CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216016Orig1s000
216017Orig1s000

MULTI-DISCIPLINE REVIEW

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

NDA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2) New Drug Application
Application Numbers	NDA 216017 & NDA 216016
Priority or Standard	Standard
Submit Dates	November 30 & December 14, 2023, respectively
Received Dates	November 30 & December 14, 2023, respectively
PDUFA Goal Date	November 30 & December 14, 2024, respectively
Division/Office	Division of Imaging and Radiation Medicine, Office of Specialty Medicine
Review Completion Date	November 26, 2024
Established/Proper Name	Iomeprol
Trade Name	Iomervu
Pharmacologic Class	Radiographic contrast agent
Code name	B16880, E 7337
Applicant	Bracco Diagnostics Inc.
Dosage form	Injection
Applicant Proposed Dosing Regimen	Varies with indication
Applicant Proposed Indications and Populations	(b) (4) (iomeprol injection) is a radiographic contrast agent indicated for: Intravenous Procedures Adults • Computed tomography (CT) of head and body ((b) (4) -250, 300, 350, 400) • Computed tomography angiography (CTA) (b) (4) -300, 350, 400) • Coronary computed tomography angiography (CCTA) ((b) (4) -400) • (b) (4) • Computed tomography (CT) urography (b) (4) -350) Pediatric patients • Computed tomography (CT) of head and body (b) (4) -250, 300, 350, 400) • Computed tomography angiography (CTA) ((b) (4) -300, 350, 400) • Coronary computed tomography angiography (CCTA) (b) (4) -300, 400) • (b) (4) • Computed tomography (CT) urography (b) (4) -300) Intraarterial Procedures Adults • Coronary arteriography and ventriculography; (b) (4) • Cerebral, peripheral and visceral angiography, and aortography, including digital subtraction angiography ((b) (4) -300) Pediatric patients • (b) (4) • Cerebral, peripheral, and visceral angiography, including digital subtraction angiography (b) (4) -300)
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	711232001 | Computed tomography of head with contrast (procedure) 718527007 | Computed tomography of whole body with contrast (procedure) 419545005 | Computed tomography arteriography of coronary artery with contrast (procedure) 418659001 | Computed tomography arteriography of cerebral artery with contrast (procedure) 448443000 | CT arteriography (b) (4) 710305000 | Computed tomography angiography (b) (4) (b) (4) 713859006 | Computed tomography of urinary tract excretory phase with contrast (procedure) 419364000 | (b) (4) angiography of cerebral artery with contrast (procedure) 241234000 | (b) (4) angiography (procedure) 271993009 | Peripheral angiography (procedure) 702766003 (b) (4) Peripheral angiography (procedure)

	34945008 | Angiocardiography (procedure) 33367005 | Coronary angiography (procedure) (b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indications and Populations	IOMERVU is a radiographic contrast agent indicated for: Intra-arterial Procedures† • Cerebral arteriography, including intra-arterial digital subtraction angiography (IA-DSA), in adults and pediatric patients • Visceral and peripheral arteriography and aortography, including IA-DSA, in adults and pediatric patients • Coronary arteriography and cardiac ventriculography in adults • Radiographic evaluation of cardiac chambers and related arteries in pediatric patients Intravenous Procedures† • Computed tomography (CT) of the head and body in adults and pediatric patients • CT angiography of intracranial, visceral, and lower extremity arteries in adults and pediatric patients • Coronary CT angiography in adults and pediatric patients • CT urography in adults and pediatric patients †Specific concentrations are recommended for each type of imaging procedure.
Recommended SNOMED CT Indication Disease Term for each Indication	Lesion (morphologic abnormality) 52988006
Recommended Dosing Regimen	Varies with indication, refer to Table 12, Table 13, Table 14, and Table 15

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRM=Division of Risk Management
DPV=Division of Pharmacovigilance
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Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AQ	adequate quality
AR	adverse reaction
AUC	area under the concentration-time curve
BP	blood pressure
BMI	body mass index
BSV	between-subject variability
C_{20}	concentration at 20 minutes post-dose
C_{30}	concentration at 30 minutes post-dose
CCTA	coronary computed tomography angiography
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
CL_{inulin}	inulin clearance
Cmax	maximum concentration
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CRCL	creatinine clearance
CSR	clinical study report
CT	computed tomography
CTA	computed tomography angiography
CTU	computed tomography urography
CTV	computed tomography venography
CV	coefficient of variability
DBP	diastolic blood pressure
DPV	Division of Pharmacovigilance
DSA	digital subtraction angiography
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	good clinical practice
GD	gestation day
GFR	glomerular filtration rate
GLP	good laboratory practice
HED	human equivalent dose
hERG	human Ether-à-go-go-Related Gene
HPLC	high-performance liquid chromatography
HR	heart rate
IA	intra-arterial
IA-DSA	intra-arterial digital subtraction angiography

ICH	International Conference on Harmonization
ICM	iodinated contrast media
IEC	independent ethics committee
IKr	rapidly activating delayed rectifier cardiac potassium current
IND	investigational new drug application
IRB	institutional review board
IRT	Interdisciplinary Review Team for Cardiac Safety Studies
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IV	intravenous
KDIGO	Kidney Disease Improving Global Outcomes
MedDRA	Medical Dictionary for Regulatory Activities
mgI	milligrams organically bound iodine
MRI	magnetic resonance imaging
NDA	new drug application
NME	new molecular entity
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OECD	Organization for Economic Cooperation and Development
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
PMC	postmarketing commitment
PMR	postmarketing requirement
PPK	population pharmacokinetics
QTc	heart rate-corrected QT interval
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
T_3	triiodothyronine
T_4	thyroxine
TEAE	treatment emergent adverse event
TI	technically inadequate
Vss	volume of distribution at steady state
XRF	X-ray fluorescence

1 Executive Summary

1.1. Product Introduction

Iomervu (iomeprol) injection is an iodinated radiographic contrast agent that opacifies the vessels and body structures where the contrast agent is present following intravascular administration, permitting visualization of the internal structures through attenuation of x-ray photons.

Iomervu is recommended for intra-arterial (IA) administration in the following angiographic examinations:

- Cerebral arteriography, including intra-arterial digital subtraction angiography (IA-DSA), in adults and pediatric patients
- Visceral and peripheral arteriography and aortography, including IA-DSA, in adults and pediatric patients
- Coronary arteriography and cardiac ventriculography in adults
- Radiographic evaluation of cardiac chambers and related arteries in pediatric patients

Iomervu also is recommended for intravenous (IV) administration in the following computed tomography (CT) examinations in adults and pediatric patients:

- CT of the head and body
- CT angiography of intracranial, visceral, and lower extremity arteries
- Coronary CT angiography
- CT urography

Iomervu is available in concentrations of 250, 300, 350, and 400 mg organically bound iodine/mL (mgI/mL). The recommended dose and injection rate varies by indication.

Iomeprol has not been approved in the United States and is a new molecular entity (NME). Iomeprol was first approved for marketing in 1992 in the United Kingdom and is currently authorized for use in 50 countries. In many markets it is sold under the proprietary name Iomeron, and this name was used in study titles that will be referenced in this review.

New drug application (NDA) 216017, for IV indications, and NDA 216016, for IA indications, were submitted approximately 2 weeks apart. The Applicant, with FDA concurrence, is using NDA 216017 as a “flagship” NDA, and the two NDAs share much of their data through cross-referencing. The nonclinical and clinical pharmacology data for both routes of administration are essentially identical and the clinical data are closely related. Therefore, this single review document serves for both NDA 216016 and NDA 216017.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has submitted substantial evidence of effectiveness for Iomervu for the indications recommended in Section 1.1. Efficacy is supported by adequate and well-controlled studies conducted by the Applicant and published in the literature, which also provide mutually supportive confirmatory evidence among the related indications.

The studies that supported efficacy of Iomervu for the adult structure delineation indications, including coronary arteriography and cardiac ventriculography, cerebral arteriography, visceral and peripheral arteriography and aortography, intra-arterial digital subtraction angiography, CT head and body, and CT urography evaluated the adequacy of visualization of the indicated vessels and anatomical structures. Multiple blinded readers independently scored visualization using rating scales adapted to each imaging task. Results demonstrated adequate visualization of the intended arteries and anatomic regions. Structure delineation indications are approved for all currently marketed, intravascularly administered iodinated contrast agents and are generally considered to have inherent clinical utility.

The studies that supported the efficacy of Iomervu for CT angiography and coronary CT angiography evaluated diagnostic performance for the detection of significant stenosis at the arterial segment level. Images were independently evaluated by two or more blinded readers. Results demonstrated adequate sensitivity and specificity for the detection of significant stenosis in the peripheral, cerebral, and visceral arteries with CT angiography compared to digital subtraction angiography as the reference standard, and in the coronary arteries with coronary CT angiography compared to invasive coronary angiography as the reference standard.

The Applicant also conducted a pharmacokinetic study in patients 3 to 17 years of age and population pharmacokinetic modeling and simulation in patients younger than 3 years of age that served as the basis for extrapolation of effectiveness to pediatric patients.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Angiography and contrast CT imaging encompass a broad range of radiologic diagnostic procedures that are applied to evaluate a variety of clinical presentations and disease processes. Administration of a contrast agent is required for angiography and often required to obtain optimal imaging information with CT.

Iomervu is an iodinated contrast agent proposed for intra-arterial use in cerebral, visceral, and peripheral arteriography and aortography, including digital subtraction arteriography, in adults and children, coronary arteriography and cardiac ventriculography in adults, and radiographic evaluation of cardiac chambers and related arteries in children. Iomervu is also proposed for intravenous use in CT of the head and body, CT angiography of intracranial, visceral, and lower extremity arteries, coronary CT angiography, and CT urography in adults and children.

The efficacy of Iomervu was evaluated in adequate and well-controlled clinical studies for each proposed indication. The studies that supported efficacy of Iomervu for use in cerebral arteriography, visceral and peripheral arteriography and aortography, coronary arteriography and cardiac ventriculography, intra-arterial digital subtraction angiography, CT head and body, and CT urography demonstrated adequate visualization of the intended portions of the vascular system and anatomical structures. The studies that supported efficacy of Iomervu for use in CT angiography including coronary CT angiography demonstrated adequate diagnostic performance for the detection of significant stenosis at the arterial segment-level.

The safety of Iomervu was evaluated in 4,923 patients, of whom 4,804 patients received Iomervu at up to the recommended total iodine dose of 86 grams. Additional safety data from post-marketing experience outside the United States were also considered. The safety profile of Iomervu is broadly similar to the profile of other iodinated contrast agents, and risks associated with the class, such as hypersensitivity reactions, severe cutaneous adverse reactions, and acute kidney injury, can be mitigated through labeling. The safety data do not suggest safety issues that are new to the class.

Overall, the data demonstrate a favorable benefit-risk balance for Iomervu in the indicated patient populations. Approval of this application is recommended.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Radiography, fluoroscopy, and CT are anatomic imaging modalities relying on attenuation of x-rays to create images that are widely used for assessment of many diseases. • Iodinated contrast agents nonspecifically localize in areas with increased blood flow or vascular permeability, which allows for broad clinical utility of these drugs in distinguishing between normal and abnormal anatomy.	• Angiography (fluoroscopy) provides important clinical information for the diagnostic evaluation of a wide spectrum of vascular diseases. • Contrast is necessary for arteriography. • CT provides important information for diagnosis and management of many diseases, including serious conditions. • Contrast is often necessary to obtain optimal results with CT.
Current Treatment Options	• Nonionizing imaging modalities, such as ultrasound and magnetic resonance imaging (MRI), are often used as alternatives to CT and have different contexts of use for diagnostic indications depending on the clinical situation. • Several MRI and ultrasound contrast agents are approved and in some cases can add similar information about vascularity as iodinated contrast drugs. • Currently, six approved iodinated contrast agents are marketed for various IA and IV indications. • Shortages of iodinated contrast drugs occurred during the COVID-19 pandemic due to supply chain disruptions.	• Multiple iodinated contrast agents are available for use in routine diagnostic imaging indications. • None of the approved iodinated contrast agents are currently indicated for CT angiography of the intracranial, visceral, and lower extremity arteries or for CT urography. • Availability of additional iodinated contrast drugs has potential to improve supply chain resilience.
Benefit	• Multiple adequate and well-controlled studies were submitted in this NDA. • Studies for coronary, cerebral, visceral, and peripheral arteriography, intra-arterial digital subtraction angiography, and CT head and body, and CT urography demonstrated adequate visualization quality of the vessels and anatomic structures of interest. • Studies for CT angiography including coronary CT angiography	• The study results provided adequate support of effectiveness for the use of Iomervu in various arteriography and CT indications. • Structure visualization assessments and sensitivity and specificity to detect significant vascular stenosis are clinically

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	demonstrated adequate sensitivity and specificity for the detection of significant stenosis in the peripheral, cerebral, visceral, and coronary arteries. • Pediatric pharmacokinetic data and population pharmacokinetic modeling and simulation demonstrated that plasma exposures of Iomervu in pediatric patients were predicted to be within the range of exposures in adults and were used to support the proposed dosing regimen and extrapolation of efficacy.	meaningful endpoints that have been used in studies demonstrating effectiveness for related indications among approved iodinated contrast drugs. • Data were sufficient to establish effectiveness and weight-based dosing regimens for the pediatric population of all ages.
Risk and Risk Management	• The safety of Iomervu was evaluated in 4,923 patients, of whom 4,804 patients received Iomervu at up to the recommended total iodine dose of 86 grams. • No death related to Iomervu was reported. Serious adverse events related to Iomervu that were reported at up to the recommended dose are similar to the class-wide risks for iodinated contrast agents. • Overall, one or more adverse reactions occurred in 9.8% of patients who received Iomervu at up to the recommended total iodine dose of 86 grams. • The most common adverse reactions were feeling hot, headache, nausea, chest pain, back pain, and vomiting. • Key safety issues for Iomervu are similar to issues for other iodinated contrast agents and include hypersensitivity reactions, severe cutaneous adverse reactions, and acute kidney injury.	• No unexpected safety concerns are identified for the use of Iomervu for intra-arterial and intravenous procedures. • The safety data indicate that current class labeling for iodinated contrast agents will be sufficient to manage potential risks including those of hypersensitivity reactions, severe cutaneous adverse reactions, and acute kidney injury.

1.4. Patient Experience Data

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

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment data, such as		
		☐	Patient reported outcome	
		☐	Observer reported outcome	
		☐	Clinician reported outcome	
		☐	Performance outcome	
	☐	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 were not submitted as part of this application and were not needed.**			

2 Therapeutic Context

2.1. Analysis of Condition

Radiography, fluoroscopy, and computed tomography (CT) are anatomic imaging techniques that have a broad range of applications in the evaluation of various clinical conditions in adults and pediatric patients. These modalities rely on differential absorption of x-rays by body tissues to produce images. Tissues can be broadly grouped into air, fat, water (most non-adipose soft tissues), and bone densities, and there is little difference in x-ray attenuation between tissues within each category. Thus, imaging is often performed with contrast drugs to further differentiate tissues and obtain additional diagnostic information.

Iodine can attenuate x-rays in the energy ranges typically used for clinical imaging and is employed in many contrast drugs for this purpose. Iodine is not used directly, but instead is incorporated into organic molecules that influence pharmacokinetic properties and limit osmolarity of the drug. Currently approved iodinated contrast agents are not intended to target specific organs or systems. Instead, when administered into the intravascular space they opacify the injected vessel. As they proceed through the circulatory system, additional vessels will be opacified. This allows for various angiographic applications.

Iodinated contrast agents also rapidly distribute from the vessels into the extracellular fluid and have increased concentration in areas with increased blood flow or vascular permeability when compared to adjacent regions. These vascular features are seen in a wide variety of pathologic processes, including many inflammatory and neoplastic diseases. Iodinated contrast is generally excluded from the central nervous system by the blood-brain barrier, but accumulates in areas where there is disruption of the blood-brain barrier, a common characteristic of many lesions in the central nervous system (CNS). Similar accumulation is also observed in many types of lesions located elsewhere throughout other tissues in the body. Therefore, most iodinated contrast agents can be considered relatively nonspecific and likely to have broad clinical utility. From a regulatory perspective, this justifies lesion visualization indications that are not limited to one or more specific diseases. However, it is important to note that such broad lesion visualization indications do not imply suitability for determining the exact diagnosis of particular diseases.

2.2. Analysis of Current Treatment Options

In addition to radiography, fluoroscopy, and CT, magnetic resonance imaging (MRI) and ultrasound are other widely available, largely anatomic, imaging modalities that are utilized both with and without contrast in the diagnostic evaluation of various clinical conditions. The selection of optimal imaging modality and technique is complex and depends on characteristics of the imaging modality as well as the body part and suspected pathology.

Currently marketed FDA approved iodinated contrast agents for intravascular use are shown in Table 1. These drugs are indicated for various intra-arterial and intravenous uses, with several indications that are common across all drugs. Some are also indicated for other routes of administration, but these are not listed as they are not relevant to the current application. None are currently approved for general CT angiography or CT urography, although off-label use of iodinated contrast for these indications is widespread.

