study PH-108. Study 32-521-6 was conducted in 103 pediatric patients undergoing MRI of the CNS. In this study, two patients were 18 years of age, 88 patients were between the ages of 2 and less than 18 years and 13 were below the age of 2 years. In this study, investigators recorded vital signs (heart rate, temperature, blood pressure (BP), respiration rate) immediately prior to and following ProHance injection and at 2 and 24 hours postdose. Laboratory evaluation included complete blood count, chem screen panel, clotting function panel, and an iron metabolism panel (including transferrin, serum iron, serum iron binding capacity, and serum ferritin) prior to and at 24 hours following injection of ProHance.

Study PH-108, was conducted in 125 patients ≤2 years. Safety data from before and after ProHance included vital signs (systolic BP, diastolic BP, heart rate, respiration rate), clinical laboratory investigations (hematology and clinical chemistry), and ECG as available at Predose (1 hour prior to sedation and post start of sedation) and Postdose (+ 1 hour,+2 hours and at any other available timepoints). When available, investigators reported a screening serum creatinine value. The normal reference ranges were included for any available laboratory data. Predose to postdose changes in laboratory values outside the Applicant's guideline were considered to be adverse events in this study.

8.2.4. Safety Results

Deaths

No death was reported in the safety database in the Pediatric Population (less than 18 years). Two deaths were reported in the Adult Population in ProHance Clinical Trials, both in patients experiencing a serious adverse event and neither was considered related to ProHance administration.

Serious Adverse Events

There were three reports (0.1%) of serious adverse events in the Adult Patient Population of 2,854 patients enrolled in a CNS study of ProHance. Two (aneurysm ruptured, grand mal convulsion) of the three cases in whom the outcome was fatal were deemed to have been related to the underlying disease. A relationship to ProHance was considered possible in the

third case (suspected vasospastic event) and the patient was reported to have recovered from the event.

There were no reports of serious adverse events in the Pediatric Patient Population (less than 18 years).

Dropouts and/or Discontinuations Due to Adverse Effects

There were no reports of dropouts and/or discontinuations in the Pediatric Population (less than 18years). Two adult patients were reported to have discontinued due to an adverse event.

Significant Adverse Events

Study PH-108: No adverse events were considered to be clinically important. No clinically meaningful changes in vital signs or clinical laboratory results from baseline have been observed in patients below the age of 2 years receiving ProHance. Although ECGs were obtained in only two patients, no signs of clinical concerns were reported in these two patients.

Treatment-Emergent Adverse Events and Adverse Reactions

Table 19 (source Table J from iss.pdf) below summarizes the most frequently reported adverse events and related adverse drug reactions – greater than 0.4%. In the 3,174 patients who received ProHance in 29 clinical studies. A total of 6.9% of the patients reported one or more adverse events, 5.8% of the patients reported one or more related adverse events (adverse reactions) during a follow-up period that ranged from 24 hours to 7 days after ProHance administration. No new safety signals have been identified and these adverse reactions are adequately described in the labeling. The most commonly reported adverse reactions were nausea (1.4%), dysgeusia (0.9%), headache (0.7%), dizziness (0.5%), and urticaria (0.4%). Most of these adverse reactions were mild to moderate in intensity and resolved without treatment or sequelae.

Table 19. Adverse Events and Adverse Drug Reactions (ADR Reported in ≥0.4% of Subjects) by SOC and PT, ProHance, Overall Population

	No. (%) of Subjects With at Least 1 AE (N=3,174) c	
MedDRA System Organ Class [a] Preferred Term [b]	**All AEs N (%)**	**Related AEs N (%)**
Number (%) of subjects with adverse events	218 (6.9)	185 (5.8)
Gastrointestinal disorders	74 (2.3)	63 (2.0)
Nausea	49 (1.5)	45 (1.4)
Nervous system disorders	81 (2.6)	70 (2.2)
Dizziness	17 (0.5)	13 (0.4)
Dysgeusia	28 (0.9)	27 (0.9)
Headache	23 (0.7)	22 (0.7)

MedDRA System Organ Class [a] Preferred Term [b]	No. (%) of Subjects With at Least 1 AE (N=3,174) [c] All AEs N (%)	Related AEs N (%)
Skin and subcutaneous tissue disorders	27 (0.9)	25 (0.8)
Urticaria	12 (0.4)	12 (0.4)

Source: End-of-Text Safety Table 1.5
Related AEs include definite, probable, possible, reasonably possible, remote, unknowns, or missing relationship to ProHance.
[a] Subjects with more than one event within a MedDRA system organ class were counted once.
[b] Subjects with more than one event assigned to the same MedDRA preferred term were only counted once.
[c] Denominator used for calculation of percentage.
Abbreviations: ADR, adverse drug reaction; AE, adverse event; N, number of subjects; PT, preferred term; SOC, system organ class

Table 20 below (source Table JJ; Clinical Overview) summarizes the adverse events separately for adult patients, pediatric patients from 2 years to less than 18 years of age and pediatric patients less than 2 years of age. While the numbers of patients are different across these age-based subgroups, the overall safety profile appears to be similar across the populations. In the Pediatric Population (for both less than 2 years and 2 to less than 18 years subgroups), no serious adverse events or deaths were reported, and no patient discontinued study due to an adverse event.

Table 20. Summary of Adverse Events in the Adult Patient Population and Pediatric Patient Populations

	Adult Patients N =2854[a]		Pediatric Patients (2 to <18 Yrs) N =112[a]		Pediatric Patients (<2 Yrs) N =138[a]	
Category	**All AE**	**Related AE**	**All AE**	**Related AE**	**All AE**	**Related AE**
Number of adverse events	252	201	5	4	13	2
N (%) with at least 1 AE	184 (6.4)	158 (5.5)	4 (3.6)	3 (2.7)	7 (5.1)	2 (1.4)
N (%) with adverse events local site reactions [b]	3 (0.1)	3 (0.1)	0	0	0	0
N (%) with adverse events by intensity [c]						
Mild	152 (5.3)	134 (4.7)	4 (3.6)	3 (2.7)	5 (3.6)	2 (1.4)
Moderate	27 (0.9)	22 (0.8)	0	0	1 (0.7)	0
Severe	2 (<0.1)	1 (,0.1)	0	0	0	0
Not recorded/not collected	2 (0.1)	1 (<0.1)	0	0	1 (0.7)	0
N (%) with at least 1 serious AE	3 (0.1)	1 (<0.1)	0	0	0	0
N (%)who discontinued due to AE	2 (<0.1)	2 (<0.1)	0	0	0	0
N (%) of deaths	2 (<0.1)	0	0	0	0	0

Source: Module 5, Section 5.3.5.3, Safety Update End-of-text Tables 3.4, 5.4 and 6.4.
[a] Denominator used for calculation of percentages.
[b] Adverse events due to local site reaction was a subset of all adverse events.
[c] If more than one event occurred for a patient, the occurrence with the maximum intensity was counted.
Abbreviations: AE, adverse event; N, number of subjects

Laboratory Findings

Adult patients – No new data related to changes in laboratory investigations in adult patients post ProHance administration were submitted with this sNDA and none were needed. Based on previous submissions, no concerning changes in laboratory investigations have been identified in adult patients receiving ProHance at doses from 0.1 mmol/kg to 0.3 mmol/kg.

Pediatric Patients (2 to less than 18 years of age) - Among the 112 patients who were dosed with ProHance and completed their study, laboratory investigation data were available in 103 patients who participated in study 32,251-6. Changes (both increases and decreases) from baseline blood chemistry or hematology values were seen in 38 patients (36.9%). Depending on the parameter assessed, changes outside the Applicant's guidelines were observed in 0 to 10 patients. These included changes in white blood cell count (increased in six patients, decreased in three patients), serum potassium (increased in four patients, decreased in six patients), and creatinine (increased in five patients). Serum iron values changed from baseline in 14 patients (12 decreases and 2 increases). In two of these patients corresponding changes in transferrin, iron binding capacity, and serum ferritin were observed. Most importantly, none of the changes in blood chemistry or hematology was considered to be clinically significant.

Study PH-108: 13 mild or moderate adverse events were reported in seven patients and all of these were related to changes in laboratory values that occurred from 4 to 66 hours after intravenous ProHance administration (dose of 0.10 mmol/kg). Most of these laboratory value related adverse events were categorized as mild by the Investigators except for one event which was categorized as moderate and another for which categorization was not available. Of note, the patients in this study were hospitalized and had serious CNS disease and changes in laboratory values in such a population are expected. These laboratory value changes included alteration in platelet count, red blood cell count, hemoglobin, blood sodium and chloride levels. The relationship of these adverse events to the administration of ProHance was deemed by the Investigator to be of "no reasonable possibility" in 11 of the 13 laboratory value changes in 5 patients. For the other two adverse events in two subjects the Investigator assessed "reasonable possibility" in relationship to ProHance administration but also commented that there was "insufficient/poor evidence of relationship to ProHance." Most importantly, all patients recovered without any sequelae.

Vital Signs

Adult patients – No new data related to vital signs in adult patients were submitted with this sNDA and none were needed. Based on previous submissions, vital sign data from the Phase 3 program in adult patients with CNS disease did not indicate any concerning changes in vital signs in patients receiving ProHance at doses from 0.1 mmol/kg to 0.3 mmol/kg.

Pediatric Patients (2 to less than 18 years of age) – Among the 112 patients who were dosed with ProHance and completed their study, vital sign data were available in 103 patients who participated in study 32,2516. A total of 38 (36.9%) of these patients showed changes in heart

rate from baseline of at least 20% (increases in 26 patients and decreases in 12 patients). A total of 24 (23%) patients showed changes of at least 20% from baseline in systolic BP and 42 (41%) patients showed changes in diastolic BP. Fifty patients (49%) were reported to have shown maximum post dose respiratory changes of at least 20%, including increases in 26 (25%) patients and decreases in 24 (23%) patients. A total of 22 patients showed changes in temperature (a mean increase of 1.5ºC or a mean decrease of 1.4ºC.) None of the postdose changes in vital signs in study 32,521-6 were considered to be clinically significant.

Study PH-108: No signs of potential concern in the vital signs were reported.

Electrocardiograms

Adult patients – No new data related to changes in electrocardiograms post ProHance administration were submitted with this sNDA and none were needed. Based on previous submissions, data related to electrocardiograms from the Phase 3 program in adult patients with CNS disease did not indicate any concern in patients receiving ProHance at doses from 0.1 mmol/kg to 0.3 mmol/kg.

Pediatric Patients (2 to less than 18 years of age) – No ECG data were available in this patient group.

Study PH-108 - ECGs were obtained in only two patients and no concerns were reported.

QT

A formal QT clinical study was not needed and was not performed.

Immunogenicity

Not applicable

8.2.5. Analysis of Submission-Specific Safety Issues

The general principles related to GBCA efficacy and safety are generally similar in pediatric patients and adults. However, there are a few pediatric-specific issues regarding GBCAs including ProHance that are discussed below.

Osmolality

The osmolality of GBCAs varies (Table 1). Osmolality of contrast agents can be particularly important in infants and neonates, as they could be susceptible to fluid shifts and manifest a lower tolerance for intravascular osmotic loads relative to adult patients. However, compared to iodinated contrast agents, this concern is lower for GBCAs because they are used in much smaller volumes. The potential for vessel injury and extravasation is also lower in general for

GBCAs because of the relatively slower injection flow rates and pressure. Among the GBCAs, ProHance has the lowest osmolality (630 mOsm/kg HO- Table 1).

Allergic-Like/Hypersensitivity Reactions

Allergic-like reactions to intravenous administration of GBCAs are rare (Granata et al. 2016; Rozenfeld and Podberesky 2018). The incidence of immediate hypersensitivity reactions to GBCAs is reported to be around 0.79% in adults and 0.4% in children (Ingelmo et al. 2016). Overall, these reactions can be graded as mild (0.05%, moderate (0.01%) and severe (0.005%) (Dillman et al. 2007; Fraum et al. 2017; Rozenfeld and Podberesky 2018). A metanalysis study (Behzadi et al. 2018) reports an occurrence of nine allergic-like reactions per 10,000 administrations, with severe reactions occurring in approximately in five per 100,000 administrations. Although considered to be rare, anaphylactic and anaphylactoid reactions that involve cardiovascular, respiratory, and/or cutaneous manifestations following ProHance administration have been reported (Witte and Anzai 1994; Galera et al. 2010; Takahashi et al. 2015). Hypersensitivity reactions have been reported less frequently in pediatric patients compared to adult patients. (b) (4)

There is evidence suggesting cross-reactivity across GBCAs to hypersensitivity reactions, within linear agents and within macrocyclic agents as well as between linear and macrocyclic agents (Moreno Escobosa and Cruz Granados 2018). When there is a history of a reaction to a GBCA, there is an eight-times increased risk of an adverse reaction to GBCA administration and the second reactions could be of greater severity (Rozenfeld and Podberesky 2018).

Therefore, patients with history of allergy, drug reactions or other hypersensitivity-like disorders need to be closely monitored during ProHance administration. Clinical practice guidelines have been put forth for the diagnosis and management of hypersensitivity reactions (Ingelmo et al. 2016). Medications, equipment and personnel trained to treat hypersensitivity reactions should be available prior to ProHance administration. Hypersensitivity reactions are listed in Section 6 ADVERSE REACTIONS of the labeling. A contraindication to ProHance in patients with known allergic or hypersensitivity reactions to ProHance is included in Section 4 CONTRAINDICATIONS of the labeling. The labeling also includes the following text in Section 5-WARNINGS AND PRECAUTIONS “Severe and fatal hypersensitivity reactions including anaphylaxis have been observed with administration of gadolinium products, including ProHance. Prior to ProHance administration, ensure the availability of trained personnel and medications to treat hypersensitivity reactions. Patients with a history of allergy, drug reactions or other hypersensitivity-like disorders should be closely monitored during the procedure and for several hours after drug administration. If a reaction occurs, stop ProHance and immediately begin appropriate therapy including resuscitation.”

Gadolinium Retention

Long-term retention of small quantities of administered gadolinium occurs. This finding has been described in animals and patients with normal renal function following the administration of GBCAs (Gibby et al. 2004; White et al. 2006; Darrah et al. 2009; Huckle et al. 2016). The retention of gadolinium has been demonstrated in various tissues including bone, kidney, and the brain in patients with preserved renal function, normal hepatic clearance and an intact blood brain barrier (Thomsen 2009; Ramalho and Ramalho 2017). Within the brain, autopsy studies have shown deposition of gadolinium in the dentate nuclei, basal ganglia, substantia nigra, red nucleus, thalami, colliculi, superior cerebellar peduncles, cerebral and cerebellar white matter, and cerebral cortex (Radbruch et al. 2016; Zhang et al. 2017). Of note, the retention of Gd in neuronal tissues is not associated with histologic changes (Kanda et al. 2015; McDonald et al. 2015). A more recent study (McDonald et al. 2017b) also failed to detect cytotoxicity-related histological changes from gadolinium retention in neural tissues.

Although gadolinium retention is less evident with macrocyclic GBCAs compared to linear GBCAs on MRI (T1 shortening), gadolinium retention following macrocyclic GBCAs is detected using inductively coupled mass spectrometry and transmission electron microscopy (Kanda et al. 2016; Murata et al. 2016). The relative difference in retention between the two classed of GBCAs, linear versus macrocyclic, is related to the greater stability of macrocyclic agents compared to the linear agents. Among the macrocyclic GBCAs, evidence from animal studies suggest lower retention and more efficient clearance of gadoteridol in cerebral, cerebellar, and renal tissue (Bussi et al. 2018a; Bussi et al. 2019; Bussi et al. 2020). Evidence thus far from studies in pediatric patients who have received multiple injections of ProHance does not show T1 hyperintensity in deep brain nuclei (Tibussek et al. 2017; Young et al. 2018).

The potential clinical impact of gadolinium retention remains under study. In July 2015, the FDA issued a public statement indicating that, while it is unclear if gadolinium retention could lead to adverse health effects, to reduce the potential for gadolinium accumulation, health care professionals should consider limiting GBCA use to clinical circumstances in which the additional information provided by the contrast is necessary. In March 2016, the National Institutes of Health issued a public statement recommending that physicians consider the use of a macrocyclic GBCA rather than a linear agent (Malayeri et al. 2016). The American College of Radiology and the American Society of Neuroradiology (ASNR) issued a joint statement in May 2016 indicating that further research was needed, but did not issue specific practice guidelines. In March 2017, the Pharmacovigilance Risk Assessment Committee of the European Medical Agency (EMA) submitted a formal recommendation to suspend the use of linear GBCAs with few exceptions. In April 2017, the American College of Radiology stated that there is no compelling evidence that GBCAs pose safety risk with respect to brain deposition of gadolinium. In May 2017, the FDA updated its earlier statement to say: “We identified no evidence to date that gadolinium retention in the brain from any of the GBCAs, including GBCAs associated with higher retention of gadolinium, is harmful, and restricting GBCA use is not warranted at this time”. In July 2017, the EMA concluded its review of GBCAs and confirmed that in the European

Union suspension of the marketing authorization for linear GBCAs was necessary with exception for gadoxetate (Eovist) and gadobenate dimeglumine (MultiHance) for their use in liver MR imaging, as well as gadopentetate dimeglumine (Magnevist) for intra-articular injections. This action was taken to "prevent any risks that could potentially be associated with gadolinium brain deposition." The FDA Medical Imaging Drugs Advisory Committee during a meeting in September 2017 voted to include a new warning regarding gadolinium retention on the labeling of all GBCAs. The Committee acknowledged a higher retention with linear agents compared to macrocyclic agents and recommended all GBCA manufacturers study this issue further to determine if additional regulatory action would be needed.

The potential clinical consequences of gadolinium retention on the developing brain are of particular concern. Given the potential latency of onset and the possibility of repeat GBCA administrations, pediatric patients might be more vulnerable to potential adverse effects of gadolinium retention. Therefore, GBCAs should be used only when the potential clinical benefits clearly outweigh any potential or theoretical risks.

The current labeling for all GBCAs including ProHance includes gadolinium retention in Section 5 WARNINGS AND PRECAUTIONS. Based on the evaluation of FAERS reports and the medical literature, the DPV at the FDA in their recent review concluded that current labeling of gadolinium retention in GBCA product labels remains appropriate and does not recommend any labeling changes at this time.

Nephrogenic Systemic Fibrosis (NSF)

Nephrogenic systemic fibrosis (NSF) is primarily distinguished by its occurrence following GBCA administration in the setting of severe renal impairment leading to decreased GBCA clearance, and dechelation of gadolinium from a weak gadolinium ligand bond found in some GBCAs. Gadolinium is deposited in body tissues provoking an immunologic reaction, not fully characterized, that may precede to clinical NSF. Possible associated inciting conditions are: inflammatory events, metabolic acidosis or erythropoietin exposure(Nardone et al. 2014). NSF is a rare condition that is clinically characterized by distinct skin lesions, and the thickening and tethering of the skin leading to contractures and fibrosis of internal organs as well (Penfield 2008).).

The incidence of NSF is reportedly lower in pediatric patients than in adults. Further, the Applicant's submission and the postmarketing data collected by the FDA through FAERS indicate no reports of NSF in patients less than 2 years of age who had been administered ProHance.

Labeling for all GBCAs carry one of two boxed warnings that classify GBCAs into two groups based upon NSF risk and also provide recommendations regarding renal function screening. The inclusion of these boxed warnings and changes in clinical practice have resulted in a reported decline in new cases of NSF in recent years. The labeling for ProHance and other GBCAs

associated with lower risk of NSF (Eovist, Gadavist, MultiHance, and ProHance) contain the following a boxed warning:

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with noncontrasted MRI or other modalities.

- **The risk for NSF appears highest among patients with:**
  - **Chronic, severe kidney disease (GFR <30 mL/min/1.73m2), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age greater than 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**

The labeling for GBCAs associated with a higher risk of NSF (Magnevist, Omniscan, and Optimark) carry the following boxed warning:

WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)

Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with noncontrasted MRI or other modalities.

- **Do not administer [GBCA] to patients with:**
  - **Chronic, severe kidney disease (GFR <30 mL/min/1.73m2), or**
  - **Acute kidney injury.**
- **Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age greater than 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.**

While there have been no reported cases of NSF in very young pediatric patients to date, renal immaturity in infants calls for particular caution when considering use of GBCAs in this patient population.

8.2.6. Specific Safety Studies/Clinical Trials

The Applicant provided a report of the safety from clinical study PH-108. They report no serious adverse events that occurred during the course of this study. Only mild or moderate adverse events were reported for seven patients and all of these were related to changes in laboratory values which occurred from 4 to 66 hours after ProHance administration (dose of

0.10 mmol/kg). In five of these seven patients, the relationship of the adverse event to ProHance administration was considered by the Investigator to be of “no reasonable possibility”, and a relationship to ProHance was considered “unlikely” in the other two cases. All patients recovered without any sequelae. Further, there were no signs of potential concern in the vital signs, laboratory values, or electrocardiograms (ECGs were performed in only two patients). Additionally, there were no differences in adverse event profiles across subgroups based on age , gender or race.

(b) (4)

8.2.8. Integrated Assessment of Safety

Overall, the cumulative results of safety evaluations from 3,174 subjects who received ProHance in 29 completed clinical studies conducted in North America, Europe, and Asia as of

November 30, 2019, show no change in the safety profile of ProHance. The overall incidence of adverse events following administration of ProHance in the completed clinical studies was 6.9% (5.8% related to ProHance administration) as shown in Table 21. Most of the reported adverse events were mild or moderate in intensity and resolved without sequelae. The most frequently reported adverse reactions after ProHance (with an incidence of 0.4% to 1.4%) were nausea, dizziness, dysgeusia, headache and urticaria.

Table 21. Incidence of Adverse Events

Incidence	All Subjects (29 Clinical Studies)	Adult Subjects	Pediatric Subjects <18 Years*	Pediatric Subjects 2<18 Years	Pediatric Subjects <2 Years**	Study PH-108 Subjects
N	3174	2854	278	140	138	125
Incidence of adverse events	6.9%	6.4%	6.5%	3.6%	5.1%	5.6%
Incidence of related adverse events (adverse reactions)	5.8%	5.5%	4.3%	2.7%	1.4%	1.6%

Source: table values are sponsor's
* includes 140 subjects between 2 and <18 years of age and 138 subjects <2 years of age
** includes 125 subjects from study PH-108

In pediatric studies, the incidence of adverse events was 6.5% (4.3 % deemed related to ProHance administration). The incidence of adverse events in children 2 to less than 18 years of age was 3.6 (related: 2.7%) and in patients below the age of 2 years it was 5.1% (related: 1.4%). All reported adverse events in pediatric patients were mild or moderate in intensity and resolved without sequelae. In the overall pediatric population, there were no reports of deaths or serious adverse events, and no patient discontinued from a study due to an adverse event.

In study PH-108 on the safety and efficacy of ProHance in 125 children below the age of two years, mild or moderate adverse events related to changes in laboratory values outside normal ranges were reported for seven (5.6%) patients. In five of these patients these adverse events were deemed to be definitely unrelated to ProHance. Most importantly all these patients were reported to have recovered without sequelae.

Per the Applicant, to date in the cumulative postmarketing experience, close to 31 million patients have been exposed to ProHance from July 1, 1997 through November 30, 2019. During this period, about 0.042% reported any adverse events and 0.007% experienced serious adverse events. No new or unexpected events were observed in the postmarketing experience.

(b) (4)

The peer-reviewed literature revealed no untoward effects from the intravenous administration of ProHance in patients below the age of 2 years. Further, a review of the FAERS reports, published case reports, and the Applicant safety reports by DPV did not identify any reports of gadolinium retention or NSF in patients less than 2 years of age who had been administered ProHance.

In summary, based on these evaluations, the safety profile of ProHance in children less than 2 years of age is comparable to that in adults 1 and in children from 2 years of age to less than 18 years of age. Most of the reported adverse events were mild or moderate in intensity and resolved without sequelae. Overall, the review team identified no major safety issue in the use of ProHance when administered at the dose of 0.1 mmol/kg for the evaluation of the brain and spine in pediatric patients less than 2 years of age.

8.3. Statistical Issues

Study PH-108

Study Title: The Safety and Efficacy of ProHance at the Dose of 0.10 mmol/Kg in Magnetic Resonance Imaging (MRI) of the CNS in Pediatric Patients Who Are Younger Than 2 Years of Age.

Primary Objective: To assess the efficacy of ProHance in MRI of the CNS in patients less than 2 years of age in terms of changes in visualization levels from predose image reads to paired image reads (paired = pre plus post).

Preliminaries: Study PH-108 consists of a prospective read of images collected retrospectively. Five sites provided images from 125 patients who were less than 2 years of age and who were either confirmed or highly suspicious for CNS tumors. The three image types were collected as follows. Pre: Pre-ProHance enhancement images; Post: Post-ProHance enhancement images; Paired: Pre plus Post ProHance enhancement images. Three blinded readers independently evaluated three image types for quality of visualization. The readers applied scores for visualization levels to each detected lesion (each reader provided his/her own detections for each image type).The three readers evaluated the image types in two read sessions:

- Session#1: Type#1: Pre-ProHance Images and Type#2: Post-ProHance Images
- Session#2: Type#3: Paired Images (Pre plus Post together)

Coprimary Visualization Parameters: The three visualization parameters were: Border Delineation; Internal Morphology; Contrast Enhancement. The scores for each visualization parameter for *detected* lesions were: 1=Poor; 2=Moderate; 3=Good; 4=Excellent.

If a lesion was detected on one image type but not the other, it was scored as zero for the type where it was undetected. An independent adjudicator had the responsibility of identifying lesions across types. As the results will confirm, detections on one image type but not another was not a rare occurrence.

Primary efficacy visualization objective is as follows:

- (*): D = Improvement in Visualization Scores, from Pre-Images to Paired Images, for all three visualization endpoints.