Table 1. Approved, Marketed Iodinated Contrast Agents with Intra-arterial and Intravenous Indications

Established Name	Proprietary Name	Intra-arterial Indications	Intravenous Indications
iothalamate meglumine	Conray	Adults and pediatric patients: cerebral arteriography, peripheral arteriography, DSA	Adults and pediatric patients: CT head and body, excretory urography, venography, DSA
iopamidol	Isovue	Adults: cerebral arteriography, coronary arteriography, ventriculography, peripheral arteriography, visceral arteriography, aortography Pediatric patients: radiographic evaluation of cardiac chambers and related arteries	Adults: CT head and body, excretory urography, venography Pediatric patients: CT head and body, excretory urography
iohexol	Omnipaque	Adults: cerebral arteriography, coronary arteriography, ventriculography, peripheral arteriography, visceral arteriography, aortography, DSA Pediatric patients: radiographic evaluation of cardiac chambers and related arteries, pulmonary angiography, aortography	Adults: CT head and body, excretory urography, venography, DSA Pediatric patients: CT head and body, excretory urography, venography
ioversol	Optiray	Adults: cerebral arteriography, coronary arteriography, ventriculography, peripheral arteriography, visceral arteriography, aortography, renal arteriography Pediatric patients: radiographic evaluation of cardiac chambers and related arteries	Adults: CT head and body, excretory urography, venography, DSA Pediatric patients: CT head and body, excretory urography, venography
iopromide	Ultravist	Adults: cerebral arteriography, coronary arteriography, ventriculography, peripheral arteriography, visceral arteriography, aortography Pediatric patients (≥2 years): radiographic evaluation of cardiac chambers and related arteries	Adults: CT head and body, excretory urography, contrast mammography as an adjunct following mammography and/or ultrasound Pediatric patients (≥2 years): CT head and body, excretory urography
iodixanol	Visipaque	Adults and pediatric patients ≥12 years: cerebral arteriography, coronary arteriography, ventriculography, peripheral arteriography, visceral arteriography, aortography, DSA Pediatric patients (<12 years): radiographic evaluation of cardiac chambers and related arteries, cerebral arteriography, visceral arteriography	Adults and pediatric patients ≥12 years: CT head and body, excretory urography, venography, coronary CT angiography Pediatric patients (<12 years): CT head and body, excretory urography

Source: U.S. prescribing information
Abbreviations: CT = computed tomography, DSA = digital subtraction angiography

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Iomervu is a new molecular entity that has not been approved in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

Iomervu was approved in the United Kingdom on December 11, 1992, and is currently authorized for use in 50 countries for various radiological diagnostic procedures including intra-arterial, intravenous, intrathecal, and intracavitary procedures.

(b) (4)

Development recommenced in 2019. Major events of the regulatory history are summarized in Table 2.

Table 2. Summary of Regulatory History for Iomervu

Date	Application	Description
(b) (4)		
7/24/2019	IND 144003	Type B pre-IND meeting
1/10/2020	IND 144003	Type B meeting
7/1/2020	IND 144003	Type C meeting
4/16/2021	IND 144003	Initial pediatric study plan submission
4/16/2021	IND 144003	Type C meeting
6/21/2021	IND 144003	Submission of statistical analysis plan for the re-read studies
11/5/2021	IND 144003	Agreement on pediatric study plan
11/23/2021	NDA 216017	Initial submission

12/10/2021	NDA 216016	Initial submission
1/21/2022	NDA 216017 NDA 216016	Refusal to file due to CMC issues (drug product and manufacturing)
11/30/2023	NDA 216017	Resubmission
12/14/2023	NDA 216016	Resubmission

Key regulatory interactions, beginning in 2019, for the current submission are discussed in further detail below.

- 7/16/2019 – Pre-IND Type B meeting
  - FDA requested the Applicant submit visualization rating scales used for each study and present efficacy data for each reader separately where possible.
  - Although the IOM-104 re-read studies were designed to demonstrate non-inferiority of Iomervu to an approved drug, FDA requested the Applicant also include point estimates with confidence intervals for the visualization endpoints for Iomervu.
  - FDA recommended the Applicant review the literature and submit published experience with Iomervu to support indications for pediatric body CT imaging, CT urography, (b) (4).
  - FDA recommended the submission of separate NDAs or subsequent efficacy supplements for each proposed route of administration (intravenous, intra-arterial, (b) (4)) unless the product(s) for use by all routes were quantitatively and qualitatively identical in composition.
  - FDA agreed with the Applicant's plans to cross-reference a "flagship" NDA for CMC information, provided that unique drug substance, product, microbiological, and manufacturing information for each route of administration is included.
- 1/10/2020 – Type B meeting
  - FDA indicated an alternative NDA submission plan could be considered with submission of a single NDA for a single concentration for all proposed routes of administration, followed by submission of one or more efficacy supplements for additional concentrations and indications.
- 7/1/2020 – Type C meeting
  - FDA confirmed that a "flagship" NDA approach beginning with intravenous indications and a single labeling approach would be reasonable.
- 9/2/2021 – FDA comments on the statistical analysis plan for the IOM-104 blinded re-read studies included:
  - For the primary analysis, success of at least 2 of 3 readers would be considered necessary for study success.
  - All images, including technically inadequate or poor quality images, should be included in the efficacy analyses.
  - Although the IOM-104 blinded read studies used non-inferiority study designs evaluating the efficacy of Iomervu against a comparator, FDA would focus review on the efficacy of Iomervu itself, even in the absence of related pre-specified endpoints.
- 1/21/2022 – Refuse-to-file determination

- A clear and complete description of the drug product was not provided, and incomplete batch data and stability data were provided.

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

4.1. Office of Scientific Investigations (OSI)

Inspections of the clinical sites and investigators for the major Applicant-sponsored studies in this application were not feasible due to the length of time since they were conducted. No specific data quality issues were identified during review, and inspections are not considered necessary to reach a decision on this application.

4.2. Product Quality

Iomeprol injection (b) (4) solutions are sterile aqueous solutions of iomeprol packaged in bottles for single dose administration. This product is a clear, colorless to pale yellow aqueous solution containing the active pharmaceutical ingredient, iomeprol, with tromethamine (b) (4) hydrochloric acid (pH), and Water for Injection. The lowest strength is provided in a single presentation of 100 mL fill in 100 mL bottles, while the other strengths are each packaged as 50 mL fill in 50 mL bottles, 100 mL fill in 100 mL bottles, 150 mL fill in 250 mL bottles, and 200 mL fill in 250 mL bottles. The product is sensitive to light and is stored in a secondary package carton to protect from light. The proposed product expiry of 24 months at 25°C protected from light is supported by stability data.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Iomervu (iomeprol) injection is a non-ionic, water-soluble iodinated contrast agent. Iomeprol produces image contrast due to differential absorption of x-rays to opacify structures with iomeprol distribution.

CNS safety pharmacology studies revealed transient (mainly at 1h, no longer at 4h) alterations (mainly slight cyanosis, decreases in spontaneous activity, respiratory rate, and body temperature, and increases in palpebral closure) mainly in the 8 grams of iodine per kg (gI/kg) iomeprol group. No statistically significant iomeprol-related changes were noted in cardiovascular and respiratory safety pharmacology studies when compared with the osmolality control mannitol or iodinated contrast control iohexol. Transient (mainly from 1 to 15 min with peak increase at 5 or 15 min) increases in blood pressure, heart rate, and QTc were noted in all groups including in the mannitol group. However, increases in blood pressure and heart rate were longer-lasting (1 to 240 min vs. 1 to 15 min) and of greater magnitudes in the 8 gI/kg iomeprol or iohexol group.

Distribution studies using ^{125}I-iomeprol revealed rapid tissue distribution, high kidney distribution (highest at 1h), and accumulation in thyroid (highest at 1h, detectable at 48h) in rats and detectable radioactivity in placenta, fetus, and fetal liver in pregnant rats. Radioactivity was detected in milk samples from rats (D10 post-natal), increasing over time (questionable at 15 min, peaked at 6h, and remained at high levels at 48h after single IV dose at 500 mgI/kg). Only unchanged iomeprol was detected in plasma, liver, kidneys, thyroid, urine, and feces in rats.

Four-week repeat dose (0, 1, 2, or 4 gI/kg/day) toxicity studies were conducted in rats and dogs. Target organs were kidneys and liver with reversible findings. Vacuolation of hepatocytes and convoluted tubules of the renal epithelium was observed in the 4 gI/kg group only in dogs while increased incidence of vacuolation in liver, kidneys, and bladder was observed in a dose- and treatment duration-related manner in rats. Dose-related increase in urea values in dogs and in urinary protein values in rats were noted. In addition, drug-related transient (mainly immediately after dosing) increases in incidence and frequency of vomiting and hypersalivation and dose-related increase in incidence and severity (slight to moderate) of inflammation in liver, cortex of kidneys, and lungs were noted in dogs. The clinical safety margins were low (0.38-, 0.75-, 1.51-fold in dogs, 0.11-, 0.23- or 0.45-fold in rats based on human equivalent dose (HED) using the maximal human dose as 86 gI per administration).

Iomeprol did not demonstrate mutagenic or clastogenic potential with in vitro bacterial reverse mutation assay or in vivo rat bone marrow micronucleus assay. Embryofetal developmental toxicity studies were performed with IV administration of iomeprol to rats at daily doses of 0.6, 1.5, or 4.0 gI/kg from gestation days (GD) 6 to 15 and to rabbits at daily doses of 0.3, 0.8, or 2.0

gI/kg from GD 6 to 18. No drug-related teratogenic effects were observed in the highest doses evaluated.

In summary, no significant drug-related toxicities are identified which could preclude the approval.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Iomervu (iomeprol injection) is a non-ionic water-soluble iodinated contrast agent. Iomeprol produces image contrast due to differential absorption of x-rays to opacify structures with iomeprol distribution.

5.3.1. Safety Pharmacology

5.3.2. Evaluation of the CNS

Study/Number: Behavioral effects of lomeron 400 after intravenous administration to mice: Irwin test/ CdS166

GLP Compliance: Yes
QA Statement: Yes

Study Objective:

The objective of the Irwin test was to examine potential effect of iomeprol on behavioral and physiological parameters covering central and peripheral nervous system function including: spontaneous activity, passivity, curiosity, reactivity, vocalization, irritability, pain response, Straub tail, tremors, twitches, convulsions, startle, ataxia, limb position, movement, righting reflex, body and abdominal tone, grip strength, pinna reflex, corneal reflex, toe-pinch responses, piloerection, heart rate, respiratory rate, cyanosis, flushing, blanching, pupil size, palpebral opening, salivation, and lacrimation. Testing was performed following IV administration of 2, 4, or 8 gI/kg iomeprol 400 (726 mOsmol/kg) or control (0.9% NaCl or D-mannitol solution as 732 mOsmol/kg) in CD-1 mice (n=6 males/group, small group size). Irwin test with a score of 0-8 was conducted during the first hour after dosing, hourly in the following four hours, and daily for the following 4 days after dosing.

Key Findings:

Transient alterations (mainly at 1h after dosing, no longer at 4h) were observed mainly in the 8 gI/kg iomeprol group. Only slight changes in one (1/6) mouse at 1h in either mannitol (increased reactivity +1) or 2 gI/kg iomeprol (decreased toe-pinch responses -1) groups were observed. Increased incidence of slight cyanosis (+1) was observed at 1h in a dose-related manner in the iomeprol groups (0/6, 0/6, 0/6, 5/6, or 6/6 in the 0.9% NaCl, mannitol, 2, 4, or 8 gI/kg groups, respectively). Additional alterations were observed in the 8 gI/kg iomeprol group including decreases in spontaneous activity (-1 or -2 in 2/6 mice), curiosity (-1 in 1/6 mice), abdominal tone (-1 in 1/6 mice), and respiratory rate (-1, in 3/6 mice) and increases in passivity (+1 in 1/6 mice) and palpebral closure (+1 or +2 in 5/6 mice). The alterations were transient (mainly at 1h after dosing with up to 3h in one mouse only). Decreased body temperature was also observed in the 8 gI/kg iomeprol group up to 2 h after dosing.

5.3.3. Evaluation of the Cardiovascular System

Study/Number: Effect of Iomeron 400 and Omnipaque 350 on HERG tail current recorded from stably transfected HEK293 cells/ DGMH1007

GLP Compliance: Yes
QA Statement: Yes

Study Objective:
The objective of the study was to evaluate the in vitro effects of iomeprol on the human Ether-à-go-go-Related Gene (hERG) potassium channel current (surrogate for IKr, rapidly activating delayed rectifier cardiac potassium current) at near physiological temperatures.

Key Findings:
- Iomeprol produced a concentration-related (1, 4, 10, or 40 mgI/mL) inhibition of hERG tail current with 37% inhibition at 40 mgI/mL.
- Inhibition was probably related to high osmolarity, as concentration-related inhibition of hERG tail current was observed in mannitol osmolarity controls and for iohexol.

No IC_{50} or Hill coefficient was determined, and the iomeprol IC_{50} is expected to be > 40 mgI/mL (the highest dose tested). The simulated Cmax (using dose as 0.868 gI/kg) was 8.6 mgI/L based on the PPK analysis. The safety margin will be large.

Study/Number: Cardiovascular effects of Iomeron after intravenous infusion in conscious dogs using telemetry / 6030

GLP Compliance: Yes
QA Statement: Yes

Study Objective:
This study evaluated the effects of mannitol (osmolality control, 732 mOsmol/kg), iomeprol at up to 8 gI/kg (726 mOsmol/kg), or iohexol (8 gI/kg, 890 mOsmol/kg; iohexol 350 mgI/mL) on

cardiovascular parameters including arterial blood pressure, heart rate, and electrocardiogram in conscious Beagle dog (n=4 males) using telemetry.

Study Design Issues:
Fridericia (QTcF), Bazett (QTcB), or QTc 100 methods were used for rate corrections. Latin square design (rather than the sequential design used in this study) and individual probabilistic (QTca) rate-corrections (Henry et al. 2014) are the recommended best practices, especially when the drugs affect heart rates, rather than generic rate-corrections used in this study; QTcF is considered adequate but not optimal and QTcB as unsatisfactory; QTc 100 was proposed as a more accurate method than QTcF or QTcB (Toshiyuki et al. 1998).

Key Findings:
Systolic and diastolic blood pressure (SBP and DBP) significantly increased in all groups mainly from 1 to 15 min (peak increase at 15 min) after the start of IV infusion compared with the baseline values. Blood pressure (BP) increases in the 8 gI/kg iomeprol group were longer-lasting compared to the mannitol group (1 to 240 min vs. 1 to 15 min, respectively) and of greater magnitude compared to the mannitol group (36% and 54% increase in SBP and DBP, respectively vs. 19% and 33% increase at 15 min, respectively). However, there were no statistically significant differences among the mannitol group and iomeprol groups. Furthermore, BP profiles in the 8 gI/kg iomeprol group were similar to those in the 8 gI/kg iohexol group.

Heart rate (HR) significantly increased in all groups mainly from 1 to 15 min (peak increase at 5 or 15 min) after the start of IV infusion compared with the baseline values. HR increases in the 8 gI/kg iomeprol group were longer-lasting compared to the mannitol group (1 to 240 min vs. 1 to 15 min, respectively) and of greater magnitude compared to the mannitol group (61% increase vs. 43% increase at 15 min, respectively). However, there were no statistically significant differences among the mannitol group and iomeprol groups.

Iomeprol induced transient (5 to 30 min after the start of IV infusion) increases in QTcF but not in a dose-related manner (19, 25, or 20 ms increases over baseline values in the 4, 6, or 8 gI/kg groups, respectively, at 5 min after the start of IV infusion). The effects were not statistically significantly different from those induced by mannitol (14 ms increase) and iohexol (20 ms increase). Using QTc 100, ≥ 10 ms increases were noted in the iomeprol 6 gI/kg group (12 and 10 ms increases at 5 and 15 min after the start of IV infusion) and the iohexol 8 gI/kg group (10 ms increase at 5 min after the start of IV infusion) only.

Conclusions:
A single IV injection of iomeprol at all dose levels induced modest changes in systolic and diastolic blood pressures. IV injection of mannitol (osmolality control) or iohexol induced similar, transient changes in systolic and diastolic blood pressures; the changes in blood pressure induced by iomeprol or iohexol were not significantly different from mannitol. Iomeprol, mannitol, and iohexol produced increases in heart rate during the infusion period,

but the effects were transient and not significant. Intravenous administration of iomeprol at up to 8 gI/kg did not have significant effects on blood pressure, heart rate, and ECG intervals in conscious male Beagle dogs.

5.3.4. Evaluation of the Respiratory System

Study/Number: Effects of Iomeron 400 on respiratory parameters in anaesthetized rats / DGMH1009

GLP Compliance: Yes
QA Statement: Yes

Study Objective:
The objective of the study was to examine the effects of a single IV infusion of mannitol (osmolality control, 732 mOsmol/kg) or iomeprol 400 (726 mOsmol/kg) at up to 6 gI/kg on respiratory function parameters (respiratory rate, tidal volume, minute volume) in anesthetized Sprague Dawley rats (n=5 males/group, small group size) at -15 and 0 min before dosing and at 1, 5, 10 ,15, 30, 45, and 60 min after dosing.