The applicant's hypotheses, powering assumptions, and primary statistic that inform (*) are presented directly below. The reviewer found the applicant's statistics to be problematic. The difficulties will be discussed directly after the statement of the hypotheses and powering assumptions.

For powering purposes, the applicant proposed (for each visualization endpoint) a mean change in Score of D =0.6 at the lesion level.

Hypotheses: Null H_0: D≦ 0; Alternative H_a: D >0

Testing Statistic and Powering: The Applicant assumed that D had a standard deviation of 1.9 and calculated that 108 patients would suffice to ensure rejection of the null hypothesis of "No Improvement" at a 2-sided alpha level of 0.05 and with 90% power if the difference D exceeded 0.6. The Applicant proposed a paired t-test for evaluation of the hypotheses.

The Applicant stated that the proposed values of D =0.6 and Sigma =1.9 were borrowed from a similarly designed study (MH-150) for an approved drug, MultiHance. No rationale was provided for these figures, other than the fact that they had been accepted by the FDA for the MultiHance study planning. Moreover, the current submission does not provide an explicit mathematical formula for the primary endpoint D. However, upon request from the Reviewer, the Applicant provided the formula and other relevant details for the MultiHance Study MH-150. The formula for the estimator $\hat{D}$ of D is: $\hat{D}$ = sum of visualization differences over detected lesions/number of lesions.

Win Criterion: The win on the primary endpoint of improved visualization required, at a minimum, that the 95% 2-sided confidence interval for the mean differences, paired score minus prescore, (namely D), have lower limits (LL) that exceed zero, for all three visualization parameters for at least two readers.

Reviewer's Assessment of the Calculation of the LL

For powering, the Applicant postulated a difference in visualization of D = 0.6 at the lesion level but determined a sample size through patients (=108). Thus, the calculation that 108 patients

suffices for rejection of the null, with respect to a paired t-test, and under the powering assumptions, is consistent with applying the paired t-test, paired score minus prescore, to exactly one lesion per patient.

However, the Applicant's variances for the differences $\hat{D}$ that provide the Applicant's LLs in Table 22 are consistent with sample sizes consisting of numbers of lesions, not numbers of patients. That is, the LLs for mean differences D in scores reflect divisions by numbers of lesions, not numbers of patients.

This approach assumes that:

- (a): Scores from lesion to lesion within a patient are independent.
- (b): Denominators (numbers of lesions) can be considered a constant rather than a variable sum of lesions per patient.

There is no reason to believe that either (a) or (b) holds. Consequently, the variances for $\hat{D}$, and the subsequent LLs, need to be recalculated to account for both the correlations in visualization scores from lesion to lesion within-patient and the variances in numbers of lesions per patient.

The correct variances can be calculated through the Delta Method. The Reviewer has calculated these variances and their associated LLs. These LLs are entered into Table 22 below, in parentheses, next to the Applicant's LLs. The Applicant's sigmas for $\hat{D}$, namely the entries S, are preserved in Table 22 for purposes of validating that the Applicant's incorrect LLs employ numbers of lesions, not numbers of patients. The statistic $\hat{D}$ is simply a statistic that is approximately normally distributed and about which inferences can be drawn once means and variances are calculated. In particular, the corrected LLs are slightly lower than the Applicant's LLs but are still sufficient for rejection of the null hypothesis.

Thus, this study is successful with respect to the Win Criterion. However, as stated earlier, the lesion-by-lesion improvement in the 4 - valued visualization scores has no clear meaning. Therefore, additional statistics are presented below with the intention of evaluating visualization from several other perspectives.

Statistical Results

Five tables are provided below. These tables address both primary and secondary issues. **Table 22** presents the primary endpoint results, with LLs of CIs as determined both by the Applicant and by the Reviewer (in parenthesis). The table also provides similar results for a secondary (patient-level) statistic:

- D(*) = "within-patient" visualization difference, i.e., D(*) = (1/N) (D(1)/L(1) + D(2)/L(2) +. + D(N)/L(N)) where
- L(K) = # lesions detected in patient K that are common to pre and paired MRI scans
- D(K) = sum of differences in visualization scores over the L(K) lesions

This statistic is presented as an alternative way of viewing visualization.

Table 23 addresses a possible concern that the improved visualization achieved on paired images could rest on large increases in scores on a small subset of lesions rather than on a more uniform improvement across most lesions. The approach here is to provide lesion-by-lesion scorings as better/same/worse.

Table 24 is simply a smoothed version of Table 23 that is intended to make the results of Table 23 more transparent**.**

Table 25 addresses the concern that the improved visualization scores for paired over pre could be due to the default to a zero score on lesions detected by paired but not by pre.

Table 26 provides visualization results conditioned on dispositions of detections:

- All Detections
- Common Detections (made by both paired and pre reads)
- "Alone" detections (made by one type but not the other)

Table 22. Primary (Lesion Level) and Secondary (Patient Level) Results

	Border		Morphology		Contrast	
Reader	**Lesion**	**Patient**	**Lesion**	**Patient**	**Lesion**	**Patient**
RDR#1						
N	283	107	283	107	283	107
Paired	3.2	3.7	3.1	3.7	3.3	3.9
Pre	2.3	2.9	2.3	2.8	2.3	2.9
Diff	0.9 (S=2.0)^	0.8 (S=.78)	0.9 (S=2.0)	0.8 (S=.84)	1.0 (S=2.0)	1.0 (S=.84)
LL	0.7 (0.5)	0.7	0.7 (0.5)	0.7	0.7 (0.6)	0.8
RDR#2						
N	252	107	252	107	252	107
Paired	2.6	3.3	2.5	3.1	2.6	3.2
Pre	1.8	2.5	1.6	2.2	1.6	2.3
Diff	0.8 (S=1.94)	0.8 (S=0.84)	0.9	0.9 (S=0.77)	0.9	0.9 (S=0.8)
LL	0.6 (.4)	0.7	0.7 (0.6)	0.7	0.7 (.6)	0.8
RDR#3						
N	185	106	185	106	185	106
Paired	3.3	3.8	3.4	3.9	3.3	3.8
Pre	2.3	2.9	2.2	2.9	2.2	2.9
Diff	1.1 (S=2.0)	0.9 (S=.67)	1.2 (S=2.0)	1.0 (S=0.75)	1.1 (S=2.03)	0.9 (S=0.73)
LL	0.8 (.5)	0.8	0.9 (0.7)	0.9	0.8 (0.5)	0.8

Source: table values are sponsor's; those in parentheses () are from FDA statistical reviewer.
Abbreviations: LL, lower limit; N, number

Table 23 below addresses the concern that gains in visualization scores could be driven by large gains on a small subset of lesions. The table provides partitions of Paired versus Pre lesion scores into Better, Same, Worse. The table also provides the same distinctions for Post versus Pre Scores. Table 24 that follows is intended as a simplified smoothed version of Table 23.

Table 23. Number of Lesions With Changes in Lesion Visualization

	Reader 1		Reader 2		Reader 3	
Visualization	Change Postdose Minus Predose N (%)	Change Pre Plus Postdose Minus Predose N(%)	Change Postdose Minus Predose N (%)	Change Pre Plus Postdose Minus Predose N(%)	Change Postdose Minus Predose N (%)	Change Pre Plus Postdose Minus Predose N (%)
Lesion border delineation						
Number of lesions	291	283	246	252	196	185
Worse	77 (26.5)	43 (15.2)	80 (32.5)	52 (20.6)	39 (19.9)	27 (14.6)
Same	54 (18.6)	59 (20.8)	43 (17.5)	51 (20.2)	32 (16.3)	30 (16.2)
Better	160 (55.0)	181 (64.0)	123 (50.0)	149 (59.1)	125 (63.8)	128 (69.2)
Visualization of lesion internal morphology						
Number of lesions	291	283	246	252	196	185
Worse	72 (24.7)	45 (15.9)	73 (29.7)	45 (17.9)	36 (18.4)	25 (13.5)
Same	54 (18.6)	55 (19.4)	39 (15.9)	47 (18.7)	26 (13.3)	26 (14.1)
Better	165 (56.7)	183 (64.7)	134 (54.5)	160 (63.5)	134 (68.4)	134 (72.4)
Lesion contrast enhancement						
Number of lesions	291	283	246	252	196	185
Worse	80 (27.5)	41 (14.5)	70 (28.5)	49 (19.4)	37 (18.9)	27 (14.6)
Same	38 (13.1)	49 (17.3)	43 (17.5)	40 (15.9)	21 (10.7)	29 (15.7)
Better	173 (59.5)	193 (68.2)	133 (54.1)	163 (64.7)	138 (70.4)	129 (69.7)

Data source: *End-of-Text Table 14.12*
Note: This analysis was performed under consideration of lesion tracking and of data imputation rules specified in the SAP (see *Appendix 16.2, Preface A*). Up to 10 of the largest lesions were assessed per subject.
Abbreviations: N, number

Table 24. Previous Table 23 Averaged Over Readers

Visualization	Paired Versus Pre
Border Delineation	Better =64% Same =19% Worse =17%
Internal Morphology	Better =67% Same =17% Worse =16%
Contrast Enhancement	Better =67% Same =16% Worse =17%

It should be noted that paired versus Pre presents an average performance: Paired scores higher than Pre in about 2 of every 3 lesions and Paired scores either same or worse in about 1 in 3 lesions, equally split - Same and Worse, each, for about 1 in 6 lesions.

The Table 25 presents differences in numbers of lesions detected per patient. “Same” means both Pre and Paired detected the same number of lesions. Thus, for Reader#1, the same number of lesions were detected in 51% of the 118 patients. Paired – Pre =1 means Paired

detected one lesion more than Pre. It should be noted that "Same" not mean that the same lesions were detected, only that the same number were detected.

The number of patients in this table differ from those given in Table 22 because in that table, patient-level data are based on common-lesions scenario while Table 25 is based on lesion-level data after adjudication and following data imputation rules. In this table, up to 10 largest lesions were counted per patient.

Table 25. Disposition of Detections-Paired Versus Pre for Patient Level Data

Reader	Same Number Lesions	Paired – Pre =1	Paired – Pre>=2	Paired > Pre
RDR#1		25%	6%	31%
#Patients =118	51%	17%	1%	18%
RDR#2	57%	17%	12%	29%
#Patients = 120		(12%)	2%	14%
RDR#3	71%	17%	3%	20%
#Patients =115		7%	2%	9%

Source: FDA statistical reviewer analysis.

The Table 26 below addresses paired versus previsualizations with respect to various dispositions of lesions, averaged over the three Visualization parameters. Thus, for instance, for Reader#1, visualization levels over all lesions had paired mean at 3.3, pre mean at 2.3. Visualization levels over the 64% of lesions detected by both paired and pre had paired mean at 3.8, pre mean at 2.9. Visualization levels on the 21% of lesions detected only by paired had mean at 3.6, and on the 15% detected only by pre had mean at 3.0. Table 25 indicates that "more" detections per patient typically means "one more."

It is interesting that the visualization levels for each type (paired or pre) do not drop when that type alone makes the detection, which seems to imply that the loss of detection by one type of Image is not reflected in less than the usual level of visualization in the other type of mage.

Table 26. Visualization Levels Averaged Over the Visualization Parameters

Reader	All Lesions	Common Lesions	Paired or Pre Alone
RDR#1	V(Paired) =3.3 V(Pre) =2.3	Common Lesions 64% V(Paired) =3.8 V(Pre) =2.9	Paired =21%; Pre =15% V(Paired Alone) =3.6 V(Pre Alone) =3.0
RDR#2	V(Paired) =2.6 V(Pre) =1.7	Common Lesions (56%) V(paired) =3.1 V(Pre) =2.3	Paired =28%; Pre =16% V(Paired Alone) =3.1 V(Pre Alone) =2.6
RDR#3	V(Paired) =3.3 V(Pre) =2.2	Common Lesions (65%) V(paired) =3.8 V(Pre) =2.9	Paired =22%; Pre =13% V(Paired) =3.8 V(Pre) =2.4

Source: FDA statistical reviewer analysis.

The cumulative evidence from these five tables is that paired visualizations are superior to pre visualizations and thus supports Study PH-108 success.

8.4. Conclusions and Recommendations

We recommend approval of this supplemental application for NDA 020131 and NDA 021489 to extend the CNS imaging indication for ProHance 0.1 mmol/kg to include all pediatric patients (including term neonates). Our recommendation is based on review of the Applicant's pharmacokinetic and clinical safety and efficacy data as well as postmarketing experience with ProHance in pediatric patients less than 2 years of age.

The choice of a 0.1 mmol/kg dose based on PK simulation analysis conducted by the Applicant and confirmed by the Agency's Clinical Pharmacology group (see Section 6- Clinical Pharmacology) confirmed that ProHance at a dose of 0.1 mmol/kg showed similar distribution and elimination as in adults. The results from study PH-108 showed that ProHance administered at this dose significantly improved overall CNS lesion visualization and thereby clinical utility in young children less than 2 years of age with CNS disease when compared with noncontrast MR images. The safety profile of ProHance in pediatric patients less than 2 years of age at this dose was also found to be similar to that of adults and children older than 2 years of age.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not needed for this efficacy supplement.