Key Findings:

- No statistically significant, consistent, dose-related effects on respiration rate, tidal volume, or minute volume were identified for iomeprol when compared to the mannitol group.
- Respiratory system parameters were more variable in 4 and 6 gI/kg iomeprol groups when compared with the mannitol group.

Conclusions:
A single intravenous infusion of iomeprol 400 at 2, 4, or 6 g I/kg to Sprague Dawley rats did not affect the respiratory system. Under the conditions of the study, the NOEL was determined to be 6 gI/kg.

5.4. ADME/PK

Table 3. ADME/PK Study Findings

Type of Study	Major Findings
Absorption	
N/A	No absorption studies were conducted because Iomeprol will be administered by the intravenous route.
Distribution	

Type of Study	Major Findings
125I-B16880 Disposition of the radioactivity in pregnant rats (RBM 880038)	In a maternal and fetal distribution study of Iomeprol in pregnant rats (18/group), uptake was evaluated following a single intravenous injection of ^{125}I Iomeprol at a dose of 1 gI/kg on the 7th, 13th, or 19th day of pregnancy. Radioactivity was found in the placenta, fetus, and fetal liver and there was no accumulation over time. The placenta/fetus ratio increased from 0.8:1 on PD13 to 7.5:1 on PD19.
Experiment and research of absorption, distribution, metabolism, and excretion of 125I-E 7337 in rats (EI-9054 S2)	• Rapid tissue distribution (radioactivity in tissues of male rats at 15 min after IV administration, levels decreased rapidly after 6h) • High kidney levels (highest at 1h) • Accumulation in thyroid (highest at 1h, detectable at 48h)
Metabolism	
Experiment and research of absorption, distribution, metabolism, and excretion of 125I-E 7337 in rats (EI-9054 S2)	Only unchanged iomeprol in plasma, liver, kidneys, thyroid, urine, and feces.
Excretion	
Experiment and research of absorption, distribution, metabolism, and excretion of 125I-E 7337 in rats (EI-9054 S2)	• Radioactivity in milk samples from rats (D10 post-natal), increased with time (4.48 mcgI/mL at 15 min, 83.00 mcgI/mL at 6h [the highest level], and 61.72 mcgI/mL at 48h after single IV dose at 500 mgI/kg) • High excretion rate in the urine at early time point • Approximately 9% excretion in the feces
TK data from general toxicology studies	
Toxicokinetic study of Iomeron after intravenous administration in rats (CdS173)	There were no significant differences in the TK parameters calculated for male and female rats for Iomeprol at up to 8 gI/kg. Iomeprol mean $t_{1/2}$ (terminal elimination phase) ranged from 1.1 to 17.6 hr and 1.1 to 13.2 hr for male and female rats, respectively, and increased with increasing dose. Systemic exposure by C_{max} increased with increasing dose in a non-linear manner. Maximal mean plasma concentrations were 22603, 37174, and 63007 mcg/mL in male rats and 19350, 38094, and 61588 mcg/mL in female rats 1 min after intravenous administration of 2, 4, and 8 gI/kg, respectively. Mean values for the volume of distribution at steady state, Vss, ranged from 316 to 699 mL/kg for male rats and 325 to 568 mL/kg for female rats; values exceeded the extracellular volume.

Type of Study	Major Findings
Toxicokinetic study of Iomeron after intravenous administration in dogs (CdS172)	There were no significant differences in the TK parameters calculated for male and female dogs for Iomeprol at up to 8 gI/kg. Iomeprol mean $t_{1/2}$ (terminal elimination phase) ranged from 3.6 to 8.7 hr and 5.55 to 8.8 hr for male and female dogs, respectively, and increased with increasing dose. Systemic exposure by C_{max} increased with increasing dose in a linear, dose-dependent manner. Maximal mean plasma concentrations were 14272, 26685, and 50064 mcg/mL in male dogs and 15865, 29167, and 54587 mcg/mL in female dogs 5 min after intravenous administration of 2, 4, and 8 gI/kg, respectively. $AUC_{0\text{-}inf}$ mean values were in the range of 16.4 and 65.7 mg/mL.h and 16.3 and 69.5 mg/mL.h for male and female dogs, respectively. Mean values for the volume of distribution at steady state, Vss, ranged from 317 to 370 mL/kg for male dogs and 317 to 337 mL/kg for female dogs; values were in the range of the extracellular volume for dogs.
TK data from reproductive toxicology studies	
Not conducted.	

Source: Reviewer's table
Abbreviations: ADME, absorption, distribution, metabolism, excretion; AUC, area under the curve; Cmax, maximum observed plasma concentration; PK, pharmacokinetics; t1/2, half-life; TK, toxicokinetics; Vss, volume of distribution at steady state

5.5. Toxicology

5.5.1. General Toxicology

Toxicological evaluation of iomeprol was conducted in mice, rats, dogs, and monkeys with the majority of toxicity studies conducted in rats and dogs, which were selected as the rodent and non-rodent species, respectively. A clinically relevant route of exposure (intravenous) was used for all in vivo toxicological studies, which included single-dose and repeat-dose toxicology, genotoxicity studies, developmental and reproductive toxicology studies (fertility and early embryonic development, embryofetal development, and pre/postnatal development), as well as local tolerance studies in rats and rabbits (subcutaneous, intravenous, intra-arterial, perivenous, and intramuscular) and other toxicity studies to evaluate hypersensitivity reactions. The Applicant conducted studies evaluating other routes of administration, including intracarotid, intraperitoneal, and intrathecal. Many of the studies were not considered to be adequate as they were conducted prior to current guidelines for the design and conduct of toxicity studies to support safety.

5.5.2. Repeat-Dose Toxicity Studies

Study/Number: Four-week repeated dose toxicity study by intravenous route (dogs) / Study#: 1954 (The study report submitted was the translation from Italian to English of the original final report dated August 20, 1984, of Study No. 1954.)

Key Findings:

- Dose-related, reversible increase in urea values
- Non-lipidic cytoplasmic, slight to marked vacuolation of hepatocytes (5/6, 83.3%) and of convoluted tubules of the renal epithelium (4/6, 66.7%) in the 4 gI/kg group only, reversible
- Dose-related increase in incidence and severity (slight to moderate) of inflammation in liver, cortex of kidneys, and lungs

The clinical safety margins were low (0.38-, 0.75-, 1.51-fold based on HED using the maximal human dose as 86 gI per administration).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 4. Methods for Study No. 1954

Methods	Details
Dose and frequency of dosing:	0 (negative control), 1 (LD), 2 (MD), and 4 (HD) gI/kg (0, 2.044, 4.088, or 8.176 g/kg iomeprol (B16880)), daily for 4 weeks
Dose multiples of clinical dose:	0.38x (LD), 0.75x (MD), 1.51x (HD) based on HED (g/m^2) using the maximal human dose as 86 gI per administration
Route of administration:	Intravenous
Formulation/Vehicle:	Iomeprol (B16880), batch # RG6/84 and RG7/84 / Sterile non-pyrogenic physiologic solution
Species/Strain:	Dog/beagle
Number/Sex/Group:	3/sex/group (main study) and 2/sex/group (vehicle and HD for recovery only)
Age:	7-9 months at dosing
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	Unknown, no protocol provided

Source: Reviewer's table
Abbreviations: HD, high dose, LD, low dose; MD, mid dose

Table 5. Observations and Results: Changes from Control (Study No. 1954)

Parameters	Major findings
Mortality	There were no deaths. All animals survived to scheduled necropsies.

Parameters	Major findings
Clinical Signs	• Test article-related transient (mainly immediately after dosing) increase in incidence and frequency of vomiting (0%, 33% [1 episode], 50% [1, 2, or 4 episodes], or 30% [2 or 3 episodes] in the 0, LD, MD, or HD groups, respectively) • Test article-related transient increase in incidence of hypersalivation (0%, 17%, 17%, or 40% in the 0, LD, MD, or HD groups, respectively, single episode immediately after dosing)
Body Weights	No significant drug-related changes
Ophthalmoscopy	No significant drug-related findings
ECG	Not conducted
Hematology	No significant drug-related changes
Clinical Chemistry	Test article-related, reversible increase in urea values (Wk 4: urea mean: 24.59, 29.65, 35.40*, or 45.72* mg/100 mL in the 0, LD, MD, or HD groups, respectively, * $p<0.05$; high values in 2/5 females in the MD group and 4/5 females in the HD groups; Wk 6: urea mean: 27.63 or 33.2 mg/100 mL in the 0 or HD groups, respectively)
Urinalysis	Test article-related increase (but $p>0.05$) of diuresis (mean urine volume Wk 4: 83.80, 97.33, 118.67, or 134.00 mL in the 0, LD, MD, or HD groups, respectively).
Gross Pathology	No significant drug-related findings
Organ Weights	Test article-related, slight increase in mean absolute and relative liver and adrenal weights in the HD group at the terminal sacrifice (absolute liver weights 239.59 vs. 307.11 g in the 0 or HD group, respectively, absolute adrenal weights 975.33 vs. 1222.67* g in the 0 or HD group, respectively, * $p<0.05$)

Parameters	Major findings
Histopathology Adequate battery: No. Only for adrenals, cerebrum, cerebellum, epididymides, heart, injection site, intestine (duodenum, colon), kidneys, liver, lung, pituitary, spleen, stomach, testes or ovaries, thymus, thyroids, urinary bladder, uterus, gallbladder.	At Wk 4 sacrifice: Adrenals: Slight hypertrophy of the zona fasciculata (glomerular) of the adrenals in the HD group only (4/6, 66.7%) Liver: • Non-lipidic large droplet cytoplasmic, slight to marked vacuolation of hepatocytes in the HD group only (83.3%, 2 slight, 2 moderate, 1 marked • Dose-related increase in incidence of scattered microgranulomata (mainly slight) (50.0%, 66.7%, 83.3%, or 100% in the 0, LD, MD, or HD groups, respectively) • Test article-related increase in incidence of slight (mainly) to moderate (one each in the 2 or 4 gI/kg group) portal inflammatory infiltration (16.7%, 66.7%, 83.3%, or 83.3% in the 0, LD, MD, or HD group, respectively) Renal system: • Non-lipid large droplet cytoplasmic, slight to moderate vacuolation of convoluted tubules of the renal epithelium in the HD group only (66.7%, 3 slight, 1 moderate) • Test article-related increase in incidence and severity of subacute inflammation in cortex of kidneys (incidence: 33.3%, 50%, 50%, or 66.7%; severity: 1, 1, 1.3, or 1.8 in 0, LD, MD, or HD group, respectively, moderate in 50% dogs in the HD group) • Test article-related increase in incidence of slight basophilia in cortex of kidneys (incidence: 0%, 16.7%, 50%, or 50% in 0, LD, MD, or HD group, respectively) • Increased incidence of slight hemorrhages of the bladder mucosa and/or submucosa mainly in the HD group (16.7%, 33.3%, 16.7%, 66.7% in the 0, LD, MD, or HD group, respectively) Lungs: • Test article-related increase in incidence of slight to moderate subacute inflammation in lungs (16.7%, 33.3%, 50.0%, or 83.3%; mean severity: 1.0, 2.0 [2 moderate], 1.0, or 1.4 [3 slight, 2 moderate] in the 0, LD, MD, or HD group, respectively) • Slight to moderate acute inflammation in the LD or MD groups only (16.7% [1 moderate] or 33.3% [1 slight, 1 moderate] in the LD or MD groups, respectively) • Slight emphysema in the drug groups only [0%, 33.3%, 16.7% or 16.7% in the 0, LD, MD, or HD group, respectively) At recovery sacrifice: No significant drug-related findings

Source: Reviewer's table
Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Study/Number: Iomeprol toxicity study in rats by intravenous administration for up to 4 weeks with a 4-week recovery / Study#: BRO 51/931007

Key Findings:

- Dose- and treatment duration-related increase in urinary protein (at Wk 1, in females in the 4 gI/kg Old Synthesis (IOS) group only, at Wk 4, dose-related increase), reversible
- Increased incidence of vacuolation in the liver, kidneys, and bladder in a dose- and treatment duration-related manner.

The study report described 1 gI/kg New Synthesis (INS) as the NOAEL. The clinical safety margins were low (0.11-fold based on HED using the maximal human dose of 86 gI per administration).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 6. Methods for Study No. BRO 51/931007

Methods	Details
Dose and frequency of dosing:	0 (negative control), 1 (LD), 2 (MD), and 4 (HD) gI/kg, IOS and INS; daily for 1 week or 4 weeks
Dose multiples of clinical dose:	0.11x (LD), 0.23x (MD), 0.45x (HD) based on HED (g/m^2) using the maximal human dose of 86 gI per administration.
Route of administration:	Intravenous
Formulation/Vehicle:	Iomeprol (B16880), batch # RG4/92 and RG5/92 / 0.9% NaCl
Species/Strain:	Rat/Crl:CD(SD)BR
Number/Sex/Group:	5/sex/group for 1 week dosing, 10/sex/group for 4-week dosing, 5/sex/group for recovery
Age:	7 weeks at dosing
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	Unknown, no protocol provided

Source: Reviewer's table
Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Table 7. Observations and Results: Changes from Control (Study No. BRO 51/931007)

Parameters	Major findings
Mortality	There were no deaths. All animals survived to scheduled necropsies.

Parameters	Major findings
Clinical Signs	No significant test article-related findings
Body Weights	No significant test article-related changes
Ophthalmoscopy	No significant test article-related findings
Hematology	No significant test article-related changes
Clinical Chemistry	No consistent irreversible dose-related findings
Urinalysis	• Dose- and treatment duration-related increase in urinary protein: at Wk 1, significant increase in urinary protein in females in the HD IOS group only (58, 64, 66, or 77* mg/dL for females in the 0, 1, 2, or 4 gI/kg IOS groups, respectively); at Week 4, dose-related increase in urinary protein (136, 219, 197, or 314 mg/dL for males and 59, 64, 76*, or 80** mg/dL for females in the 0, LD, MD, or HD INS group, respectively, 136, 224, 336*, or 419** mg/dL for males and 59, 79*, 82*, or 74* mg/dL for females in the 0, LD, MD, or HD IOS group, respectively; * p<0.05, ** p<0.01) • Dose-related decrease in Na and Cl values and urinary volume and dose-related increase in urinary specific gravity mainly in males at Wk 4 in the INS and IOS group. Reversible
Gross Pathology	No significant test article-related findings
Organ Weights	No consistent test article-related alterations

Parameters	Major findings
Histopathology Adequate battery: Yes, except aorta, larynx and pharynx, sciatic nerve, and skeletal muscle; only kidneys, liver, lungs, thymus, and urinary bladder for the 1-wk treatment groups	• Test article-related alterations in the liver, kidneys, and urinary bladder, mainly increased incidence of vacuolation (mainly minimal) in a dose- and treatment duration-related manner (periportal vacuolation in liver, cortical tubular epithelial vacuolation in kidneys, and epithelial vacuolation in urinary bladder); higher incidence and slower recovery in MD and HD INS groups: incidence of vacuolation in kidneys: 15/20 or 8/20 in MD INS or IOS groups, respectively, at 4-week sacrifice; 6/10 or 1/10 in HD INS or IOS groups, respectively, at 4-week recovery sacrifice (20/20 in both HD INS and IOS groups at 4-week sacrifice); vacuolation in LD IOS group but not in LD INS group • Increased incidence of minimal centrilobular enlargement in the drug groups in a dose-, treatment duration-, and synthesis process-related manner: increased incidence in the HD groups only at 1-week sacrifice (3/10 or 1/10 in the INS or IOS group, respectively) but in both MD and HD groups at 4-week sacrifice (2/20 in MD or HD INS group, 1/20 or 16/20 in MD or HD IOS group, respectively); much higher incidence in the HD IOS group (16/20 vs. 2/20 in the HD INS group); minimal centrilobular hepatocyte enlargement in 2/10 in MD INS group only at 4-week recovery sacrifice

Source: Reviewer's table
Abbreviations: HD, high dose; LD, low dose; MD, mid dose

5.5.3. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)
Study/Number: Reverse mutation study of iomeprol in bacteria/Study #: 917105

Key Findings:

- The results of the bacterial mutagenicity assay indicated that under the experimental conditions of the study, iomeprol did not cause a positive mutagenic response with any of the tester strains in either the absence or presence of S9 metabolic activation.
- Iomeprol was negative (non-mutagenic) in the bacterial reverse mutation assay.

GLP Compliance: No signed statement. The study report stated, "The study was conducted in compliance with "The Good Laboratory Practice Standards for Safety Studies on Drugs",

Pharmaceutical Affairs Bureau Notification No. 313, March 31, 1982, and its amendment and "Guidelines for Toxicity Studies Required for Application for Approval to Manufacture (Import) Drugs", Pharmaceutical Affairs Bureau Notification No. 24, September 1989, Japan Ministry of Health and Welfare. However, concentrations of the drug preparations were not determined."
QA Statement: Yes

Test system: *Salmonella typhimurium* histidine auxotrophs TA98, TA100, TA1535, TA1537, and E. coli WP2uvrA in the absence and presence of phenobarbital/5,6 benzoflavone induced rat liver.