10. Pediatrics

Under the Pediatric Research Equity Act, (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(in pediatric patients unless this requirement is waived, deferred, or inapplicable. ProHance achieved FDA-approval in August 1994 for use in pediatric patients 2 years and older, pre-dating Pediatric Research Equity Act legislation passed by Congress in 2003.

On December 18, 2017, FDA issued LABELING SUPPLEMENT AND POSTMARKETING REQUIREMENT letters to all gadolinium-based contrast agent sponsors requiring two nonclinical studies and one clinical postmarketing study to assess the effects on motor skills and/or

cognitive neuropsychological functioning possibly deriving from exposure to GBCAs. There are three pending postmarketing requirements (PMRs) are listed below:

> A study that will examine the safety of ProHance following perinatal exposure through repeated dosing in pregnant dams. The study will provide safety data assessing behavioral, neurological and histopathology findings. The study will also examine the pharmacokinetics of Gadolinium Based Contrast Agents (GBCA) including gadolinium retention in the brain and other organs/tissues.
>
> A study that will examine the safety of ProHance in juvenile animals, following repeated dose administrations. The study will provide safety data assessing behavioral, neurological and histopathology findings. The study will also examine the pharmacokinetics of Gadolinium Based Contrast Agents (GBCA) including gadolinium retention in the brain and other organs/tissues.
>
> 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 Clinical Protocol. Note, the Odyssey Study, the "Effect on Body Movement and Mental Skills in Patients Who Received Gadolinium-based Contrast Media for MRI Examination Multiple Times within 5 Years", has not begun recruiting as of May 4, 2020.

See the Nonclinical Review written by Jonathan Cohen, Pharmacology Toxicology Reviewer, Division of Imaging and Radiation Medicine (DIRM); Adebayo Laniyonu, Pharmacology Toxicology Team Leader, DIRM; and the Maternal Health Team Review written by Jane Liedtka, MD, DPMH, on details of these outstanding PMRs.

The DPMH consult labeling review by Carolyn L. Yancey, MD, primarily focusing on pediatric labeling recommendations is filed separately under sNDA 020131/S-035 ProHance (gadoteridol) Injection and sNDA 021489/S-014 ProHance Multipack (gadoteridol) Injection in the Document Archiving, Reporting, and Regulatory Tracking System.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The review team reviewed the Applicant's proposed changes to the prescribing information under NDA 020131 (single-dose vials or pre-filled syringes, "single-dose PI", original approval 1992, original sNDA submission February 26, 2020) and NDA 021489 (pharmacy bulk package, "multipack PI", original approval 2003, original sNDA submission February 26, 2020, amended April 23, 2020). On July 22, 2014, for the multipack but not single-dose PI, the review division approved a supplemental NDA submission amending the PI for alignment with the Physician Labeling Rule (PLR). On November 16, 2020, the Applicant and FDA reached agreement on labeling for the multipack PI, single-dose PI (including PLR reconciliation), and medication guide (covering both PIs). The labeling revisions are detailed and available for reference in FDA's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS):

- Multipack PI: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af805b7bc9&_afrRedirect=296038887464722
- Single-dose PI: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af805b7c27&_afrRedirect=296574945032260

Additional documents focused on labeling review by team members from the Division of Pediatric and Maternal Health (DPMH, November 6, 2020), Office of Prescription Drug Promotion (OPDP, November 2, 2020, November 10, 2020), and Division of Medication Error Prevention and Analysis (DMEPA), as well as from the Applicant in response to FDA's request for PLR-to-non-PLR tracking for the single-dose PI (November 16, 2020), are also available for reference.

12. Risk Evaluation and Mitigation Strategies

No risk evaluation mitigation strategies were required for the original ProHance application. No safety issues were identified in this supplemental application that would require an initiation of a risk evaluation and mitigation strategy.

13. Postmarketing Requirements and Commitment

The review team does not recommend any PMRs or PMCs.

14. Division Director (Clinical)

I concur with the review team's assessment and with their unanimous recommendation that these supplemental applications be approved.

15. Office Director (or Designated Signatory Authority)

The designated signatory authority for this efficacy supplement is the Director of the DIRM, Libero Marzella, MD, PhD

16. Appendices

16.1. References

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16.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): PH-108, NCT03750188, Bracco Diagnostics Inc.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 9		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial	Yes ☐	No ☐ (Request details from

interests/arrangements:		Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

16.3. Nonclinical Pharmacology/Toxicology

Not Applicable

16.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

Summary of Modeling Results

The population pharmacokinetic (PK) analysis was conducted based on a pooled dataset of observed 1055 plasma gadoteridol concentrations in 79 subjects from Study 29, Study 27, and Study 12. A summary of the three PK studies for population PK analysis is provided in Table 27.

Table 27. Summary of the Three Data Sets Combined for PK Model Building

Protocol	Title	Population	Population Characteristics	Age (years)	Assay Matrix	Assayed Moiety	Assay Method	Administ-ration	Dose (mmol/kg)	Subjects Enrolled
32,521-12	A Clinical Investigation of the Safety and Pharmacokinetics of ProHance in Renally-Impaired Patients	Adults	Renal impaired	26-73	Serum/Urine	Gadoteridol	Immunoassay	Slow Infusion (10 ml/min)	0.1 & 0.3	24
32,521-27	A clinical evaluation of the safety and pharmacokinetics of ProHance (gadoteridol injection) in adult subjects with impaired hepatic function	Adults	Normal & Hepatic impaired	37-50	Blood/Urine	Gadolinium	ICP-AES	Slow Infusion (1 min)	0.1	28
32,521-29	A Clinical Evaluation Of The Safety And Pharmacokinetics Of ProHance (Gadoteridol Injection) In Normal Healthy Pediatric Subjects	Pediatric	Healthy	5-15	Blood/Urine	Gadolinium	ICP-AES	Slow Infusion (1 min)	0.1	28

Source: Population PK Report, Table 1.
Abbreviations: ICP-AES, inductively coupled plasma atomic emission spectroscopy; PK, pharmacokinetic

Summary statistics of the continuous and categorical covariates that were evaluated in the population PK analysis are shown in Table 28 and Table 29, respectively.

Table 28. Summary Statistics for the Continuous Covariates in the Population PK Analysis

Covariate Code	Description	Unit	Statistic	Study 12	Study 27	Study 29	Study All
	Patient count	n		24	27	28	79
AGE	Age	years	median	46.5	47	10.5	42
			mean	48.6	46.2	10.5	34.3
			min	26	37	5	5
			5th percentile	28.2	40.6	5.35	7
			95th percentile	72.1	50	15	67
			max	73	50	15	73
BMI	Body Mass Index	kg/m^2	median	29.0	27.5	18.4	24.0
			mean	29.2	28.6	18.9	25.3
			min	19.0	21.5	13.3	13.3
			5th percentile	20.8	22.1	14.5	15.3
			95th percentile	39.1	38.4	25.0	37.2
			max	52.3	43.3	27.3	52.3
BSA	Body Surface Area	m^2	median	1.89	1.97	1.34	1.83
			mean	1.93	1.96	1.27	1.70
			min	1.36	1.55	0.813	0.813
			5th percentile	1.64	1.63	0.819	0.901
			95th percentile	2.30	2.32	1.78	2.31
			max	2.78	2.35	1.89	2.78
BUN	Blood Urea Nitrogen	mg/dL	median	29.5	10	10	12
			mean	34.7	10.8	10.2	17.8
			min	14	4	6	4
			5th percentile	18	6	6	6
			95th percentile	58.7	20.1	15.3	52.5
			max	72	21	16	72
CRCL	Creatinine clearance	ml/min	median	47.8	121	108	102
			mean	46.1	136	117	102
			min	15.1	87.8	61.5	15.1
			5th percentile	19.2	96.0	69.0	24.1
			95th percentile	70.4	194	181	179
			max	77.0	270	228	270
FFM	Fat Free Mass	kg	median	54.3	59.0	29.8	48.0
			mean	53.8	56.3	30.1	46.3
			min	30.2	36.0	15.2	15.2
			5th percentile	40.1	38.2	16.1	19.2
			95th percentile	69.5	68.0	49.8	69.1
			max	82.2	72.8	53.6	82.2
HCT	Hematocrit	%	median	38.8	41	39.5	40
			mean	37.8	41.6	39.5	39.7
			min	25.2	34	32	25.2
			5th percentile	26.5	35.3	36	32.5
			95th percentile	42.8	48.7	45.3	47.1
			max	49.2	50	47	50
HGB	Hemoglobin	g/dL	median	13.0	13.9	12.8	13.1
			mean	12.6	13.9	12.8	13.1
			min	8.50	11.4	10.3	8.50
			5th percentile	8.78	11.7	11.1	10.9
			95th percentile	14.1	16	14.4	16
			max	16.8	16.8	18.8	18.8
HT	Height	cm	median	168	170	144	165
			mean	167	170	144	160

Covariate Code	Description	Unit	Statistic	Study 12	Study 27	Study 29	Study All
			min	146	145	114	114
			5th percentile	149	157	117	119
			95th percentile	180	184	169	180
			max	183	185	178	185
ISCR	Inverse Serum creatinine	L/umol	median	0.00514	0.0141	0.0226	0.0141
			mean	0.00577	0.0152	0.0230	0.0151
			min	0.00209	0.0103	0.0126	0.00209
			5th percentile	0.00238	0.0113	0.0141	0.00280
			95th percentile	0.0109	0.0215	0.0377	0.0283
			max	0.0126	0.0283	0.0377	0.0377
SCR	Serum creatinine	umol/L	median	194	70.7	44.2	70.7
			mean	219	69.4	47.4	107
			min	79.6	35.4	26.5	26.5
			5th percentile	92.4	46.9	26.5	35.4
			95th percentile	420	88.4	70.7	357
			max	477	97.2	79.6	477
WT	Body weight	kg	median	76.9	79.5	44	72
			mean	81.5	82.0	40.9	67.3
			min	45.5	55	20	20
			5th percentile	56.7	60.1	21	24.6
			95th percentile	112	112	69.3	110
			max	160	118	72	160

Source: Population PK Report, Table 3.
Abbreviation: n, number of subjects in subgroup; PK, pharmacokinetics

Table 29. Summary Statistics for the Categorical Covariates in the Population PK Analysis

Covariate Code	Category	Study 12	Study 27	Study 29	All Studies
	n	24	27	28	79
SEX	Male	15	20	10	45
	Female	9	7	18	34
RACE	White	20	19	0	39
	Other	2	0	0	2
	Black	2	2	2	6
	Hispanic	0	6	26	32
AGE2	Adult	24	27	0	51
	12 to <18	0	0	14	14
	6 to <12	0	0	12	12
	2 to <6	0	0	2	2
AGE3	Adult	24	27	0	51
	12 to <18	0	0	14	14
	6 to <12	0	0	12	12
	4 to <6	0	0	2	2
PATH	Renal Impaired	24	0	0	24
	Normal	0	13	28	41
	Hepatic Impaired	0	14	0	14

Source: Population PK Report, Table 4.
Abbreviation: n, number of subjects in subgroup; PK, pharmacokinetics

The PK of gadoteridol in pediatric and adult subjects was best characterized by a two-compartment model with structural covariates for creatinine clearance (CRCL) on gadolinium clearance, fitted allometric scaling for body weight (BW), random effects on clearance (CL), intercompartmental clearance (Q), central (V1) and peripheral (V2) volumes of distribution, an omega block on the random effects and a proportional residual error model with a different residual error for Study 29 versus the other studies. The allometric coefficients of BW was estimated to be 0.368 (95% CI: 0.164 to 0.572) for CL and Q, and 0.869 (95% CI: 0.731 to 1.007) for V1 and V2 based on BW referenced to a standard BW of 70 kg. The coefficient of CRCL on CL using a power model was estimated to be 0.512 referenced to a standard CRCL of 115 ml/min. Covariate analysis showed that CL was 53.6% lower in subjects with renal impairment than that in subjects with normal renal function in addition to the reductions explainable by changes in CRCL.

The final gadoteridol PK model parameter estimates are presented in Table 30. The bootstrap analysis of the final gadoteridol PK model based on 1000 runs showed similar estimates and 95% CI for all PK parameters.

Table 30. Final Model Parameter Values

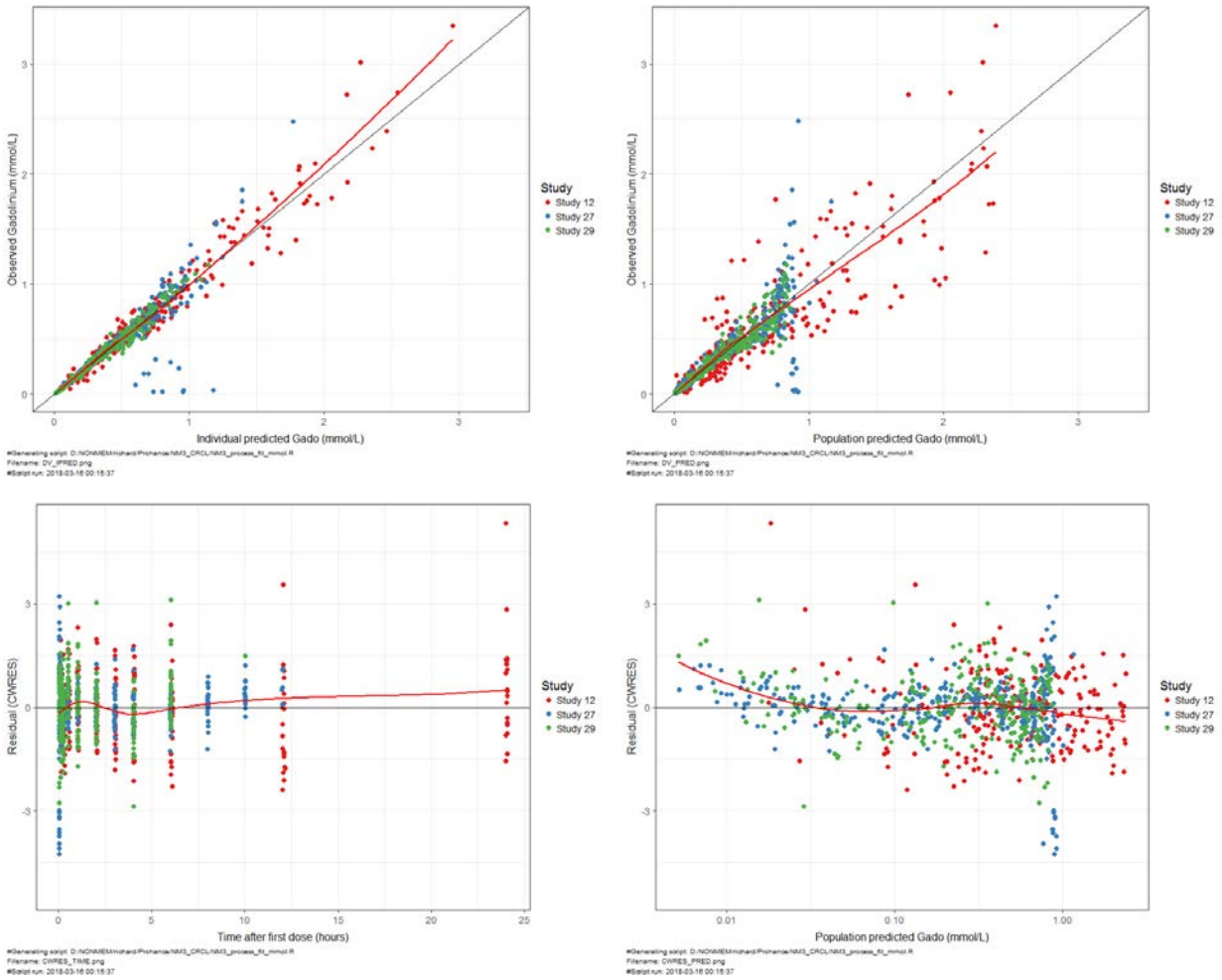
Code	Description	Unit	Pop value	se (%)	BSV (ratio)	se (%)	Etabar p-value	Eta shrinkage (%)
CL	Clearance	L/h	5.81	4.6	0.251	9	0.939	2.4
V1	Central volume	L	8.02	4.6	0.266	10.5	0.594	12.4
Q2	Inter-compartmental clearance	L/h	9.9	12.9	0.659	15.9	0.6	18
V2	Peripheral volume	L	6.1	6	0.407	14.3	0.681	13.3
LAMCL	Allometric coefficient for CL/Q2		0.368	28.3	.	.	.	.
LAMV	Allometric coefficient for V1/V2		0.869	8.1	.	.	.	.
CRCLCL	Covariate for CRCL on CL		0.512	15.9	.	.	.	.
RFCL	Covariate for renal impairment on CL		-0.536	9.9	.	.	.	.
RUVCV	Proportional residual error (not Study 29)	ratio	0.196	6.3	.	.	.	.
RUVCV29	Proportional residual error (Study 29)	ratio	0.114	12.4	.	.	.	.

	CL	V1	Q	V2
CL	1			
V1	0.226	1		
Q	0.352	-0.57	1	
V2	0.338	-0.14	0.767	1

Source: Population PK Report, Table 13.
Abbreviations: BSV, between-subject variability; Pop, population; se, standard error

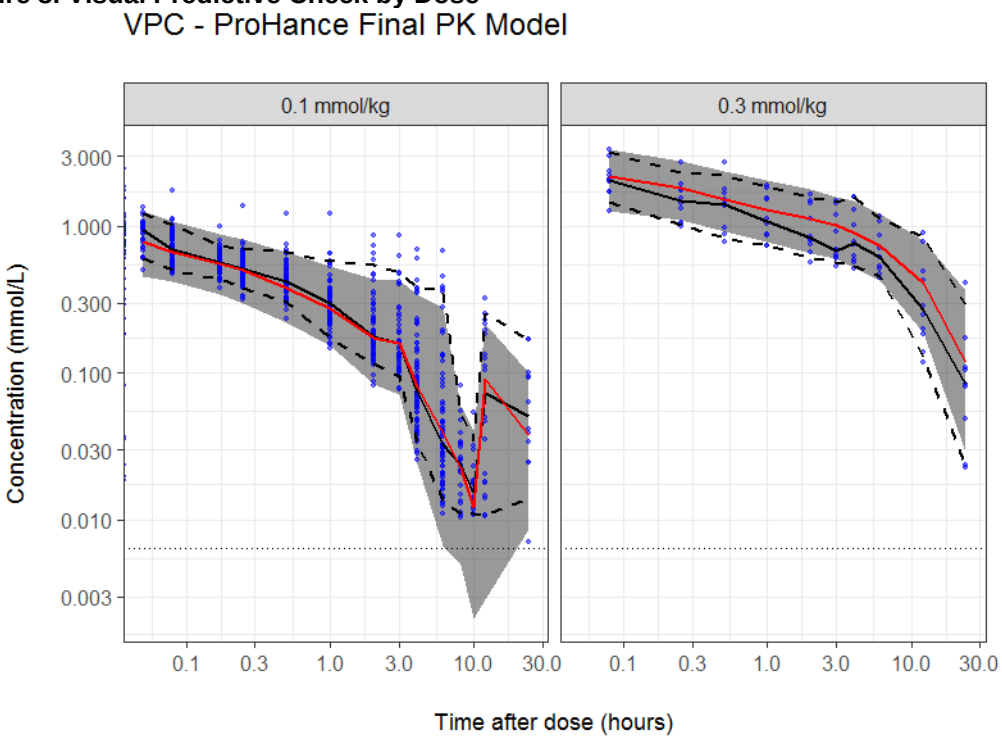
The goodness-of-fit plots (Figure 7), visual predictive check by dose (Figure 8), pathology (Figure 9), age (Figure 10) and NPDE (Figure 11) overall showed that the final gadoteridol PK model describes the plasma PK data well, with little bias or apparent model misspecification.

Figure 7. Observed Versus Individual Predictions of Gadoteridol Concentrations in Plasma for the Final Model, Stratified by Time After Dose



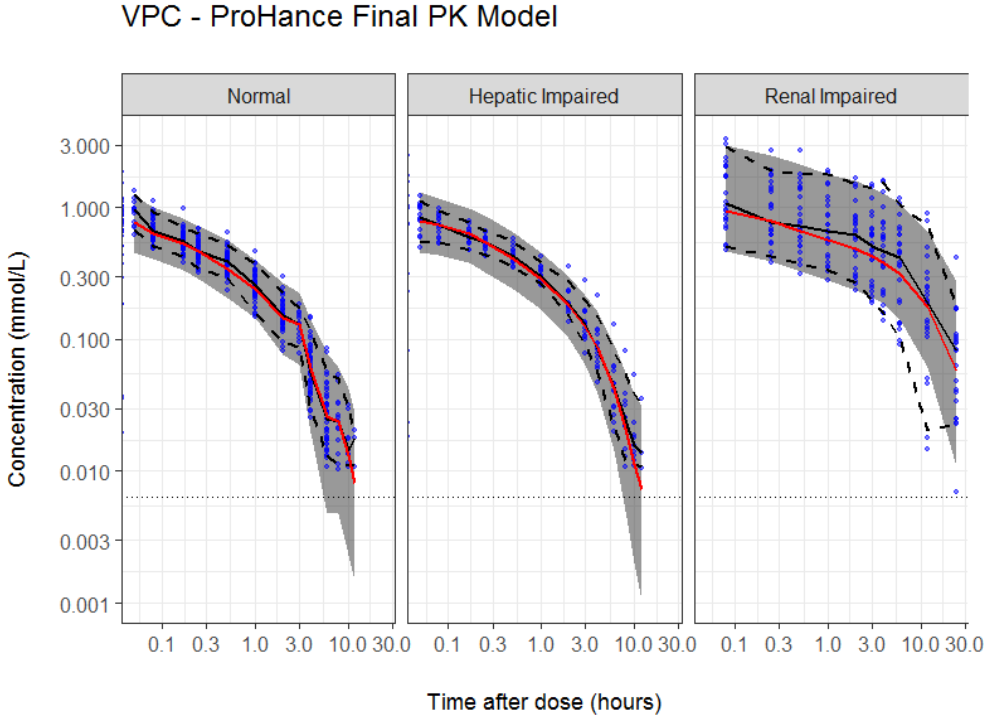
Source: Population PK Report, Figures 17, 18, 19, and 20.

Figure 8. Visual Predictive Check by Dose



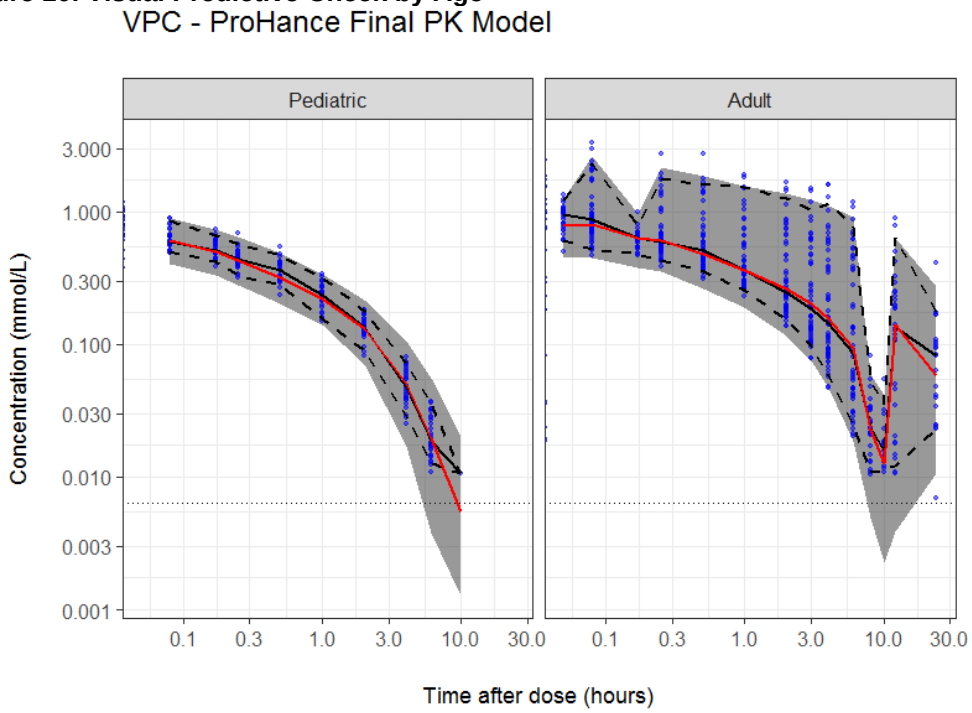
Source: Population PK Report, Figure 28.
Abbreviations: PK, pharmacokinetic; VPC, visual predictive check