Study is valid: Yes. No historical control data were provided in the study report. However, the negative control counts were low and within published historical control ranges. The positive controls induced a greater than 3-fold increase in mean revertant colony numbers over that of the vehicle control.

In Vitro Assays in Mammalian Cells
Study/Number: Chromosome aberration study of E7337 with Chinese hamster cells in culture/ Study #: 907407

Key Findings:

- Iomeprol did not cause any increase in the incidence of aberrant cells or polyploid cells in the absence or presence of S9 metabolic activation when compared to vehicle control.
- Iomeprol was negative for genotoxic potential by the chromosome aberration study.

GLP compliance: Yes

Test system: CHL/IU cells derived from Chinese hamster lung cells; testing conducted in the absence and presence of phenobarbital/5, 6 benzoflavone induced rat liver.

Study is valid: No. Only 200 metaphase cells per concentration were scored instead of at least 300 cells as recommended by OECD guideline 437. No historical control data were provided. The results had many zero values (greater than the expected 5% according to OECD guideline 437).

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Study/Number: Iomeron rat micronucleus test /Study #: KFF 010/024208

Key Findings:

- Iomeprol at doses up to and including 8 gI/kg did not show any genotoxic activity in this in vivo test for induction of chromosome damage (ratio of polychromatic erythrocytes to normochromatic erythrocytes and mean frequency of micronucleated polychromatic erythrocytes).

- Based on the findings, iomeprol was negative for genotoxic potential in the assay.

GLP compliance: Yes

Test system: Sprague Dawley CD rats (males only); rat bone marrow

Study is valid: The study is considered valid except 2000 polychromatic erythrocytes per animal were analyzed for the frequency of micronuclei, which was based on OECD guideline 474 Mammalian Erythrocyte Micronucleus Test published in 1997. Based on revised OECD guideline 474 in 2016, 4000 polychromatic erythrocytes are the recommended number.

Other Genetic Toxicity Studies
None.

5.5.4. Carcinogenicity

Carcinogenicity studies of iomeprol were not conducted and are not recommended for a single or infrequent use radiographic contrast agent.

5.5.5. Reproductive and Developmental Toxicology

Reproductive and developmental toxicology studies were conducted to evaluate the potential for iomeprol effects on fertility, reproduction, teratogenicity, and any effects on perinatal/postnatal development. However, many of the conducted studies were not considered to be adequately designed and/or conducted because they were performed prior to acceptance of current FDA and ICH guidelines.

Fertility and Early Embryonic Development
There was no adequately designed and conducted study to evaluate effects of iomeprol administration during fertility and early embryonic development (Segment I study was conducted prior to acceptance of current ICH guidelines). The Applicant was not recommended to conduct a new study to support a single or infrequent use radiographic contrast agent.

Embryo-Fetal Development
The Italian final reports were translated into English under the supervision of a qualified bilingual interpreter at Bracco in Milan according to the study report.

Study/Number: Topic BRF2. Teratogenesis study with iomeprol (BI6880) in the rat administered by intravenous route / Study #: RF479UK1

Key Findings:
- All females survived to scheduled necropsy.
- No significant test article-related malformation.

- An increase in the incidence of minor skeletal anomalies (mainly incomplete ossification and/or bipartite centrum) in all drug groups but not in a dose-related manner.

Conducting laboratory and location:	Bracco S.p.A - Via E. Folli, 50 -20134 Milan, Italy
GLP compliance:	Yes, in accordance with Buone Pratiche di Laboratorio (Italian GLP, DM 26-6-86; Suppl. G.U. No.198, 27-8-1986)

Table 8. Methods for Study No. RF479UK1

Methods	Details
Dose and frequency of dosing:	0 (vehicle), 600 (LD), 1500 (MD), or 4000 (HD) mgI/kg, daily from GD 6 through GD 15
Dose multiples of clinical dose:	0.07x (LD), 0.17x (MD), 0.45x (HD) based on HED (g/m^2) using the maximal human dose as 86 gI per administration
Route of administration:	Intravenous
Formulation/Vehicle:	Iomeprol (B16880), 400 mgI/mL solution, batch # RG3/87 / 0.9% NaCl
Species/Strain:	Rat/Crl:CD (SD)
Number/Sex/Group:	22, 23, 19, or 20 pregnant females in the 0, LD, MD, or HD groups, respectively
Satellite groups:	None
Study design:	100 virgin females were paired with untreated males (10 females for every 3 to 4 males). The females with a vaginal smear containing spermatozoa were considered as Day 0 of gestation.
Deviation from study protocol affecting interpretation of results:	No study protocol was provided. Dosing GD 6-15 instead of GD 6-17 according to ICH S5(R3).

Source: Reviewer's table
Abbreviations: GD, gestational day; HD, high dose; HED, human effective dose; LD, low dose; MD, mid dose

Table 9. Observations and Results: Changes from Control (Study No. RF479UK1)

Parameters	Major findings
Mortality	No unscheduled deaths
Clinical Signs	No significant test article-related findings
Body Weights	No significant test article-related changes

Parameters	Major findings
Necropsy findings Cesarean Section Data	LD: No significant test article-related changes. There was significantly higher pre-implantation loss in the LD group only (20.8%, 30.4% ($p<0.05$), 17.5%, or 17.3% in the 0, 600, 1500, or 4000 mgI/kg groups, respectively). The increase was considered occasional as the pre-implantation loss in the MD and HD groups was comparable to the control group. No historical control data were provided. MD: No significant test article-related changes. HD: No significant test article-related changes.
Necropsy findings Offspring	Increase in the incidence of minor skeletal anomalies (mainly incomplete ossification and/or bipartite centrum) was observed in all drug groups but not in a dose-related manner [fetuses: 2.0%, 9.5% ($p<0.05$), 5.2%, or 5.8%, litters: 14%, 33% ($p<0.05$), 37%, or 30% in the 0, LD, MD, or HD group, respectively]. LD: No major test article-related changes. An increase in minor visceral anomalies (2.2% fetuses, 7% litters, two with hemorrhage in cerebral ventricle, one with left subclavian artery reduced diameter) was observed in the LD group only. The increase was considered to be incidental as no minor visceral anomalies were observed in the MD and HD groups according to the study report. MD: Major visceral malformations in 1.5% of fetuses (one with bilateral hydronephrosis and one with hydrocephalus in two separate litters) vs. 0.7% in the control group (one with bilateral hydronephrosis); hydrocephalus was considered to be occasional as the finding was not dose-dependent and close to the spontaneous percentage of 0.2%. HD: Major visceral malformations in 0.7% of fetuses (one with reduced caliber of aortic arch, left carotid and subclavian arteries, and truncus brachiocephalicus, hypoplasia of the cardiac ventricles) vs. 0.7% in the control group (one with bilateral hydronephrosis). The findings were considered incidental given lack of dose-relationship and only a single fetus was affected.

Source: Reviewer's table

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

Study/Number: Topic BRF19. Teratogenesis study with iomeprol administered by intravenous route in the rabbits/ Study #: RF1430-2

Key Findings:

- All females administered iomeprol at ≤ 800 mgI/kg survived to the scheduled necropsy. One death was observed in a female at 2000 mgI/kg (HD) on GD 27.
- No major visceral or skeletal malformations.
- An increase in the incidence of minor skeletal anomalies, reduced ossification, in the 2000 mgI/kg group.

Conducting laboratory and location:	Bracco S.p.A - Via E. Folli, 50 -20134 Milan, Italy
GLP compliance:	Yes, in accordance with Buone Pratiche di Laboratorio (Italian GLP, DM 26-6-86; Suppl. G.U. No.198, 27-8-1986)

Table 10. Methods for Study No. RF1430-2

Methods	Details
Dose and frequency of dosing:	0 (vehicle), 300 (LD), 800 (MD), or 2000 (HD) mgI/kg; GD 6 through GD 18
Dose multiples of clinical dose:	0.07x (LD), 0.18x (MD), 0.45x (HD) based on HED (g/m2) using the maximal human dose as 86 gI per administration
Route of administration:	Intravenous
Formulation/Vehicle:	Iomeprol (B16880), 400 mgI/mL solution, batch # RG9/87 / 0.9% NaCl
Species/Strain:	Rabbit/ Hy/Cr albino
Number/Sex/Group:	Pregnant females: 15, 14, 12, or 12 in the 0, LD, MD, or HD group, respectively
Satellite groups:	None
Study design:	60 females were mated with untreated male rabbits and then subjected to vaginal smears for detection of spermatozoa.
Deviation from study protocol affecting interpretation of results:	No protocol provided Dosing GD 6-18 instead of GD 6-19 according to ICH S5(R3) Small group size n=12-15, minimum number of pregnant females should be 16 according to ICH S5(R3)

Source: Reviewer's table
Abbreviations: GD, gestational day; HD, high dose; LD, low dose; MD, mid dose

Table 11. Observations and Results: Changes from Control (Study No. RF1430-2)

Parameters	Major findings
Mortality	One pregnant female in the HD group found dead on GD27; only adverse finding was weight loss after discontinuation of dosing (4.45 kg on Day 26 vs. 4.59 kg on Day 18). Because there were no macroscopic changes on autopsy or adverse symptoms during the dosing period, the death was not considered drug-related, and the data were excluded from calculations according to the study report. All fetuses showed generalized edema or autolysis indicating that fetal death occurred before the death of the dam. Two pregnant females were sacrificed (one in the control group on Day 7 and one in the MD group on Day 8) after incidental dislocation of spine.
Clinical Signs	No significant drug-related findings; spontaneous delivery on GD 28 in one dam in the control group
Body Weights	No significant drug-related changes except the one found dead aforementioned
Necropsy findings Cesarean Section Data	LD: No significant drug-related changes MD: No significant drug-related changes HD: Lower mean weights of fetuses (45.9, 45.6, 45.1, or 41.7 g in the 0, LD, MD, or HD group, respectively, but p>0.05)
Necropsy findings Offspring	LD: No significant drug-related changes MD: No significant drug-related changes HD: An increase in incidence of minor skeletal anomalies, mainly reduced ossification (minor skeletal anomalies, fetuses: 8.0%, 4.3%, 5.1%, or 15.1%; litters: 46%, 14%, 36%, or 73% in the 0, LD, MD, or HD group, respectively, but p>0.05).

Source: Reviewer's table
Abbreviations: GD, gestational day; HD, high dose; LD, low dose; MD, mid dose

Prenatal and Postnatal Development

There were no adequately designed and conducted studies to evaluate effects of iomeprol administration during pre- and post-natal development (Segment III study was conducted prior to acceptance of current ICH guidelines). The Applicant was not recommended to conduct a new pre- and post-natal development study to support a single or infrequent use radiographic contrast agent.

6 Clinical Pharmacology

6.1. Executive Summary

Iomervu is an injectable solution of iomeprol for use as a contrast agent in radiological examinations. The active moiety is iomeprol, a nonionic, water-soluble compound containing three iodine (I) atoms responsible for the contrast effect in radiographic procedures. Iomeprol is proposed to be indicated for:

Intra-arterial (IA) Procedures

- Cerebral arteriography in adult and pediatric patients
- Visceral and peripheral arteriography and aortography, including digital subtraction angiography in adult and pediatric patients.
- Coronary arteriography and cardiac ventriculography in adult patients
- Radiographic evaluation of cardiac chambers and related arteries in pediatric patients

Intravenous (IV) Procedures

- Computed tomography (CT) of the head and body in adult and pediatric patients
- CT angiography of intracranial, visceral, and lower extremity arteries in adult and pediatric patients
- Coronary CT angiography in adult and pediatric patients
- CT urography in adult and pediatric patients

The proposed pediatric indications are for patients from 0 to 17 years of age. The proposed Iomervu dosing regimens, including single injection dose and maximum total dose, as determined during this NDA review are listed in Table 12 to Table 15**.** Iomervu is formulated as an injection for IA or IV procedures at the strength of 250 mg Iodine (mgI)/mL, 300 mgI/mL, 350 mgI/mL, and 400 mgI/mL in single-dose vials or bottles.

The clinical pharmacology review questions focused on the dosing regimen recommendations for adult and pediatric patients and dosing regimen and labeling recommendations for patients with reduced renal function (patients with renal impairment) and patients 65 years or older, as iomeprol is mainly excreted unchanged in the urine.

The proposed dosing regimens for adult patients were selected based on the dosing regimens used in the safety and effectiveness in clinical studies. The safety of the proposed dosing regimens in pediatrics was supported by clinical studies conducted at the proposed dosing regimens in pediatric patients. The adverse events associated with iomeprol were generally mild or moderate. Adverse reactions reported in pediatric patients were similar to those in adult patients. The effectiveness of Iomervu in adult patients was supported by visualization score data from blinded re-reads of images obtained in prospective, randomized, double-blind, parallel group clinical studies for the following indications:

IA Procedures

- Cerebral arteriography: Study IOM-104C
- Visceral and peripheral arteriography and aortography: Study IOM-104D
- Coronary arteriography and cardiac ventriculography: Study IOM-104A

IV Procedures

- CT of the head and body: Study IOM-104E

In these studies, the patients were randomized (1:1) to an Iomervu arm or a control arm using approved iodinated contrast agents (iopamidol or ioversol). The proposed dosing regimens of Iomervu were based on the dosing regimens in these studies. The efficacy of other adult indications (CT angiography of intracranial, visceral, and lower extremity arteries; coronary CT angiography; CT urography) were supported by clinical studies from the literature. See additional details on dosing regimens in Table 16 and additional details on efficacy and safety in Section 8.

The effectiveness of Iomervu in pediatric patients was extrapolated from adult patients based on pharmacokinetic (PK) similarity between adults and pediatric patients. No clinically significant differences in the PK of iomeprol were observed in patients aged 3 years to 17 years compared to adult patients. In population pharmacokinetic simulations, no clinically significant differences in Cmax and concentration of iomeprol were found within 5 minutes after Iomervu administration (typical times when imaging would be performed) between pediatric patients younger than 3 years and adults.

The Applicant originally proposed a maximum total dose of (b) (4) mL/kg for IA procedures for patients aged (b) (4) to 17 years. The proposed (b) (4) mL/kg maximum total dose leads to more than 2-fold higher maximum total dose in certain pediatric patients (e.g., a pediatric patient with a body weight of 61 kg) compared to adult patients. During this review cycle, the FDA recommended that the Applicant reduce the maximum total dose to 5 mL/kg and cap the maximum total doses in pediatric patients at the corresponding maximum total doses in adult patients. The Applicant accepted the recommendation with the updated maximum total dose (Table 13). The proposed dosing regimens in adult and pediatric patients are acceptable after the changes in maximum total dose.

The intrinsic and extrinsic factors have been adequately evaluated to support labeling recommendations for patients with renal impairment or patients 65 years or older. As iomeprol is mainly excreted unchanged in urine, the area under the concentration-time curve (AUC) of iomeprol increases in patients with renal impairment. The risk for acute kidney injury in patients with preexisting renal impairment may increase with iomeprol. However, acute kidney injury was rare (0.0002%) in post-marketing surveillance data of patients exposed to iomeprol. The prescribing information states that preexisting renal impairment increases the risk for acute kidney injury and recommends use of the lowest necessary dose of Iomervu in patients with renal impairment. No dose modification is recommended for patients with renal impairment. Further, no overall differences in safety and effectiveness in patients 65 years or

older were found in clinical studies of Iomervu. No dose modification is recommended for patients 65 years or older.