Figure 9. Visual Predictive Check by Pathology



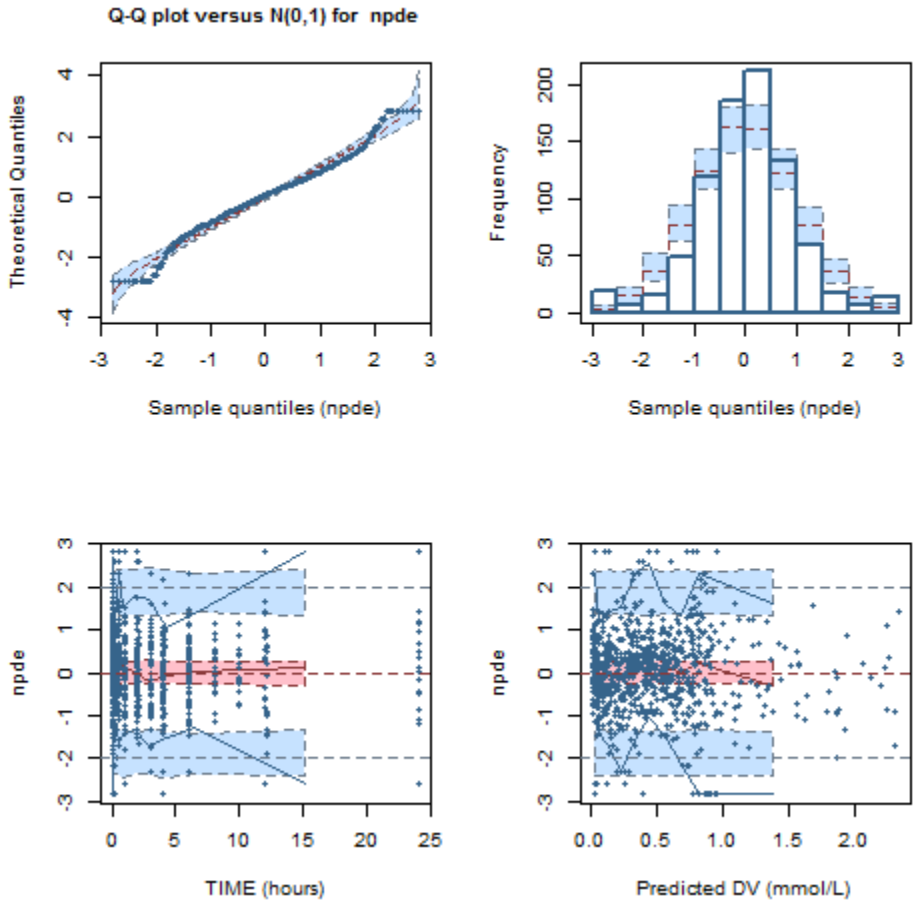
Source: Population PK Report, Figure 29.
Abbreviations: PK, pharmacokinetic; VPC, visual predictive check

Figure 10. Visual Predictive Check by Age



Source: Population PK Report, Figure 30.
Abbreviations: PK, pharmacokinetic; VPC, visual predictive check

Figure 11. Normalized Prediction Distribution Error Summary Plots



Source: Population PK Report, Figure 33.
Abbreviations: DV, daily value; npde, normalized prediction distribution error; Q-Q, quantile

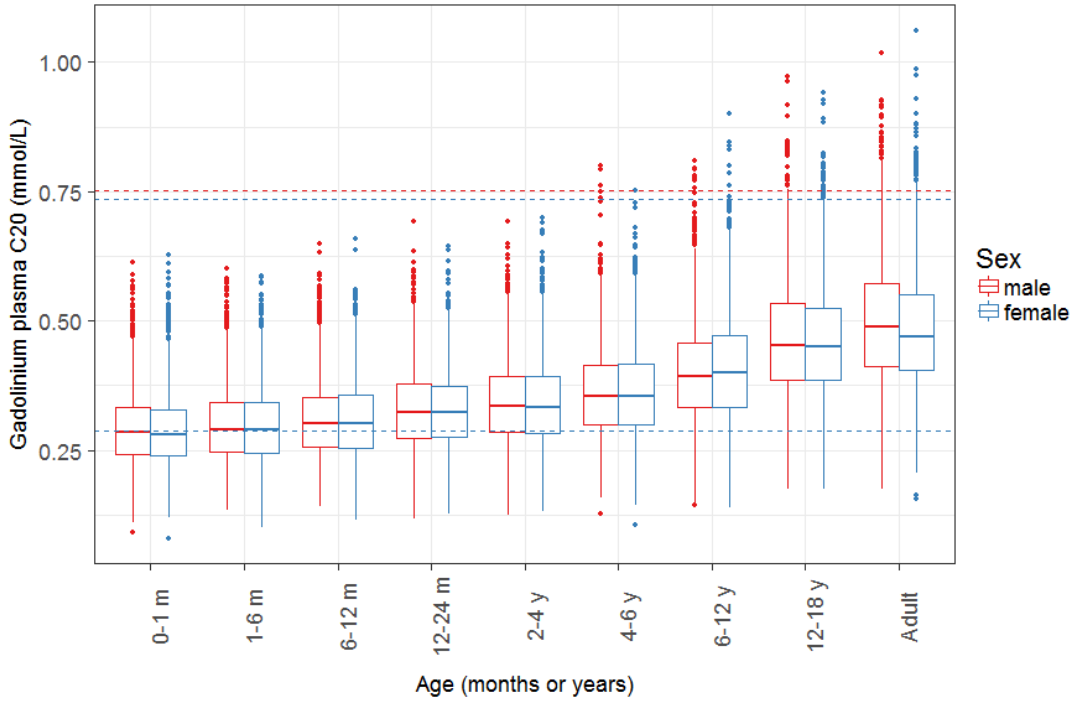
Simulations for Pediatrics Less Than 2 Years of Age

The predicted exposure of using a mass per kg dosing regimen for ProHance in younger pediatric patients (less than 2 years old) was examined by simulation using the final model. The gadolinium concentrations for a population of subjects of different ages receiving 0.1 mmol/kg of ProHance given as an intravenous infusion over 1 min were simulated. The subjects covered the age range of the subjects in the original data set (greater than 2 years), and the ages were grouped into 2 to 4, 4 to 6, 6 to 12, 12 to 18 years and adult (18 to 30 years) age bins. Additional subjects had ages below 2 years, and were grouped into 0 to 1, 1 to 6, 6 to 12 and 12 to 24 months age bins. These additional subjects extrapolated ProHance kinetics in the very young given the known physiology and maturation of GFR. For each age group, 1000 subjects were simulated and the PK simulation was run 5 times per subject (5000 subjects per age group). The distribution of ages within a cohort was generated using a random uniform distribution bounded by the age limits of the respective age bin. Sex was randomly assigned to

the subjects using a binomial distribution. The BW for age distributions were based on the model of Sumpter and Holford. This model estimates BW based on gestational age (also known as Post Menstrual Age, PMA) separately for males and females. Creatinine clearance was simulated given age and weight using the equation described by Rhodin et al.

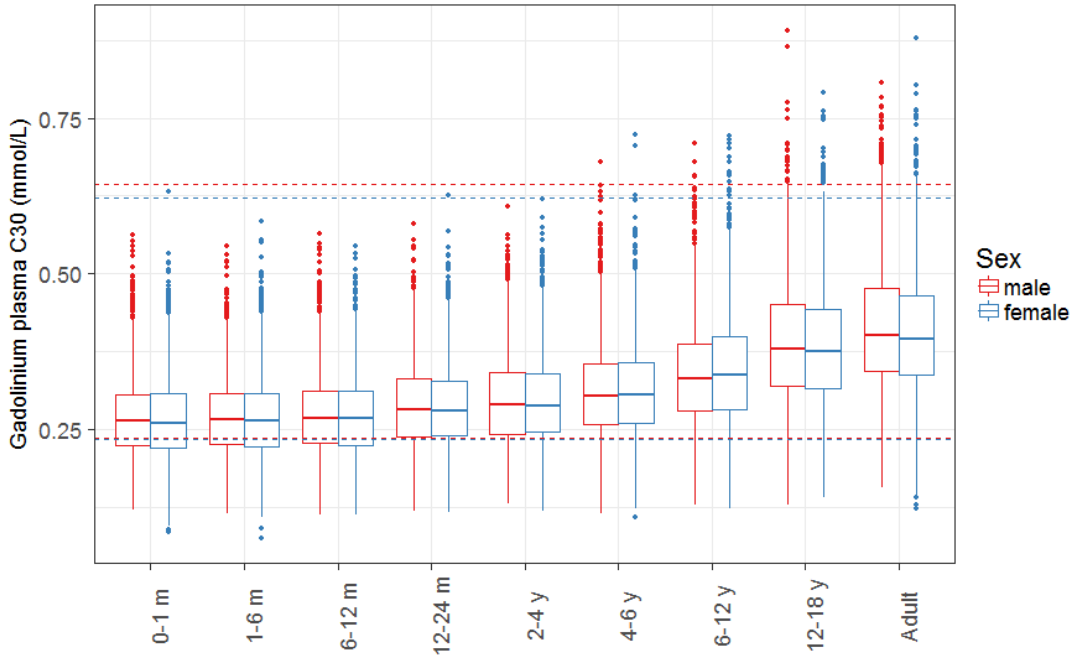
Simulated gadolinium C20 (Figure 12), C30 (Figure 13), AUC_{0-24} (Figure 14), and C_{max} (Figure 15) were summarized by age groups. The lowest AUC exposure was 63.9% (male) and 64.8% (female) of adult values for 6 to 12 month old subjects. The difference in AUC was due to the relative increase in weight normalized clearance for these ages, which reflected a balance between the effect of body size and the maturation of renal function. The maximum concentration of gadolinium decreased progressively for the younger age groups. The lowest C_{max} was 53.5% (male) and 54.2% (female) of nonrenally impaired adult values for 0 to 1 month old subjects. The concentrations of gadolinium at 20 and 30 minutes after infusion (which is thought to correspond to the time at which MRI is likely to be conducted) also decreased progressively for the younger age groups. The lowest C20 was 58.7% and 59.9 % of nonrenally impaired adult values for 0 to 1 month old male and female subjects respectively. The lowest C30 was 65.4% and 66.1% also for the 0 to 1 month old male and female subjects respectively. These results were in line with a publication describing gadobutrol, a similar GBCA to gadoteridol. In newborns, extracellular water fraction was approximately 37% compared with 20% in adults, therefore, a trend to lower concentrations in plasma paired with a trend to higher mean volumes of distribution in pediatric subjects is expected and contributes to the lower C20 and C30 in the population aged younger than 2 years.

Figure 12. Simulated ProHance Concentration at 20 Minutes (C20) by Age (0.1 Mmol/Kg)



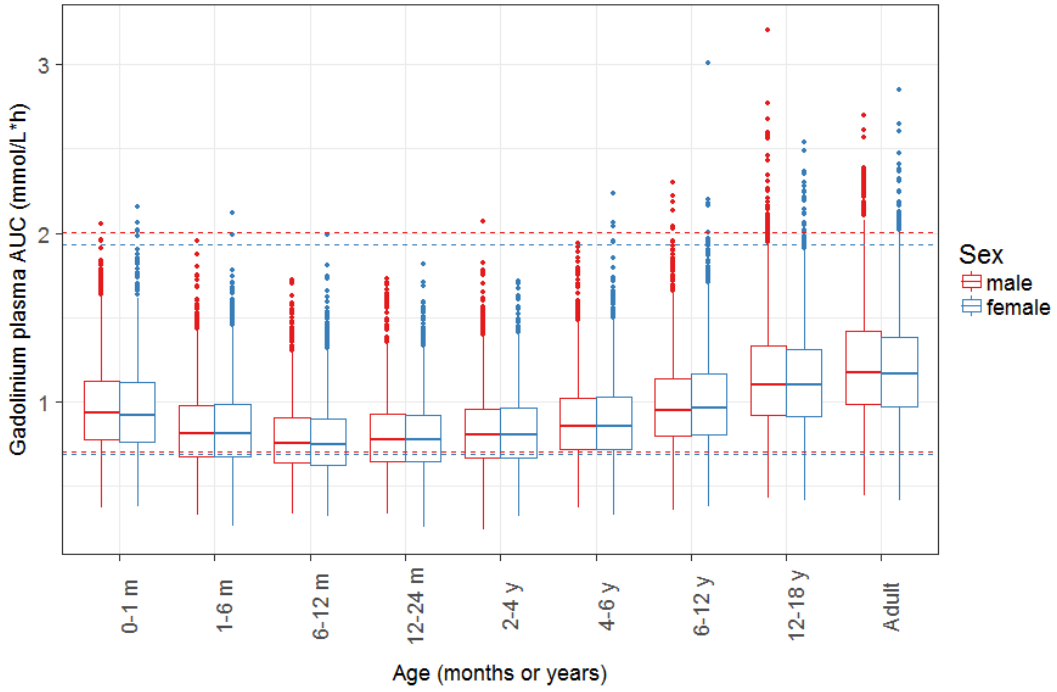
Source: Population PK Report, Figure 41.
Note: Horizontal dashed lines are the 95% prediction intervals of the male (red) and female (blue) adult data.
Abbreviations: m, month; y, year

Figure 13. Simulated ProHance Concentration at 30 Minutes (C30) by Age (0.1 Mmol/Kg)



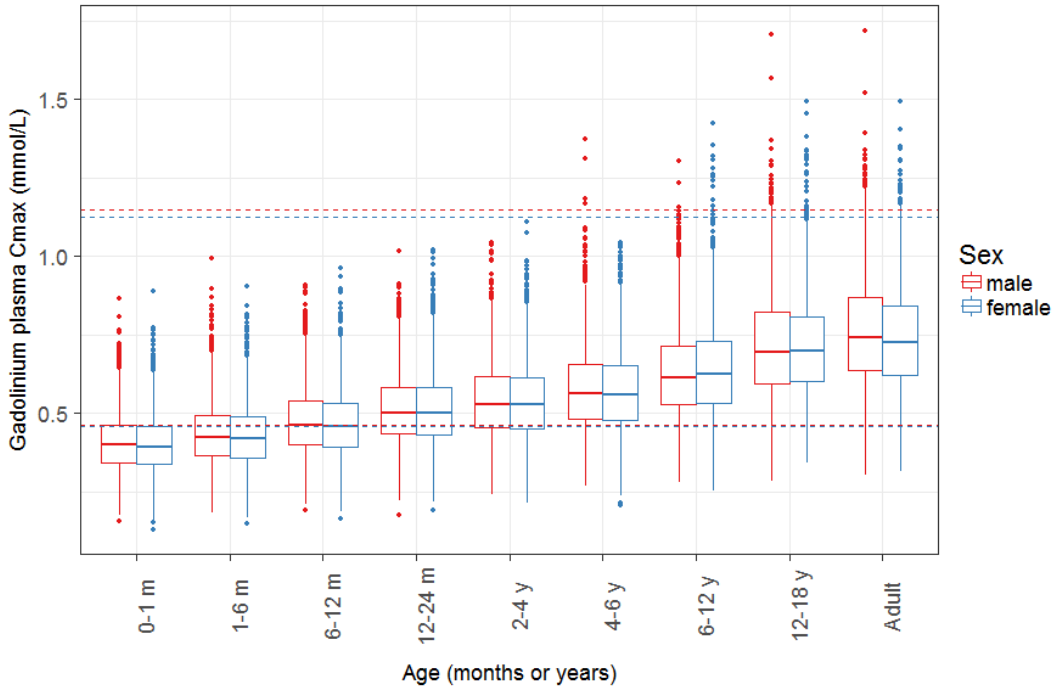
Source: Population PK Report, Figure 42.
Note: Horizontal dashed lines are the 95% prediction intervals of the male (red) and female (blue) adult data.
Abbreviations: m, month; y, year

Figure 14. Simulated ProHance Exposure (AUC) by Age (0.1 Mmol/Kg)



Source: Population PK Report, Figure 39.
Horizontal dashed lines are the 95% prediction intervals of the male (red) and female (blue) adult data.
Abbreviations: m, month; y, year

Figure 15. Simulated ProHance Maximum Concentration (C_{max}) by Age (0.1 Mmol/Kg)

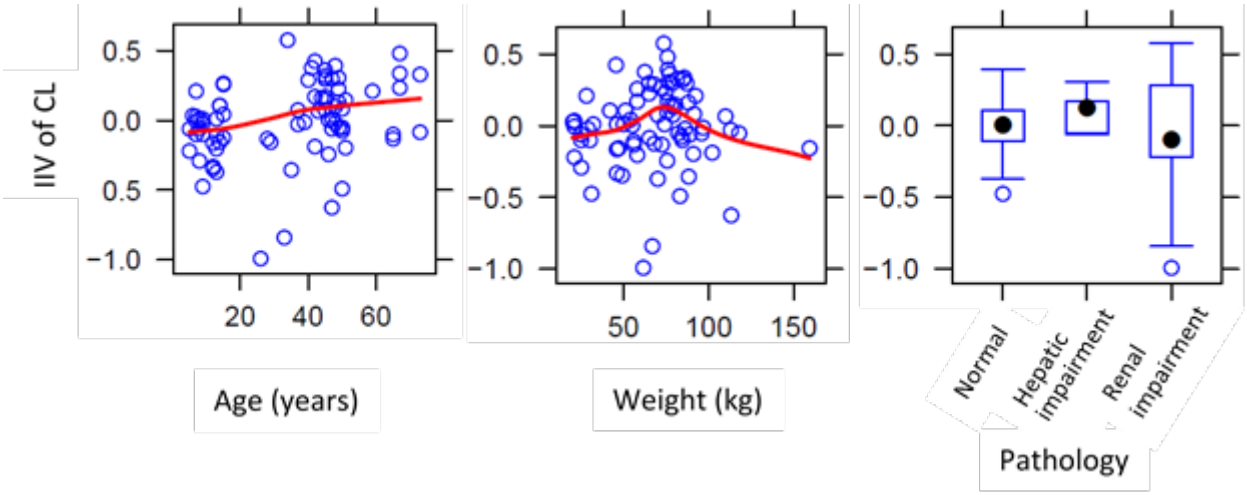


Source: Population PK Report, Figure 40.
Note: Horizontal dashed lines are the 95% prediction intervals of the male (red) and female (blue) adult data.
Abbreviations: m, month; y, year

The Applicant concluded that using weight based dosing for ProHance in pediatric subjects under 2 years old gives similar, or lower than, AUC and C_{max} values to those reported for adults, supporting that no dose adjustment is necessary for this pediatric population.

Reviewer's Comments: *The Applicant's final population PK model included BW, CRCL by Cockcroft-Gault equation and renal impairment as significant covariates on gadoteridol CL. However, there were strong correlations among these three covariates as CRCL was a function of BW, and an indicator of renal impairment. Strong correlations between covariates can preclude the ability to make inferences about individual covariate effects. Therefore, the reviewer conducted sensitivity analysis based on the model with BW on Q, Vc and Vp, and no covariates on gadoteridol CL. After including the effect of CRCL on CL using a power function (ΔOFV=-131.0, p<0.001), no other covariates, including age, BW, or pathology, were identified to be statistically significant at p<0.005 (Figure 16).*

Figure 16. Interindividual Variability of Gadoteridol Versus Age, Weight and Pathology for the Reviewer's Final PK Model



Source: Reviewer's analysis.

The reviewer's final PK model converged successfully with slightly different PK parameter estimates (Table 31) compared to the Applicant's final model.

Table 31. Parameter Estimates of the Reviewer's Final PK Model

Theta		Estimate*	SE	RSE	95% CI**
1	Typical CL at CRCL of 115 mL/min	**5**	0.162	3.2%	4.682 - 5.318
2	Typical Vc at BW of 70 kg	**7.94**	0.304	3.8%	7.344 - 8.536
3	Typical Q at BW of 70 kg	**11.4**	1.27	11.1%	8.911 - 13.889
4	Typical Vp at BW of 70 kg	**6.11**	0.325	5.3%	5.473 - 6.747
5	Exponent of power function for CRCL on CL	**1**	0.0519	5.2%	0.898 - 1.102
6	Exponent of power function for BW on Q	**0.724**	0.0663	9.2%	0.594 - 0.854
7	Exponent of power function for BW on Vc and Vp	**0.811**	0.0418	5.2%	0.729 - 0.893

Omega	1	2	3	4	Etabar (SE)	p val
1	IIV of CL 0.0802 (17%)				0.002 (0.031)	0.9452
2	IIV of Vc 0.0256 (51.6%)	0.0727 (25.9%)			-0.011 (0.027)	0.6864
3	IIV of Q 0.0161 (211.2%)	-0.0734 (51.1%)	0.251 (47.8%)		0.02 (0.042)	0.6339
4	IIV of Vp 0.0171 (102.3%)	-0.0074 (258.4%)	0.143 (42%)	0.144 (26.7%)	0.011 (0.036)	0.7504

Omega (on SD scale) *		1	2	3	4
1	IIV of CL	28.3% (8.5%)			
2	IIV of Vc	33.5%	27% (12.9%)		
3	IIV of Q	11.3%	-54.3%	50.1% (23.9%)	
4	IIV of Vp	15.9%	-7.3%	75.2%	37.9% (13.4%)

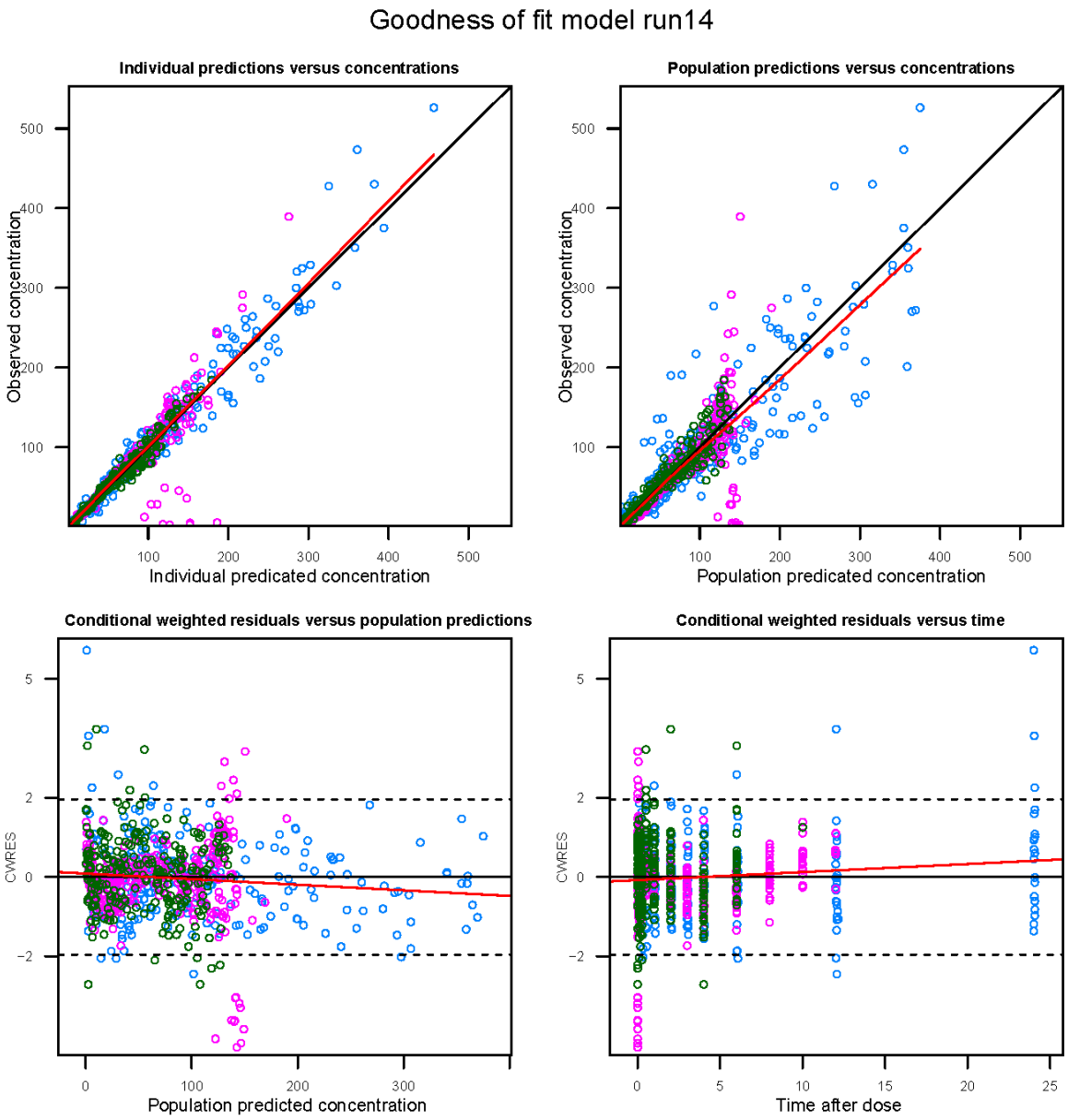
Sigma		1	2
1	Proportional RUV for Studies 12 and 27	0.0386 (9.3%)	
2	Proportional RUV for Studies 29	0	0.0132 (12%)

* Correlations in omega are shown as the off-diagonal elements. SAME blocks are not shown.