Table 12. Recommended Concentrations and Volumes of Iomervu to Administer Per Single Injection and Maximum Total Dose into Selected Arteries for IA Procedures in Adult Patients

Imaging Procedure	Concentration (mg Iodine/mL)	Volume (mL)	Maximum Total Dose (mL)
Cerebral arteriography	300	• Carotid, subclavian, and vertebral arteries: 6 mL to 12 mL • Aortic arch: 30 mL to 50 mL	200 mL
Visceral and peripheral arteriography; aortography	300	• Aortography: 30 mL to 70 mL • Renal arteries: 10 mL to 12 mL • Other major branches of aorta: 20 mL to 60 mL	200 mL
Intra-arterial digital subtraction angiography	300	• Carotid, subclavian, and vertebral arteries: 4 mL to 12 mL • Aortic arch: 20 mL to 25 mL • Aortography: 15 mL to 40 mL • Renal arteries: 6 mL to 16 mL • Other major branches of aorta: 10 mL to 40 mL • Ilio-femoral runoff: 8 mL to 40 mL	200 mL
Coronary arteriography and cardiac ventriculography	300	• Coronary arteries: 3 mL to 7 mL • Cardiac ventriculography: 30 mL to 45 mL	286 mL
	350		245 mL
	400		215 mL

Table 13. Recommended Concentrations and Volumes of Iomervu to Administer Per Single Injection and Maximum Total Dose into Selected Arteries for IA Procedures in Pediatric Patients

Imaging Procedure	Concentration (mg Iodine/mL)	Volume (mL/kg body weight)	Maximum Total Dose (mL/kg)
Cerebral arteriography	300	0.5 mL/kg to 2 mL/kg	• 5 mL/kg • Do not exceed adult maximum dose
Visceral and peripheral arteriography; aortography	300	0.5 mL/kg to 2 mL/kg	
Intra-arterial digital subtraction angiography	300	0.3 mL/kg to 1 mL/kg	
Radiographic evaluation of cardiac chambers and related arteries	300, 350, or 400	0.5 mL/kg to 2 mL/kg	

Table 14. Recommended Concentrations, Volumes, and Injection Rates of Iomervu for IV Procedures in Adult Patients

Imaging Procedure	Concentration (mg Iodine/mL)	Volume (mL)	Injection Rate[3] (mL/s)
CT of Head and Body	250 or 300	100 mL to 190 mL	2 mL/s to 4 mL/s
	350 or 400	75 mL to 150 mL	
CT Angiography[1]	300, 350, or 400	80 mL to 130 mL	4 mL/s to 6 mL/s
Coronary CT Angiography[1]	400	50 mL to 90 mL	4 mL/s to 6 mL/s
CT Urography[2]	350	90 mL to 120 mL	2.5 mL/s

[1] The Iomervu volume may be immediately followed by a 40 mL to 50 mL 0.9% sodium chloride injection flush at the same flow rate as the contrast volume.
[2] The Iomervu volume may be administered either as a single bolus, or for dual-phase protocols as divided doses.
[3] The injection rate of Iomervu should be determined according to the clinical indication and the location, size, and type of the intravenous access.

Table 15. Recommended Concentrations, Volumes Per Body Weight, and Injection Rates of Iomervu for IV Procedures in Pediatric Patients

Imaging Procedure	Concentration (mg Iodine/mL)	Volume (mL/kg body weight)	Injection Rate (mL/s)*
CT of Head and Body	250 or 300	1.5 mL/kg to 2.5 mL/kg	1 mL/s to 2 mL/s
	350 or 400	1 mL/kg to 2 mL/kg	
CT Angiography	300, 350, or 400	1 mL/kg to 2 mL/kg	2 mL/s to 3 mL/s
Coronary CT Angiography	300 or 400	1 mL/kg to 2 mL/kg	2 mL/s to 3 mL/s
CT Urography	300	1 mL/kg to 2 mL/kg	1 mL/s to 2 mL/s

* The injection rate of Iomervu should be determined according to the clinical indication and the location, size, and type of the intravenous access. In neonates and patients <15 kg in whom a 24-gauge angiocatheter is the only option, an injection rate of 1 mL/s is recommended.

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information and data submitted in NDA 216016 and NDA 216017 and recommends approval. The key review issues with specific recommendations and comments are summarized in Table 16.

Table 16. Summary of Key Review Issues and Recommendations for NDA 216016 and NDA 216017

Review Issue	Recommendations and Comments

Pivotal or supportive evidence of effectiveness

Iomervu dosages in pivotal or supportive studies are discussed in this section. See efficacy assessment and more details regarding these studies in Section 8.

IA Procedures

- Cerebral arteriography: Study IOM-104C (48,848-004A, 48,848-004B)
  Study Design: Blinded re-read of prospective, randomized, double-blind, parallel group clinical studies 48,848-004A, 48,848-004B. In 48,848-004A, patients were randomized to receive Iomervu 300 mgI/mL (N=30) or ioversol 320 mgI/mL (N=28). In 48,848-004B, patients were randomized to receive Iomervu 300 mgI/mL (N=31) or ioversol 320 mgI/mL (N=31).
  Total Dose:
  Iomervu 300 mgI/mL: 16-198 mL
  ioversol 320 mgI/mL: 29 -145 mL
  Recommended maximum Iomervu iodine dose: 60 g iodine (200 mL Iomervu 300 mgI/mL).

Table 17. Recommended Per Injection Dosage for Cerebral Angiography in Studies 48,848-004A and 48,848-004B

Volume per injection:	**Injection Rate**
Aortic Arch– 50 mL	20-25 mL/s
Common or Internal Carotid Artery – 8-10 mL	6-9 mL/s
External Carotid – 6-7 mL	5-8 mL/s
Vertebral Artery – 6-12 mL	4-7 mL/s
Subclavian Artery – 12-14 mL	6-9 mL/s

- Visceral and peripheral arteriography and aortography: Study IOM-104D (48,848-005A, 48,848-005B)
  Study Design: Blinded re-read of prospective, randomized, double-blind, parallel group clinical studies 48,848-005A, 48,848-005B. In 48,848-005A, patients were randomized to receive Iomervu 300 mgI/mL (N=29) or iopamidol 300 mgI/mL (N=30). In 48,848-005B, patients were randomized to receive Iomervu 300 mgI/mL (N=33) or ioversol 320 mgI/mL (N=31)
  Total Dose:
  Iomervu 300 mgI/mL: 47-300 mL
  iopamidol 300 mgI/mL: 55-253 mL
  Recommended maximum Iomervu iodine dose: 60 g iodine (200 mL Iomervu 300 mgI/mL).

Table 18. Recommended Per Injection Dosage for Peripheral Angiography or Visceral Angiography in Studies 48,848-005A and -005B

Volume per injection:	Injection Rate
Peripheral angiography	
Lower extremity – 72-84 mL	6-8 mL/s
Lower extremity, unilateral – 48 mL	4 mL/s
Trauma – 10-24 mL	3-6 mL/s
Upper extremity – 20-25 mL	5 mL/s
Visceral angiography	
Aorta – 40-70 mL	20-35 mL/s
Iliac Artery – 20-40 mL	8-15 mL/s
Celiac Artery – 10-12 mL	6-8 mL/s
Splenic Artery– 35 mL	5 mL/s
Common Hepatic – 35-40 mL	5 mL/s
Superior Mesenteric – 60 mL	6-8 mL/s
Inferior Mesenteric – 5-20 mL	2-4 mL/s
Inferior Vena Cava – 40 mL	20 mL/s
Pulmonary Artery – 40 mL	20 mL/s
Renal Artery – 12 mL	6 mL/s

- Intra-arterial digital subtraction angiography (DSA) supportive studies for dosing regimens
  Double-blind, randomized, parallel group, controlled clinical studies
  - Study PT-28 (cerebral DSA): patients were randomized to receive Iomervu 150 mgI/mL (N=47) or iopamidol 150 mgI/mL (N=45)
    Recommended per Injection Dosage
    - Common carotid arteries: 12 mL at 6 mL/s
    - Internal carotid artery: 8 mL at 4 mL/s
    - External carotid artery: 4 mL at 2 mL/s
    - Vertebral arteries, 3-5 ml at 3 ml/sec.
    - Aortic arch: 20-30 mL at 15 mL/s

    The total volumes of Iomervu administered ranged between 4-90 mL.
  - Study PT-22 (visceral and peripheral DSA): patients were randomized to receive Iomervu 150 mgI/mL (N=50) or iopamidol 150 mgI/mL (N=50).
    Recommended per Injection Dosage
    - Abdomen: 24 mL, 12-18 mL/s
    - Pelvis: 20-45 mL, 10-12 mL/s
    - Lower limbs: 20-50 mL, 10-12 mL/s

    The total volumes administered across the arteries visualized ranged between 20-110 mL.

- Study PT-23 (visceral DSA): patients were randomized to receive Iomervu 150 mgI/mL (N=20) or iopamidol 150 mgI/mL (N=20)
  Recommended per Injection Dosage
  - Abdominal aorta: 50 ml at 25 ml/sec
  - Renal arteries: 12 ml at 4-6 ml/sec

  The total volumes administered across the arteries visualized ranged between 23 and 150 mL.

- Coronary arteriography and cardiac ventriculography: Study IOM-104A (48,848-001A, 48,848-001B, 48,848-002A, 48,848-002B)
  Study Design: Blinded re-read of prospective, randomized, double-blind, parallel group clinical studies. In 48,848-001A and 48,848-001B, patients were randomized to receive Iomervu 400 mgI/mL (N=59) or iopamidol 370 mgI/mL(N=58). In Studies 48,848-002A and 48,848-002B, patients were randomized to receive either Iomervu 300 mgI/mL (N=59) or ioversol 320 mgI/mL (N=61).
  Total Dose:
  Iomervu 400 mgI/mL: 58.5-225 mL
  Iomervu 300 mgI/mL: 43-304 mL
  iopamidol 300 mgI/mL: 49-285 mL
  ioversol 320 mgI/mL: 50-259 mL
  Recommended maximum Iomervu iodine dose: 86 g iodine (215 mL Iomervu 400 mgI/mL; 286 mL Iomervu 300 mgI/mL).

Table 19. Recommended Per Injection Dosage in Studies 48,848-001A, -001B, -002A, and -002B

Type of Angiography	Recommended Volume (mL)	Rate of Injection (mL/sec)
Right Coronary Artery	3-6	2-3
Left Coronary Artery	4-7	2-3
Bypass grafts	4-7	2-3
Left Ventricle	30-45	10-15
Aorta	30-60	15-30
Right Ventricle	30-45	10-15
Pulmonary Artery	30-60	15-30

IV Procedures

- CT of the head and body: Study IOM-104E (48,848-007A, 48,848-007B; 48,848-008A, 48,848-008B)
  Study Design: Blinded re-read of prospective, randomized, double-blind, parallel group clinical studies. In 48,848-007A, patients were randomized

	to receive Iomervu 400 mgI/mL (N=29) or iopamidol 370 mgI/mL (N=25). In 48,848-007B, patients were randomized to receive Iomervu 400 mgI/mL (N=30) or iopamidol 370 mgI/mL (N=30). In 48,848-008A, patients were randomized to receive Iomervu 250 mgI/mL (N=28) or iopamidol 250 mgI/mL (N=28). In 48,848-008B, patients were randomized to receive Iomervu 250 mgI/mL (N=31) or iopamidol 250 mgI/mL (N=29). Dose: Iomervu 400 mgI/mL: 75-150 mL Iomervu 250 mgI/mL: 100-191 mL iopamidol 370 mgI/mL: 80-287 mL iopamidol 250 mgI/mL: 75-189 mL • CT angiography of intracranial, visceral, and lower extremity arteries (studies from literature) ○ Napoli et al. 2011 (N=21): Iomervu 400 mgI/mL 130 mL ○ Albrecht et al. 2007 (N=50): Iomervu 400 mgI/mL 100 mL ○ Iezzi et al. 2008 (N=40): Iomervu 400 mgI/mL 90 mL; Iomervu 300 mgI/mL 120 mL) ○ Gruschwitz et al. 2023 (N=109): Iomervu 350 mgI/mL 110 mL ○ Millon et al. 2012 (N=73): Iomervu 400 mgI/mL 25 mL ○ Kim et al. 2020 (N=128): Iomervu 400 mgI/mL 80-100 mL ○ Schaefer et al. 2013 (N=52): Iomervu 350 mgI/mL 100 mL • Coronary CT angiography (studies from literature) ○ Andreini et al. 2010 (N=210): Iomervu 400 mgI/mL 80 mL ○ Pontone et al. 2014 (N=184): Iomervu 400 mgI/mL 90 mL ○ Andreini et al. 2017 (N=166): Iomervu 400 mgI/mL 50 mL BMI < 24.9 kg/m^2; Iomervu 400 mgI/mL 60 mL BMI > 25 kg/m^2; ○ Brodoefel et al. 2008 (n=125): Iomervu 400 mgI/mL 80 mL • CT urography (studies from literature) ○ Portnoy et al. 2011 (N=150): Iomervu 350 mgI/mL 90 mL ○ Martingano et al. 2013 (N=35): Iomervu 350 mgI/mL 600 mgI/kg (~120 mL for a patient with body weight of 70 kg)
General dosing instructions	See Table 12 to Table 15

Dosing in patient subgroups (intrinsic and extrinsic factors)	• Acute kidney injury may occur after Iomervu administration. Preexisting renal impairment can increase the risk for acute kidney injury as renal impairment reduces the rate of elimination of iomeprol. However, acute kidney injury (0.0002%) was rare in post-marketing surveillance data of patients exposed to iomeprol. • No dose adjustment is recommended for patients with renal impairment. Use the lowest necessary dose of Iomervu in patients with renal impairment. • No dose adjustment is recommended for patients aged 65 or older. • No dosage adjustment is recommended for patients with hepatic impairment.
Drug Interactions	The drug interaction recommendations are consistent with the other approved iodinated contrast agents. • Stop metformin at the time of, or prior to, Iomervu administration in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast agents. Re-evaluate eGFR 48 hours after the imaging procedure and reinstitute metformin only after renal function is stable. Metformin can cause lactic acidosis in patients with renal impairment. Iodinated contrast agents appear to increase the risk of metformin-induced lactic acidosis, possibly as a result of worsening renal function. • Avoid thyroid therapy or testing using radioactive iodine for up to 6 weeks post Iomervu. Administration of Iomervu may interfere with thyroid uptake of radioactive iodine (I-131 and I-123) and decrease therapeutic and diagnostic efficacy. • Do not perform protein-bound iodine test for at least 16 days following administration of Iomervu. Iodinated contrast agents, including Iomervu, will temporarily increase protein-bound iodine in blood. However, thyroid function tests that do not depend on iodine estimations, e.g., triiodothyronine (T_3) resin uptake and total or free thyroxine (T_4) assays, are not affected.
Labeling	Generally acceptable. The review team has recommended specific content and formatting changes to the proposed labeling. Labeling language was reviewed, corrected, and updated according to the guidance, Clinical Labeling for Human Prescription Drug and Biological Products - Content and Format (published December 2016).
Bridge between the to-be-marketed and	The to-be-marketed formulation was used in the clinical studies to support efficacy and safety.

clinical trial formulations	

6.1.2. Post-Marketing Requirement (PMR) or Commitment (PMC)

No clinical pharmacology post-marketing requirements or commitments are needed.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Mechanism of Action: Iomeprol is a radiographic iodinated contrast agent that opacifies the vessels and body structures where the contrast agent is present following intravenous or intra-arterial administration, permitting radiographic visualization of the internal structures through attenuation of X-ray photons.

Pharmacodynamics: The degree of radiographic enhancement by iomeprol is related to the iodine concentration in the tissue of interest following the administration of Iomervu. However, the exposure-response relationships and time course of pharmacodynamic response of iomeprol have not been fully characterized.

Pharmacokinetics: The maximum concentration (Cmax) and area under the concentration-time curve (AUC) are dose-proportional across the dose range of 250 mgI/kg to 1,250 mgI/kg body weight. Refer to Section 16.3.2, Table 76 for details. The pharmacokinetic parameters of iomeprol discussed below are presented as mean (standard deviation) unless otherwise specified.

- Distribution: Iomeprol volume of distribution is 0.28 (0.05) L/kg. Iomeprol does not bind to plasma proteins.
- Elimination: Iomeprol elimination half-life is 1.8 (0.33) hr and the clearance is 0.10 (0.01) L/hr/kg.
  - *Metabolism:* Iomeprol does not undergo significant metabolism.
  - *Excretion:* Approximately 90% of the iomeprol injected dose is excreted unchanged in urine within 24 hours.

Specific Populations
Pediatric Patients: No clinically significant differences in the pharmacokinetics of iomeprol were observed in pediatric patients aged 3 years to 17 years compared to adult patients who received Iomervu. No clinically significant differences in Cmax and concentration of iomeprol were observed within 5 minutes after Iomervu administration between pediatric patients younger than 3 years of age and adults based on pharmacokinetic simulations.

Patients with Renal Impairment: The renal clearance of iomeprol decreased by 28% in patients with mild (GFR 51 to 75 mL/min, estimated by inulin clearance (CL_{inulin})), 66% with moderate (GFR 26 to 50 mL/min, by CL_{inulin}), and 84% with severe (GFR ≤ 25 mL/min, by CL_{inulin}) renal impairment. Similarly, mean elimination half-life increased 1.6-fold in mild, 2.9-fold in moderate, and 6.4-fold in severe renal impairment.

Iomeprol is dialyzable. Iomeprol plasma concentrations decreased by 83% in patients with severe renal impairment who underwent hemodialysis 2 hours after a single administration of a 20,000 mg iodine dose of Iomervu by intravenous route.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The dosing regimens for the proposed indications are supported by clinical efficacy data in adults from studies in Table 16.

The effectiveness of Iomervu in pediatric patients was extrapolated from adult patient-based PK of iomeprol. No clinically significant differences in the PK of iomeprol were observed in pediatric patients aged 3 years to 17 years compared to adult patients, and no clinically significant differences in Cmax and concentration of iomeprol were observed within 5 minutes after Iomervu administration (typical times when imaging would be performed) between pediatric patients younger than 3 years of age and adults based on population pharmacokinetic simulations.