Source: Reviewer's analysis.
Abbreviations: BW, body weight; CI, confidence interval; CL, clearance; CRCL, creatinine clearance; Q, RSE, RUV, proportional residual error; SD, standard deviation; SE, standard error; Vc, Vp,

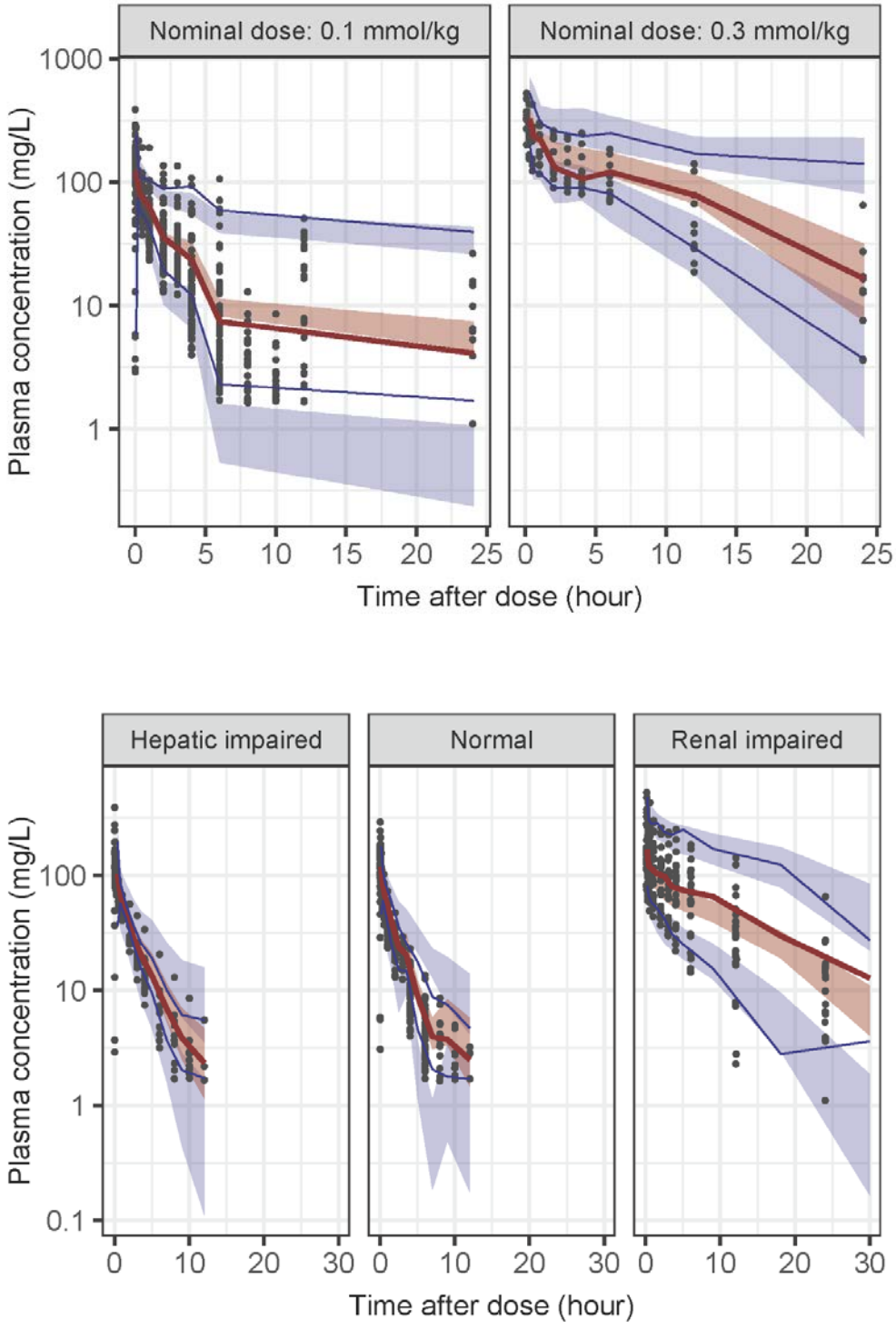
The GOF plots (Figure 17), visual predictive check stratified by nominal dose, pathology and age (Figure 18) and NPDE (Figure 19) showed that the reviewer's final PK model described the observed time profile of gadoteridol plasma concentration well.

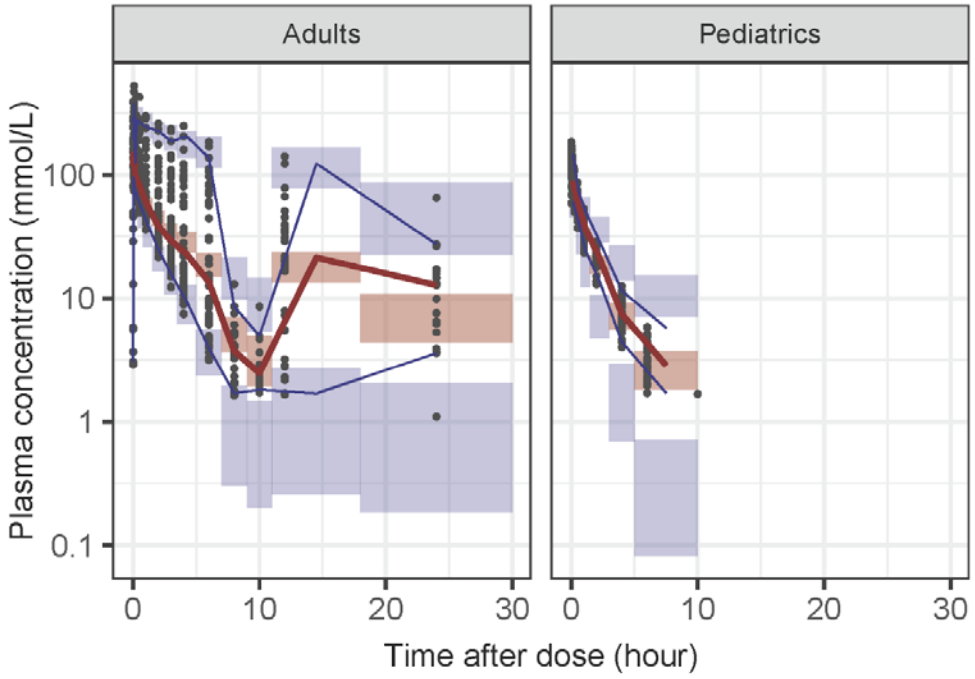
Figure 17. Goodness-of-Fit Plots for the Reviewer's Final PK Model



Source: Reviewer's analysis.
Notes: Red, green and blue dots represent data from Study 12, 27 and 29, respectively.
Abbreviation: PK, pharmacokinetic

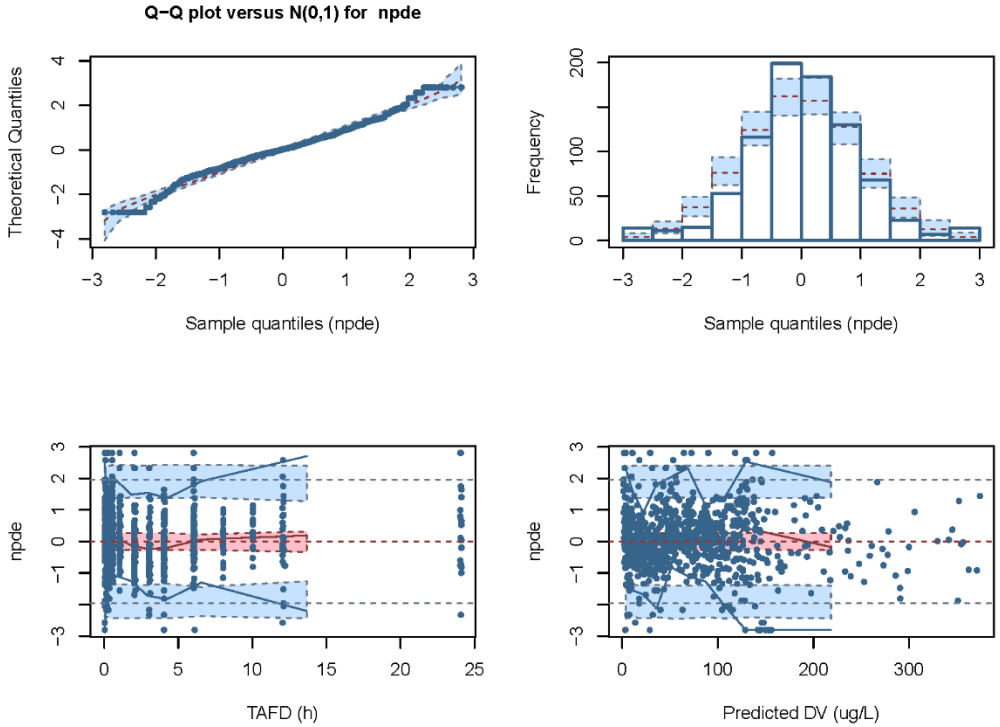
Figure 18. Visual Predictive Check Stratified by Nominal Dose, Pathology, and Age for the Reviewer's Final PK Model





Source: Reviewer's analysis.
Abbreviation: PK, pharmacokinetic

Figure 19. The Normalized Prediction Distribution Error of the Reviewer's Final Model



Source: Reviewer's analysis.
Abbreviations: DV, h, hours; npde, normalized prediction distribution error; Q-Q, quantile-quantile; TAFD, time after first dose.

Therefore, this model was considered as the final model and was further used for simulation. The simulation approach seems reasonable to support no dose adjustment for pediatrics less than 2 years of age, as gadoteridol is almost entirely cleared by the kidneys, which permits a more robust estimate of clearance in the neonate/infant population. The Reviewer's simulation showed that the simulated gadoteridol C20 (Figure 1) and C30 (Figure 2) post injection, $AUC_{0\text{-}24h}$ (Figure 3), and C_{max} (Figure 4) in pediatrics less than 2 years of age appear to fall within the range of those in adults and children over the age of 2 years at the same dose of 0.1 mmol/kg. In addition, the simulated gadoteridol PK profiles are generally consistent with the FDA-approved GBCA products, Gadavist, Dotarem and MultiHance, in pediatrics less than 2 years of age at the same dose of 0.1 mmol/kg.

16.5. Additional Clinical Outcome Assessment Analyses

N/A

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Jonathan Cohen, PhD	OSM/DIRM	Section: 5	_X_ Authored ___ Approved
	Signature: Jonathan E. Cohen -S Digitally signed by Jonathan E. Cohen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011434936, cn=Jonathan E. Cohen -S Date: 2020.12.10 10:43:32 -05'00'			
Nonclinical Team Leader	Adebayo Laniyonu, PhD	OSM/DIRM	Section: 5	___ Authored _X_ Approved
	Signature: Adebayo A. Laniyonu -S Digitally signed by Adebayo A. Laniyonu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300127170, cn=Adebayo A. Laniyonu -S Date: 2020.12.10 18:19:17 -05'00'			
Clinical	Venkata S. Mattay, MD	OSM/DIRM	Sections:1, 2, 3, 7, 8, 19.2	_X_ Authored ___ Approved
	Signature: Venkata S. Mattay -S Digitally signed by Venkata S. Mattay -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010123360, cn=Venkata S. Mattay -S Date: 2020.12.10 15:53:51 -05'00'			
Clinical Team Leader	Anthony Fotenos, MD, PhD	OSM/DIRM	Sections: 7, 11	_X_ Authored _X_ Approved
	Signature: Anthony F. Fotenos -S Digitally signed by Anthony F. Fotenos -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001526313, cn=Anthony F. Fotenos -S Date: 2020.12.11 09:39:56 -05'00'			
Clinical Pharmacology Team Leader/ Cross-Disciplinary Team Leader (CDTL)	Christy John, PhD	OCP/DCPII	Sections: 1, 6	_X_ Authored _X_ Approved
	Signature: Christy S. John -A Digitally signed by Christy S. John -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300150005, cn=Christy S. John -A Date: 2020.12.10 13:00:28 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD	OCP/DCPII	Sections: 1, 6	___ Authored _X_ Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2020.12.11 11:00:54 -05'00'			
Pharmacometrics Reviewer	Li Liang, PhD	OCP/DPM	Sections: 6, 19.4	_X_ Authored ___ Approved
	Signature: Liang Li -S Digitally signed by Liang Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Liang Li -S, 0.9.2342.19200300.100.1.1=2001459144 Date: 2020.12.09 22:29:53 -05'00'			
Pharmacometrics Team Leader	Lian, Ma, PhD	OCP/DPM	Sections: 6, 19.4	___ Authored _X_ Approved
	Signature: Lian Ma -S Digitally signed by Lian Ma -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lian Ma -S, 0.9.2342.19200300.100.1.1=2000825336 Date: 2020.12.09 22:31:16 -05'00'			
Statistical Reviewer	Jyoti Zalkikar, PhD	OB/DBI	Section: 8	_X_ Authored ___ Approved
	Signature: Jyoti Zalkikar -S Digitally signed by Jyoti Zalkikar -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jyoti Zalkikar -S, 0.9.2342.19200300.100.1.1=1300162261 Date: 2020.12.09 23:48:08 -05'00'			
Statistical Team Deputy Director	Sue-Jane Wang, PhD	OB/DBI	Section: 8	___ Authored _X_ Approved
	Signature: Suejane Wang -S Digitally signed by Suejane Wang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Suejane Wang -S, 0.9.2342.19200300.100.1.1=1300088741 Date: 2020.12.10 07:58:45 -05'00'			
DPMH Reviewer	Carolyn L. Yancey, MD	ORDPURM/DPMH	Section: 10	_X_ Authored ___ Approved
	Signature: Carolyn L. Yancey -S Digitally signed by Carolyn L. Yancey -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300214089, cn=Carolyn L. Yancey -S Date: 2020.12.10 10:02:53 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Acting DPMH Team Leader	Shetarra Walker, MD	ORDPURM/DPMH	Sections: 10	___ Authored _X_ Approved
	Signature: Shetarra E. Walker -S Digitally signed by Shetarra E. Walker -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001962330, cn=Shetarra E. Walker -S Date: 2020.12.10 07:49:22 -05'00'			
Division Director (Clinical)	Libero (Louis) Marzella, MD, PhD	OSM/DIRM	Sections: ALL	___ Authored _X_ Approved
	Signature: Libero L. Marzella -S Digitally signed by Libero L. Marzella -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300088188, cn=Libero L. Marzella -S Date: 2020.12.16 19:22:22 -05'00'			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHARON P THOMAS
12/18/2020 06:33:27 PM