Therapeutic Individualization

No dose adjustments are proposed based on intrinsic or extrinsic factors. Iomeprol is primarily excreted via glomerular filtration and excretion is reduced in patients with renal impairment and patients 65 years or older. Acute kidney injury may occur after Iomervu administration. As the AUC_{inf} of iomeprol increased in patients with renal impairment, preexisting renal impairment increases the risk for acute kidney injury. Acute kidney injury was rare (0.0002%) in post-marketing surveillance data of patients exposed to iomeprol. The lowest effective dose of Iomervu should be used in patients with renal impairment. No overall differences in safety and effectiveness were identified in patients 65 years or older compared to younger adult patients in clinical studies of Iomervu.

Outstanding Issues

There are no outstanding clinical pharmacology issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Table 20. General Pharmacology and Pharmacokinetic Highlights

Pharmacology	
Mechanism of Action	Iomeprol is a radiographic iodinated contrast agent that opacifies the vessels and body structures where the contrast agent is present following intravenous or intra-arterial administration, permitting radiographic visualization of the internal structures through attenuation of X-ray photons.
Active Moieties	Iomeprol
QT Prolongation	There is insufficient information to characterize the effect of Iomervu on the QTc interval. The relationship between iomeprol concentration and heart rate-corrected QT interval (QTc) was evaluated using a blinded evaluation of standard 12-lead and 2-lead ''rhythm strip'' ECGs obtained during four double-blind, randomized studies of Iomeprol (Studies 48848-00lA, -00IB, -002A, and -002B). Per the FDA QT-IRT review (Reference ID: 5373182), there is insufficient information to characterize the effect of Iomervu on the QTc interval as the timing of the ECGs did not capture Tmax of iomeprol. Cardiac arrest and ventricular fibrillation (0.1%; 6 out of 4739 patients) were identified as adverse reactions in patients who received Iomervu intravascularly. Five cases of cardiac arrest and ventricular fibrillation were with the intraarterial route for cardioangiography. Conduction disturbances and arrhythmias are known complications of cardioangiography and may have contributed to these cases. The remaining case, involving IV administration, was considered to be unrelated to iomeprol given the time course. In addition, cardiac arrest and ventricular fibrillation are known adverse reactions reported in the labeling for other iodinated contrast agents. Cardiac arrest and ventricular fibrillation are included as adverse reactions in the proposed Iomervu labeling.
General Information	
Bioanalysis	Bioanalytical information is provided in Section 16.3.
Healthy Volunteers vs. Patients	Health status was explored as a potential covariate in the population PK analysis. The covariate effect of healthy condition on clearance could be confounded with baseline creatinine clearance (CRCL) effect on clearance and it is difficult to define in terms of clinical application.
Dose Proportionality	The Cmax and AUC are dose-proportional across the dose range of 250 mgI/kg to 1,250 mgI/kg body weight. Additional details are provided in Section 16.3.
Adult vs. Pediatric Patients	No clinically significant differences in the pharmacokinetics of iomeprol were observed in pediatric patients aged 3 years to 17 years compared to adult patients.
Distribution	
Volume of Distribution	Volume of distribution [mean (SD)]: 0.28 (0.05) L/kg
Plasma Protein Binding	Iomeprol does not bind to plasma proteins. Plasma protein binding of iomeprol is approximately 0%.

Elimination	
Half-life	Mean elimination half-life (SD): 1.8 (0.33) hours
Clearance	Mean Clearance (SD): 0.10 (0.01) L/hr/kg
Metabolism	
Primary metabolic pathway(s)	Iomeprol does not undergo significant metabolism.
Excretion	
Primary excretion pathways	Approximately 90% of the iomeprol dose was excreted unchanged in urine within 24 hours.

6.3.2. Clinical Pharmacology Questions

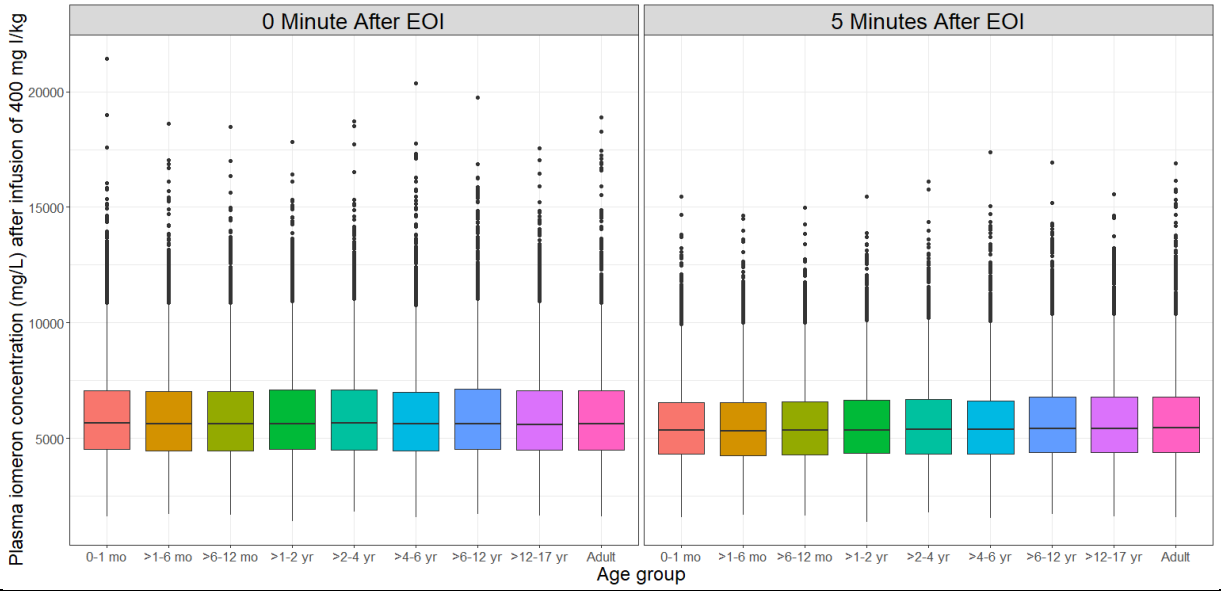
Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The effectiveness for the proposed indications is supported by clinical efficacy data in adult patients for the proposed indications. See Table 16 and Section 8 for more details regarding the study designs and efficacy assessment.

Population PK (PPK) analyses were used to extrapolate efficacy to pediatric patients from adult patients. The PPK analyses indicated:

- No clinically significant differences in the PK of iomeprol were observed between pediatric patients aged 3 years to 17 years and adult patients.
- No clinically significant differences in Cmax and concentration of iomeprol were observed within 5 minutes (typical times when imaging would be performed) of Iomervu administration between pediatric and adult patients based on pharmacokinetic simulations as indicated in Figure 1.

Figure 1. Simulated Iomervu Concentration at 0 Minute (Left) and at 5 Minutes (Right) After the End of IV Infusion of 400 mg I/kg to Patients of Different Age Groups



Source: FDA Reviewer's PPK Analyses

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

The proposed dosing regimens (IA procedures: single injection doses and maximum total dose for all proposed IA indications, Table 12; IV procedures: single bolus doses for all proposed IV indications or divided doses in CT urography, Table 14) are adequate for the indicated patient populations. In adult patients, the dosing regimens are supported by clinical efficacy data at the proposed dosing regimens for the proposed indications. See Table 16 and Section 8 for more details regarding the study designs and efficacy assessment.

In pediatric patients, body weight-based doses were proposed for single doses in IA procedures (Table 13) or IV procedures (Table 15) based on adult body weight based-doses. The effectiveness of Iomervu at proposed dosing regimens in pediatric patients is expected to be similar to that of adult patients due to the PK similarity between adult and pediatric patients at the same body weight-based dose.

The Applicant originally proposed a (b) (4) mL/kg maximum total dose for IA procedures for patients aged (b) (4) to 17 years. There were only limited clinical data to support this limit in study PT-27 where one patient (out of 43) received a dose above 5 mL/kg. However, the study protocol recommended the maximum total dose of Iomervu 400 mgI/mL to be ≤ 5 mL/kg. In addition, the proposed (b) (4) mL/kg maximum total dose causes more than 2-fold higher maximum total dose in certain pediatric patients than would be allowed in adults. For example, a 61 kg (a median weight of a 16 year, 192.5 months, male based on https://www.cdc.gov/growthcharts/html_charts/wtage.htm) pediatric patient would have a maximum total dose (b) (4) which exceeds the recommended maximum total dose of 86 g iodine in adult patients by more than 2-fold. A

review of the approved, marketed iodinated contrast agents in the U.S. with IA indications for both adult and pediatric patients showed that none had a significant difference in maximum total dose between adult and pediatric patients (Table 21). The FDA recommended that the Applicant reduce the maximum total dose to 5 mL/kg and cap the maximum total doses in pediatric patients at the corresponding maximum total doses in adult patients. The Applicant accepted the recommendation with the updated maximum total dose (Table 13). The proposed dosing regimens in adult and pediatric patients are acceptable after the change in maximum total dose in pediatric patients.

Table 21. Maximum Total Doses in Adult and Pediatric Patients for Certain Approved, Marketed Iodinated Contrast Agents in the U.S.

Drug Name	Indications[1]	Drug Conc. (mgI/mL)	Adult Maximum Total Dose	Pediatric Maximum Total Dose
Ultravist (Adults and pediatrics ≥ 2 years)	Coronary arteriography and left ventriculography	370	83 g iodine (225 mL)	90 g iodine[2] (4 mL/kg)
Visipaque Adults: Adults & pediatrics ≥ 12 years; Pediatrics: pediatrics 0 to < 12 years	Angiocardiography, peripheral, visceral, and cerebral arteriography	320	56 g iodine (175 mL) Carotid & vertebral arteries; 64 g iodine (200 mL) Right & left coronary artery and left ventricle; 80 g iodine (250 mL) Renal arteries, aortography, major branches of aorta, aortofemoral runoffs, peripheral arteries	78 g iodine[2] (4 mL/kg)
Isovue (Adults and pediatrics 0-17 years)	Coronary arteriography and ventriculography	370	74 g iodine (200 mL)	46 g iodine (125 mL)
Optiray (Adults and pediatrics 0-17 years)	Coronary arteriography and left ventriculography	320/350	80 to 87.5 g iodine (250 mL)	87.5 g iodine (5 mL/kg up to 250 mL)

Omnipaque (Adults and pediatrics 0-17 years)	Selective coronary arteriography and ventriculography	350	87.5 g iodine (250 mL)	87.5 g iodine (291 mL 300 mgI/mL; 250 mL 350 mgI/mL)
	Aortography and selective visceral arteriography	300/350	87.5 g iodine (290 mL 300 mgI/mL; 250 mL 350 mgI/mL) (290 mL 300 mgI/mL; 250 mL 350 mgI/mL)	87.5 g iodine (Not > 5 mL/kg up to 250 mL)

1. The table only includes approved iodinated contrast agents with IA indications and maximum total doses in the prescribing information for both adults and pediatric patients.
2. A body weight of 61 kg (median weight of a 16-year (192.5 months) male; https://www.cdc.gov/growthcharts/html_charts/wtage.htm) is used for the calculation.

Source: Ultravist, Visipaque, Isovue, Optiray, and Omnipaque prescribing information.

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

No alternative dosing or management strategy is recommended based on intrinsic patient factors.

Renal Impairment

Iomeprol is mainly excreted unchanged in urine. In study B16880-042, iomeprol PK were evaluated in participants with normal renal function or with renal impairment after a single intravenous administration of a 20,000 mg iodine dose of Iomervu (50 mL Iomervu 400 mgI/mL; Table 22). The renal clearance of iomeprol decreased by 28% in participants with mild (GFR 51 to 75 mL/min, estimated by inulin clearance (CL_{inulin})), 66% with moderate (GFR 26 to 50 mL/min, by CL_{inulin}), and 84% with severe (GFR ≤ 25 mL/min, by CL_{inulin}) renal impairment. AUC_{inf} increased approximately 6-fold in participants with severe renal impairment.

Acute kidney injury may occur after IOMERVU administration. As the AUC_{inf} of iomeprol increased in patients with renal impairment, the risk for acute kidney injury in patients with preexisting renal impairment may increase with iomeprol. However, in post-marketing surveillance data in over 160 million patients exposed to iomeprol, reports of serious cases of contrast-associated acute kidney injury were rare (0.0002% of exposed patients). The efficacy of iomeprol is expected to be similar between patients with normal renal function and patients with renal impairment since there are no significant differences in iomeprol Cmax and volume of distribution. No dose modification is recommended for patients with renal impairment.

Table 22. Mean (SD) Pharmacokinetic Parameters of Iomeprol in Participants with Normal Renal Function or Renal Impairment

Renal Function	Cmax (mg/mL)	AUCinf (mg*hr/mL)	Vc (L/kg)	Vss (L/kg)	CL_{total} (L/hr/kg)
Normal (N=6)	4.45 (0.85)	7.7 (2.6)	0.12 (0.027)	0.229 (0.035)	0.084 (0.029)
Mild renal impairment (N=6)	4.31 (0.40)	10.3 (1.2)	0.115 (0.027)	0.224 (0.021)	0.052 (0.007)
Moderate renal impairment (N=6)	4.71 (1.3)	22.1 (4.5)	0.102 (0.020)	0.223 (0.034)	0.025 (0.005)
Severe renal impairment (N=4)	3.70 (1.0)	46.4 (3.1)	0.157 (0.051)	0.272 (0.054)	0.013 (0.003)

Source: Table E of 5.3.4.2 Study B16880-042 Clinical Study Report.
Abbreviations: Cmax = maximum plasma concentration, AUCinf = area under plasma concentration-time curve from time 0 to infinity, Vc = central volume of distribution, Vss = steady-state volume of distribution, CL_{total} = total clearance.

Iomeprol is dialyzable. In study B16880-054, eight patients with severe renal impairment underwent 4 hours hemodialysis starting at 2 hours after a single intravenous administration of a 20,000 mg iodine dose (50 mL Iomervu 400 mgI/mL) of Iomervu. Iomeprol mean (SD) plasma concentrations decreased from 2295 (865) µg/mL before the hemodialysis to 385 (70.7) µg/mL after the hemodialysis. Iomeprol mean plasma concentration decreased by approximately 83%.

Patients 65 years and older

No dose modification is recommended for patients 65 years and older. Of the total number of patients in clinical studies of Iomervu included in the integrated summary of safety, 1,977 (43%) patients were 65 years of age and older. Similar doses were administrated in patients 65 years and older compared to younger patients. No overall differences in safety or effectiveness were observed between these patients and younger patients. See Section 8 for more details.

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

Food-drug interactions are not expected with Iomervu.

Stop metformin at the time of, or prior to, Iomervu administration in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast agents. Re-evaluate eGFR 48 hours after the imaging procedure and reinstitute metformin only after renal function is stable.

Avoid thyroid therapy or testing using radioactive iodine for up to 6 weeks post Iomervu. Administration of Iomervu may interfere with thyroid uptake of radioactive iodine (I-131 and I-123) and decrease therapeutic and diagnostic efficacy.

Do not perform protein-bound iodine test for at least 16 days following administration of Iomervu. Iodinated contrast agents, including Iomervu, will temporarily increase protein-bound iodine in blood. However, thyroid function tests that do not depend on iodine estimations, e.g., triiodothyronine (T3) resin uptake and total or free thyroxine (T4) assays, are not affected.

Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

The to-be-marketed formulation is the same as the clinical trial formulation.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 23. Listing of Clinical Studies of Intra-arterial Efficacy in Adults

Trial Identity	Trial Design	Concentration/ Volume[1]/ Flow Rate	Study Endpoints	No. of Patients[2]	Study Population	No. of Centers and Countries
Coronary arteriography and cardiac ventriculography						
IOM-104A (48,848-001A, 48,848-001B, 48,848-002A, 48,848-002B)	Prospective, multi-center, double-blind, randomized	400 mgI/mL 121 mL 3-30 mL/sec	% adequate visualization on a 2-point scale and non-inferiority to comparator	59	Adult patients with a cardiac history or diagnosis necessitating coronary arteriography and ventriculography	48,848-001A: 6 centers in US 48,848-001B: 5 centers in US 48,848-002A: 3 centers in US 48,848-002B: 4 centers in US
		300 mgI/mL 137 mL 3-30 mL/sec		59		
Cerebral arteriography						
IOM-104C (48,848-004A, 48,848-004B)	Prospective, multi-center, double-blind, randomized	300 mgI/mL 96 mL 4-25 mL/sec	% adequate visualization on a 2-point scale and non-inferiority to comparator	61	Adult patients with a history or diagnosis necessitating cerebral arteriography	48,848-004A: 4 centers in US 48,848-004B: 6 centers in US
Visceral and peripheral arteriography						
IOM-104D (48,848-005A, 48,848-005B)	Prospective, multi-center, double-blind, randomized	300 mgI/mL 161 mL 4-35 mL/sec	% adequate visualization on a 2-point scale and non-inferiority to comparator	60	Adult patients with a history or diagnosis necessitating visceral and/or peripheral arteriography	48,848-005A: 5 centers in US 48,848-005B: 5 centers in US
Intra-arterial digital subtraction angiography						
PT-28	Prospective, single-center, double-blind, randomized	150 mgI/mL 4-90 mL 2-19 mL/sec	% adequate visualization on a 4-point scale	47	Adult patients with a history or diagnosis necessitating cerebral DSA	1 center in Italy
PT-22	Prospective, single-center, double-blind, randomized	150 mgI/mL 20-110 mL 10-18 mL/sec	% adequate visualization on a 4-point scale	50	Adult patients with a history or diagnosis necessitating visceral and/or peripheral DSA	1 center in Italy
PT-23	Prospective, single-center, double-blind, randomized	150 mgI/mL 23-150 mL 3-25 mL/sec	% adequate visualization on a 4-point scale	20	Adult patients with a history or diagnosis necessitating visceral DSA	1 center in Italy

Source: FDA clinical reviewer
Abbreviations: DSA = digital subtraction angiography
[1] Volumes not presented as a range are mean values.
[2] Patients who received Iomervu.

Table 24. Listing of Clinical Studies of Intravenous Efficacy in Adults

Study Identity	Study Design	Concentration/ Volume[1]/Flow Rate	Study Endpoints	No. of Patients[2]	Study Population	No. of Centers and Countries
CT head and body						
IOM-104E (48-848-007A, 48-848-007B, 48-848-008A, 48-848-008B)	Prospective, multi-center, double-blind, randomized	400 mgI/mL 112 mL 1-5 mL/sec 250 mgI/mL 145 mL 1-5 mL/sec	% adequate visualization on a 2-point scale and non-inferiority to comparator	59 59	Adult patients with a history or diagnosis necessitating head and/or body CT for diagnostic, preoperative, or postoperative evaluation	48-848-007A, 48-848-008A: 5 centers in US 48-848-007B, 48-848-008B: 5 centers in US
CT angiography (CTA)						
Peripheral angiography						
Albrecht et al. 2007	Prospective, single center	400 mgI/mL 100 mL 4 mL/sec	Image quality: % diagnostic arterial segments Diagnostic performance: Segment-level sensitivity and specificity for detection of >50% stenosis by DSA reference standard	50	Adult patients with peripheral arterial disease (chronic or acute ischemia)	1 center in Germany
Iezzi et al. 2008	Prospective, single center	Group A (n=20): 300 mgI/mL 120 mL Group B (n=20): 400 mgI/mL 90 mL 3 mL/sec	Image quality: % adequate visualization Diagnostic performance: Segment-level sensitivity and specificity for detection of >70% stenosis by DSA reference standard	40	Adult patients with peripheral arterial disease referred for DSA	1 center in Italy
Napoli et al. 2011	Prospective, single center	400 mgI/mL 130 mL 4 mL/sec	Segment- and region-level sensitivity and specificity for detection of ≥70% stenosis by DSA reference standard	212	Adult patients with symptomatic peripheral arterial disease referred for imaging after duplex ultrasound	1 center in Italy
Gruschwitz et al. 2023	Retrospective, single center	350 mgI/mL 110 mL 3 mL/sec	Segment-level sensitivity and specificity for detection of ≥75% stenosis by DSA reference standard	109	Adult patients with known or suspected peripheral arterial disease	1 center in Germany
Cerebral angiography						
Millon et al. 2012	Retrospective, single center	400 mgI/mL 25 mL 5 mL/sec	% adequate visualization	73	Adult patients with nontraumatic subarachnoid hemorrhage	1 center in France
Kim et al. 2020	Retrospective, single center	400 mgI/mL 80-100 mL 3-4 mL/sec	Image quality: % adequate visualization on a 3-point scale Diagnostic performance: Sensitivity and specificity for evaluation of residual/recurrent aneurysms, patency of parent artery, patency of adjacent branch by 3DRA reference standard	128	Adult patients with cerebral aneurysm who underwent postoperative CT angiography, DSA, and 3DRA	1 center in Korea
Visceral angiography						
Schaefer et al. 2013	Prospective, single center	350 mgI/mL NA NA	Image quality: Image quality on a 5-point scale Diagnostic performance: Sensitivity and specificity for detection of >50% stenosis by DSA reference standard	52	Adult patients with asymptomatic aortoiliac aneurysms or penetrating atherosclerotic ulcers	1 center in Germany
Stueckle et al. 2004	Retrospective, single center	350 mgI/mL 100 mL 3 mL/sec	Sensitivity and specificity for detection of high-grade (≥85%) and low-grade (≥45%, <85%) stenosis by DSA reference standard	52	Adult patients with suspected aortic dissection, aortic aneurysm, or stenosis of the mesenteric or iliac arteries who underwent CT angiography and DSA of the abdominal vessels	1 center in Germany
Coronary CT angiography (CCTA)						

Andreini et al. 2017	Prospective, single center	400 mgI/mL 50 mL (BMI <24.9 kg/m^2), 60 mL (BMI >25 kg/m^2) 5 mL/sec	Image quality: % adequate visualization on a 4-point scale Diagnostic performance: Segment- and patient-level sensitivity and specificity for detection of >50% stenosis by ICA reference standard	166	Adult patients without known coronary artery disease scheduled for ICA	1 center in Italy
Andreini et al. 2010	Prospective, single center	400 mgI/mL 80 mL 5 mL/sec	Segment- and patient-level sensitivity and specificity for detection of >50% stenosis by ICA reference standard	210	Adult patients with suspected coronary artery disease scheduled for ICA	1 center in Italy
Brodoefel et al. 2008	Prospective, single center	400 mgI/mL 80 mL 5 mL/sec	Image quality: % adequate visualization on a 4- point scale Diagnostic performance: Segment- and patient-level sensitivity and specificity for detection of >50% stenosis by ICA reference standard	125	Adult patients with suspected (or suspected progression of) coronary artery disease scheduled for ICA	1 center in Germany
Pontone et al. 2014	Prospective, single center	400 mgI/mL 90 mL 5 mL/sec	Image quality: % adequate visualization on a 4-point scale Diagnostic performance: Segment- and patient-level sensitivity and specificity for detection of >50% stenosis by ICA reference standard	184	Adult patients with high risk for coronary artery disease scheduled for ICA	1 center in Italy
(b) (4)						
CT urography						
Portnoy et al. 2011	Retrospective, single center	350 mgI/mL 90-120 mL 2.5 mL/sec (3-phase and split-bolus dual-phase)	% adequate visualization on a 3-point scale	150	Adult patients with hematuria and other urologic diseases	1 center in Israel
Bretlau et al. 2015	Retrospective, single center	400 mgI/mL 25-50 mL NA (split-bolus dual-phase)	Disease detection rate	771	Adult patients with hematuria	1 center in Denmark
Martingano et al. 2013	Retrospective, single center	350 mgI/mL 600 mgI/kg 2 mL/sec (split-bolus dual-phase)	Image quality: Visualization score on a 6-point scale Diagnostic performance: Sensitivity and specificity for detection of urothelial malignancy	35	Adult patients with hematuria who underwent both CT urography and MR urography	1 center in Italy
Kahn et al. 2022	Retrospective, single center	300 mgI/mL 90-120 mL NA (4-phase)	Sensitivity and specificity for detection of hydronephrosis	15	Adult patients with and without hydronephrotic kidneys	1 center in Israel

Source: FDA clinical reviewer
Abbreviations: 3DRA = three-dimensional rotational angiography, BMI = body mass index, CT = computed tomography, DSA = digital subtraction angiography, ICA = invasive coronary angiography, MR = magnetic resonance, n = number of patients, NA = not available
[1] Volumes not presented as a range are mean values.
[2] Patients who received Iomervu.

7.2. Review Strategy

The Applicant submitted two NDAs for Iomervu, NDA 216016 and NDA 216017. NDA 216016 contains information regarding use of Iomervu by intra-arterial administration and NDA 216017 contains information regarding use of Iomervu by intravenous administration. The drug mechanism of action, attenuation of x-ray photons, is the same for both routes of administration, and the effectiveness of the drug for intra-arterial indications should be considered during review of intravenous indications and vice versa. Further, safety issues are expected to overlap significantly for the two routes of administration. Therefore, the clinical review in Section 8 will consider the data submitted in both NDAs.

A total of 23 primary and 130 supportive efficacy studies of Iomervu were submitted by the Applicant. Upon initial review, 19 were considered key primary efficacy studies with visualization or diagnostic performance endpoints. Eleven of these studies were conducted by the Applicant and eight were literature studies that were conducted in non-U.S. countries. The efficacy review is focused on the assessment of the 19 key primary efficacy studies. The remaining primary efficacy studies and pertinent supportive efficacy studies listed in Table 23 and Table 24 are briefly reviewed in the relevant indication subsections in Section 8.1.

Literature search strategy

The Applicant conducted a literature search to identify clinical studies that involved the intravenous use of Iomervu for CT imaging for the assessment of diagnostic performance and/or image quality and the intra-arterial use of Iomervu for percutaneous coronary intervention. The literature search was performed using Medline, Embase, Derwent, and Biosis with the search terms “Iomeprol”, “Imeron”, or “Iomeron” for abstracts, titles, and full-text articles of studies published up to May 31, 2021. An additional search was performed using the same search criteria for studies published between June 1, 2021, and June 30, 2023, which was the period between data lock point of the initial NDA submissions and the present resubmissions.

Publications to support efficacy consisted of original research with prospective enrollment or retrospective analysis of patients who received Iomervu intravenously for CT imaging procedures, included at least 40 patients, involved at least 2 blinded readers in the assessment of images for efficacy, and assessed the efficacy of Iomervu with CT procedures against a reference standard (i.e., histopathology or conventional angiography).

The Applicant identified a total of 15 primary efficacy studies of the intravenous use of Iomervu in CT angiography (n=8), coronary CT angiography (n=4), CT venography (n=2), and CT urography (n=1) procedures in adult patients. Most of the studies involved image evaluation by two readers. Seven of these studies were retrospective, including the single CT urography study. The assessment of image quality and performance varied across studies in the detail of visualization rating scales used and the thresholds used for assessing significant disease. Of the 15 studies, 7 were considered by the clinical team to be major effectiveness studies.

The Applicant also identified supportive studies that enrolled fewer than 40 patients, involved fewer than 2 readers or unblinded readers, or assessed image quality or other qualitative measurements of efficacy. This included 98 studies involving the intravenous use of Iomervu in body CT (n=40), CT angiography (n=22), coronary CT angiography (n=32), CT venography (n=1), and CT urography (n=3) procedures in adult patients. Of note, one study that was identified by the Applicant as supportive was considered appropriate for detailed review for the CT urography indication by the clinical team. A total of eight studies were also identified by the Applicant to support the intra-arterial use of Iomervu in patients undergoing percutaneous coronary intervention.

The Applicant's literature search strategy was considered acceptable. A literature search performed by the clinical team did not identify any important publications excluded from the submission.

8 Statistical and Clinical and Evaluation

8.1. Review of Individual Trials Used to Support Efficacy

8.1.1. IOM-104A: Coronary arteriography and cardiac ventriculography

Trial Design

IOM-104A was a prospective, blinded re-read study of four previously conducted prospective, multicenter, randomized, double-blind, active comparator-controlled studies with identical design enrolling adult patients undergoing coronary arteriography and cardiac ventriculography. It was conducted from March to May 2004. The original imaging studies 48,848-001A, 48,848-001B, 48,848-002A, and 48,848-002B were conducted from December 1995 to July 1996 at six, five, three, and four different sites, respectively, all in the United States.

Adult patients with a documented cardiac history or diagnosis that necessitated coronary arteriography and cardiac ventriculography for diagnostic purposes or preoperative evaluation were included in the original studies. Exclusion criteria included patients scheduled for or likely to undergo emergency procedures, surgery, or cardiac intervention, patients requiring general anesthesia, pregnant patients, patients with serum creatinine >2.5 mg/dL, and patients with known sensitivity to iodine-containing compounds. Certain predisposing risk factors for an adverse reaction from administration of iodinated contrast agents were to be recorded and considered when selecting patients. These included but were not limited to patients with allergic disorders, increased risk of thromboembolism, severe congestive heart failure, sickle cell disease, and diabetes.

In the original studies, patients were randomized to receive either Iomervu 400 mgI/mL or iopamidol 370 mgI/mL in studies 48,848-001A and -001B, while in studies -002A and -002B, patients were randomized to receive either Iomervu 300 mgI/mL or ioversol 320 mgI/mL. The concentrations of Iomervu were chosen to bracket the 350 mgI/mL concentration. The investigator determined the volume per injection and number of injections at each region of interest, which varied according to clinical need. The total procedural dose was limited to the minimum volume required to achieve a diagnostic examination, and a maximum total iodine dose of 86 g was recommended. Right coronary arteriogram, left coronary arteriogram, and left ventriculogram, all with cine acquisitions, were required for each patient. If multiple images were obtained from a single contrast injection, they were considered together as one image.

<u>Design features common to all IOM-104 re-read studies</u>
Subsequent to the completion of the original studies by the Applicant, the Agency's guidance on certain design aspects of trials for imaging agents had changed. For example, the Agency advised that in the absence of objective performance data the term "diagnostic" is not applicable to description of the efficacy outcomes of studies designed for structure delineation

indications. Moreover, FDA recommended developing standard, detailed visualization criteria describing features to be evaluated qualitatively using 5-point rating scales. The Agency had also developed guidance designed to standardize the image read process. The IOM-104 re-read study protocols were developed in consideration of these study design recommendations and in agreement with FDA.

Study design components that are identical across all re-read studies (IOM-104A, IOM-104C, IOM-104D, and IOM-104E) are described here.

Studies of a particular artery, region, or anatomical area of interest where multiple injections were given were assessed as one examination.

Image sets were processed off-site at a central imaging laboratory, (b) (4) at the time IOM-104 studies were conducted). The off-site readers were unaffiliated with the clinical sites, blinded to all patient information, blinded to the study drug, dose, and volume administered, and blinded to the study design and objectives. All readers underwent a teaching and training session to be familiarized with the reading methodology before beginning their assessment. For re-read studies IOM-104A and IOM-104E, three readers independently assessed the images from two studies for one concentration and another three readers independently assessed images from two studies of the second concentration, for a total of six readers. For re-read studies IOM-104C and IOM-104D, three readers independently assessed the images from the two original imaging studies.

Images obtained for each patient were assessed as a single set with an overall score. The off-site blinded readers were asked to determine if the image set was technically adequate or inadequate. If the image set was technically inadequate for assessment, the off-site readers did not proceed with any further assessments. Technical inadequacy of images was determined by one or more of the following:

- Patient motion made the examination uninterpretable
- Poor technique was used to acquire the examination
- Anatomy of interest was not captured by the examination
- Other (reasons were further specified)

If the image set was determined to be technically adequate, the reader qualitatively rated the images for quality of visualization using a 5-point grading scale as described in Study Endpoints below.

Study Endpoints

Study endpoints that are identical across all re-read studies (IOM-104A, IOM-104C, IOM-104D, and IOM-104E) are described here.

The primary endpoint for the IOM-104 re-read studies was the proportion of patients with

images assessed as having adequate quality of opacification and anatomic visualization in various arteriography and CT imaging applications. Adequacy was assessed using a region-specific 5-point scale, but for analytic purposes it was collapsed into a binary 2-point scale categorizing images as having either adequate or inadequate quality of visualization.

The quality of visualization on a 5-point scale was defined as:

1 = Poor
2 = Insufficient
3 = Fair
4 = Good
5 = Excellent

The quality of visualization on a derived 2-point scale was defined as:

1 = Inadequate quality (5-point scale score of 1 or 2)
2 = Adequate quality (5-point scale score of 3, 4, or 5)

The quality of visualization on a derived 3-point scale was defined as:

1 = Poor or insufficient (5-point scale score of 1 or 2)
2 = Fair (5-point scale score of 3)
3 = Good or excellent (5-point scale score of 4 or 5)

The quality of visualization on the 5-point scale for coronary arteriography and cardiac ventriculography in IOM-104A was assessed with similar definitions adapted to specific cardiovascular regions, including the left ventricle and zero order arteries, first order coronary arteries (defined as the left main, left anterior descending, left circumflex, and right), and other coronary arteries. The first order coronary artery grading scale was:

1 = Poor: Little or no opacification preventing any visualization of vascular margins, plaque, aneurysm, thrombus, or occlusion
2 = Insufficient: Some but incomplete or insufficient opacification versus adjacent myocardium, resulting in incomplete visualization of vascular margins, plaque, aneurysm, thrombus, or occlusion
3 = Fair: Enough opacification versus adjacent myocardium to allow barely adequate demonstration of intra-luminal anatomy, and visualization of margins, plaque, aneurysm, thrombus, and occlusion
4 = Good: Opacification versus adjacent myocardium allows full, though perhaps not rapid or easy, evaluation of intra-luminal anatomy, namely margins, plaque, aneurysm, thrombus, and occlusion
5 = Excellent: Opacification versus adjacent myocardium allows rapid and easy visualization of intra-luminal anatomy, namely margins, plaque, aneurysm, thrombus, and occlusion

Other study-specific definitions are described in the respective study sections.

Statistical Analysis Plan

A combined statistical analysis plan was submitted for the re-read studies IOM-104A, IOM-104C, IOM-104D, and IOM-104E.

Analysis populations include:

- Safety population/Full analysis population: All patients who were administered Iomervu
- Efficacy analysis population: All patients with technically adequate images

The predefined primary endpoint analysis was based on the efficacy analysis population. During pre-NDA interactions with the Applicant, FDA requested that technically inadequate exams that were not assessed by the blinded readers be included in the analyses of efficacy. Accordingly, post-hoc analyses were completed for all patients (safety population) with imputation of image sets graded as technically inadequate as the lowest score (poor quality of visualization). Patients in the safety population and the full analysis population are the same and are referred to as the full analysis population throughout.

As agreed upon with FDA, the success criterion of the IOM-104 re-read studies was to demonstrate non-inferiority of Iomervu versus the active comparator in providing adequate quality of visualization based on the collapsed 2-point scale using a non-inferiority margin of 10%. Handling of potential per-reader differences in performance relative to this criterion was not specified in the original protocols or SAPs. However, prior to submission of the data, FDA stated an intent to evaluate overall study success in terms of success for at least two of three readers, a rule that has been recommended for many other phase 3 studies by the Division.

Since the IOM-104 protocols were developed, FDA's thinking on non-inferiority testing for qualitative visualization score endpoints has evolved. Such endpoints are subjective and discontinuous, and they are not validated against a reference standard. There also may not be a linear relationship between perceived visualization quality and the assigned score. It is not entirely clear that a 10% difference in percent of patients with adequate visualization score is clinically unimportant. Prior to NDA submission, FDA notified the Applicant of the intent to focus the review on efficacy of Iomervu itself rather than efficacy relative to a comparator.

Secondary analyses of interest for this review included patient-level distributions of image quality on the derived 3-point scale and the original 5-point scale and inter-reader agreement. Results for the 3-point scale were similar to those observed for the primary endpoint (2-point scale) and they are not detailed in the review. Inter-reader agreement was originally to be analyzed using Cohen's kappa. Due to cases where a reader's ratings consisted of the same score for each patient, kappa statistics were not calculated and percent agreement was reported instead.

Protocol Amendments

No amendments were made to the protocol for the IOM-104A re-read study.

Four amendments were made to the protocols for the original imaging studies 48,848-001A and -001B dated November 1, 1995, November 7, 1995, January 22, 1996, and April 25, 1996. Several of the protocol amendments constitute what are now considered foundational assessments of adverse events and safety results. These studies were initiated before the E3 ICH guidance for industry titled, "Structure and Content of Clinical Study Reports", was widely accessed. Notable amendments consisted of the following:

- Modifications to the timing of the collection of AEs and ECGs, definitions for AEs, laboratory AEs, and SAEs, and AE reporting requirements.
- The number of clinical sites was changed from six to seven centers to two or more.
- The maximum patient enrollment at each clinical site was changed from 6 to 14 patients to 6 to 30 patients.

Three amendments were made to the protocols for studies 48,848-002A and -002B dated November 7, 1995, January 23, 1996, and March 22, 1996. These consisted of the same modifications as for studies -001A and -001B, with an additional change in post-procedure follow-up period from 72 hours to 24 hours.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant indicated that the study was conducted in compliance with good clinical practice (GCP) and with oversight from the local institutional review board (IRB).

Financial Disclosure

No relevant financial disclosures were reported by the Applicant for the listed clinical investigators.

Patient Disposition

A total of 241 patients were included and randomized to receive either Iomervu or active comparator (iopamidol or ioversol) in the four original imaging studies (Table 25).

Two patients randomized to receive Iomervu were not dosed due to "inadvertent administration of a non-study contrast agent" and "unable to be cannulated". Two patients randomized to receive ioversol were not dosed due to "withdrawal by the investigator for percutaneous coronary intervention" and "uric acid level of 10.2 mg/dL".

A total of 118 patients received Iomervu and 119 patients received iopamidol or ioversol and were included in the full analysis population of the IOM-104A re-read study. Iomervu 400

mgI/mL and 300 mgI/mL were administered in 59 patients each, while 58 and 61 patients received iopamidol 370 mgI/mL and ioversol 320 mgI/mL, respectively.

Four (3%) patients who were administered Iomervu were discontinued after completion of protocol-defined imaging but prior to study completion. Two patients withdrew consent, one patient discontinued due to an indication for coronary artery bypass graft surgery, and one patient was "unable to return to the site after discharge from 24-hour lab draw".

10 (8%) patients who were administered iopamidol or ioversol were discontinued after completion of protocol-defined imaging but prior to study completion. Three patients discontinued due to treatment emergent adverse events (embolus in the right femoral artery; left main coronary artery dissection and death; and increased chest pain and indication for percutaneous coronary intervention). Five patients discontinued due to indications for coronary artery bypass graft surgery. One patient withdrew consent. One patient discontinued due to "patient left hospital prior to 72-hour labs".

Table 25. Patient Disposition in IOM-104A

	48,848-001A and 48,848-001B		48,848-002A and 48,848-002B	
Disposition	**Iomervu 400 mgI/mL**	**Iopamidol 370 mgI/mL**	**Iomervu 300 mgI/mL**	**Ioversol 320 mgI/mL**
Patients randomized, n (%)	60 (100)	58 (100)	60 (100)	63 (100)
Patients not dosed, n (%)	1 (2)	0	1 (2)	2 (3)
Patients dosed, n (%)	59 (98)	58 (100)	59 (98)	61 (97)
Patients discontinued, n (%)	2 (3)	8 (14)	2 (3)	2 (3)

Source: Modified from 48-848-001A, -001B, -002A, and -002B study reports: Table 2.1, Table 2.2, and Table 2.3
Abbreviations: n = number of patients

Protocol Violations/Deviations

A total of 22 patients in IOM-104A, 11 of whom received Iomervu and 11 of whom received active comparator, did not meet selection criteria. In study 48,848-001A, one patient who received Iomervu was not an inpatient and had severe hepatic disease and one patient in the iopamidol group had a condition (not specified) which decreased the chance of obtaining reliable data. In study 48,848-001B, three patients who received Iomervu and three patients who received iopamidol were not inpatients. In study 48,848-002A, two patients who received Iomervu had a condition (not specified) which decreased the chance of obtaining reliable data. In study 48,848-002B, five patients who received Iomervu and seven patients who received ioversol were not inpatients.

Several minor protocol deviations were documented for patients that received Iomervu or active comparator (iopamidol or ioversol) in studies 48,848-001A, -001B, -002A, and -002B, but these were considered unlikely to have had a significant impact on the study results.

Demographic Characteristics

The full analysis population is generally representative of the U.S. population for which coronary arteriography and cardiac ventriculography would be indicated (Table 26). Demographics were similar for patients randomized to receive either Iomervu or active comparator (iopamidol or ioversol). The proportions of patients above and below age 65 years were generally reflective of the age ranges in which the diseases and conditions that require coronary arteriography manifest. More men were enrolled which is reflective of the higher prevalence of heart disease in men than women in the U.S. (Centers for Disease Control and Prevention, 2023). Patients enrolled were primarily white patients, however drug efficacy or safety is not expected to differ in patients of other races.

Table 26. Demographic Characteristics of Patients in IOM-104A, Safety Population

	48,848-001A and 48,848-001B		48,848-002A and 48,848-002B	
Demographic Parameters	**Iomervu 400 mgI/mL (n=59)**	**Iopamidol 370 mgI/mL (n=58)**	**Iomervu 300 mgI/mL (n=59)**	**Ioversol 320 mgI/mL (n=61)**
Age, years				
Mean (SD)	60 (14)	60 (12)	61 (12)	58 (11)
Median	61	60	62	59
Min, max	22, 85	30, 86	34, 79	36, 84
Age group, n (%)				
18 to 64 years	35 (59)	38 (66)	33 (56)	45 (74)
≥ 65 years	24 (41)	20 (34)	26 (44)	16 (26)
≥ 75 years	6 (10)	7 (12)	6 (10)	6 (10)
Sex, n (%)				
Male	41 (69)	44 (76)	43 (73)	42 (69)
Female	18 (31)	14 (24)	16 (27)	19 (31)
Race, n (%)[1]				
White	42 (71)	45 (78)	47 (79)	50 (82)
Black or African American	11 (19)	9 (15)	7 (12)	7 (12)
Hispanic	3 (5)	3 (5)	4 (7)	2 (3)
Asian	1 (2)	1 (2)	0	0
Other or unknown	2 (3)	0	1 (2)	2 (3)

Source: IOM-104A study report, Table F
Abbreviations: n = number of patients, SD = standard deviation
[1] Data on ethnicity were not collected separately from race.

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

Analysis of other baseline characteristics is not necessary given the goal of assessing contrast visualization and the enrollment of patients who received a single type of imaging procedure.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The study drug was administered by study personnel at clinical sites and therefore drug

compliance is not applicable.

Efficacy Results

The primary objective of IOM-104A was to demonstrate non-inferiority of Iomervu to the comparator in the proportion of patients with adequate quality of opacification and anatomic visualization using a 10% non-inferiority margin. For all original studies (48,848-001A and -001B combined; -002A and -002B combined), at least 98% (lower bound of 95% CI at least 91%) of image sets in the Iomervu and comparator groups were rated as having adequate quality visualization, defined as fair, good, or excellent (score of 3-5) on a 5-point scale, by all readers (Table 27). The upper limits of the 2-sided 95% confidence intervals for the difference in the proportion of patients with adequate quality visualization were within the 10% non-inferiority margin for all readers, and the proportion of patients with adequate quality visualization after receiving Iomervu was considered acceptable.

Table 27. Coronary Arteriography and Cardiac Ventriculography Visualization Score Results in IOM-104A, Efficacy Analysis Population

Reader	Patients with adequate quality visualization[1]				Difference (95% CI)[2]
48,848-001A and -001B	**Iomervu 400 mgI/mL**		**Iopamidol 370 mgI/mL**		
	n (%)	**95% CI**	**n (%)**	**95% CI**	
Reader 1	59 (100)	(94, 100)	57 (100)	(94, 100)	0 (ND)
Reader 2	57 (100)	(94, 100)	55 (100)	(94, 100)	0 (ND)
Reader 3	58 (100)	(94, 100)	58 (100)	(94, 100)	0 (ND)
48,848-002A and -002B	**Iomervu 300 mgI/mL**		**Ioversol 320 mgI/mL**		
	n (%)	**95% CI**	**n (%)**	**95% CI**	
Reader 4	59 (100)	(94, 100)	61 (100)	(94, 100)	0 (ND)
Reader 5	59 (100)	(94, 100)	60 (100)	(94, 100)	0 (ND)
Reader 6	55 (98)	(91, 100)	55 (98)	(91, 100)	0 (-4.9, 4.9)

Source: IOM-104A study report, Table G and Integrated Summary of Effectiveness, Table P
Abbreviations: n = number of patients, CI = confidence interval, ND = not defined
[1] Adequate quality visualization = rated fair, good, or excellent on a 5-point scale
[2] Proportion (%) of patients with visualization rated as adequate in the iopamidol or ioversol group minus Iomervu group

Data Quality and Integrity

No significant data quality issues were identified.

Dose/Dose Response

The concentrations and dosing of Iomervu in the original imaging studies were based on dosage recommendations of the comparator drugs as well as input from the investigators. The recommended total iodine dose was not to exceed 86 g for coronary arteriography and cardiac ventriculography in adult patients, which is about 215 mL of Iomervu 400 mgI/mL and 287 mL of Iomervu 300 mgI/mL.

The mean total volume of Iomervu 400 mgI/mL administered was 121 ± 44 mL (maximum 225 mL) and the mean total iodine dose administered was 48 ± 17 g (maximum 90 g) (Table 28). The mean total volume of Iomervu 300 mgI/mL administered was 137 ± 61 mL (maximum 304 mL) and the mean total iodine dose administered was 55 ± 24 g (maximum 122 g).

The mean number of injections administered at each anatomic location (the right coronary artery, left coronary artery, and left ventricle) were similar between the two concentrations of Iomervu that were administered and to the active comparators.

Table 28. Volume and Total Iodine Dose Administered in IOM-104A, Safety Population

	48,848-001A and 48,848-001B		48,848-002A and 48,848-002B	
Dose Parameters	**Iomervu 400 mgI/mL (n=59)**	**Iopamidol 370 mgI/mL (n=58)**	**Iomervu 300 mgI/mL (n=59)**	**Ioversol 320 mgI/mL (n=61)**
Contrast volume, mL				
Mean (SD)	121 (44)	129 (51)	137 (61)	122 (54)
Median	115	120	123	117
Min, max	59, 225	49, 285	43, 304	50, 259
Total iodine dose administered, grams				
Mean (SD)	48 (17)	48 (19)	55 (24)	45 (20)
Median	46	45	49	43
Min, max	23, 90	18, 106	17, 122	19, 96
Number of injections by site[1], mean (SD)				
Left coronary artery	5.3 (2.1)	5.6 (1.7)	5.3 (2.1)	4.9 (1.5)
Right coronary artery	2.0 (1.0)	2.4 (1.1)	2.1 (1.0)	2.3 (1.1)
Left ventricle	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)	1.1 (0.3)

Source: IOM-104A study report, Table F; 48-848-001A, -001B, -002A, and -002B study reports, Table D
Abbreviations: n = number of patients, SD = standard deviation
[1] Patients may have more than one region of interest examined

Additional Analyses Conducted on the Individual Trial

In a post-hoc analysis of the full analysis population, where technically inadequate exams were included in the primary analysis of efficacy by assigning them a score of inadequate, at least 93% (lower bound of 95% CI at least 84%) of images in the Iomervu group were rated as having adequate quality visualization by all readers (Table 29). Most technically inadequate image sets were attributed to poor technique used to acquire the examination.

Table 29. Visualization Quality in IOM-104A, Full Analysis Population

Reader	% of patients with adequate quality visualization (95% CI)

48,848-001A and -001B	Iomervu 400 mgI/mL (n=59)	Iopamidol 370 mgI/mL (n=58)
Reader 1	100 (94, 100)	98 (91, 100)
Reader 2	97 (88, 99)	95 (86, 98)
Reader 3	98 (91, 100)	100 (94, 100)
48,848-002A and -002B	**Iomervu 300 mgI/mL (n=59)**	**Ioversol 320 mgI/mL (n=61)**
Reader 4	100 (94, 100)	100 (94, 100)
Reader 5	100 (94, 100)	98 (91, 100)
Reader 6	93 (84, 97)	90 (80, 95)

Source: Integrated Summary of Effectiveness, Table Q
Abbreviations: n = number of patients dosed, CI = confidence interval

The results of the assessment of images in the re-read study using the full 5-point scale are presented below in Table 30. A single reader rated one patient's images in each of the Iomervu 300 mgI/mL and ioversol 320 mgI/mL groups as insufficient, otherwise all image sets were rated as fair, good, or excellent in keeping with the primary endpoint analysis. There were numerically more images rated as excellent for Iomervu 400 mgI/mL versus comparator for all readers and less images rated as excellent for Iomervu 300 mgI/mL versus comparator. This may be due to differences in concentration, with Iomervu 400 mgI/mL having a higher concentration than its comparator and Iomervu 300 mgI/mL having a lower concentration. The clinical impact of this finding is doubtful given the results of the primary analysis and the ability of providers to select a drug concentration appropriate to the patient and imaging procedure.

Table 30. Visualization Quality in IOM-104A as Rated on a 5-Point Scale, Efficacy Analysis Population

		48,848-001A and 48,848-001B		48,848-002A and 48,848-002B	
Reader[1]	Visualization Quality	Iomervu 400 mgI/mL	Iopamidol 370 mgI/mL	Iomervu 300 mgI/mL	Ioversol 320 mgI/mL
Readers 1 and 4	Number of patients	59	57	59	61
	Poor	0	0	0	0
	Insufficient	0	0	0	0
	Fair	11 (19%)	5 (9%)	5 (9%)	4 (7%)
	Good	45 (76%)	51 (90%)	27 (46%)	19 (31%)
	Excellent	3 (5%)	1 (2%)	27 (46%)	38 (62%)
Readers 2 and 5	Number of patients	57	55	59	60
	Poor	0	0	0	0
	Insufficient	0	0	0	0
	Fair	0	2 (4%)	1 (2%)	1 (2%)
	Good	4 (7%)	4 (7%)	21 (36%)	10 (17%)
	Excellent	53 (93%)	49 (89%)	37 (63%)	49 (82%)
Readers 3 and 6	Number of patients	58	58	56	56
	Poor	0	0	0	0
	Insufficient	0	0	1 (2%)	1 (2%)
	Fair	0	0	10 (18%)	8 (14%)

	Good	8 (14%)	11 (19%)	29 (52%)	22 (39%)
	Excellent	50 (86%)	47 (81%)	16 (29%)	25 (45%)

Source: IOM-104A study report, Table I

[1] Three readers independently assessed images for studies 48,848-001A and -001B and three different readers independently assessed images for studies 48,848-002A and -002B, comprising a total of six readers.

All three readers provided the same visualization score on the 2-point scale in 93% of patients in the efficacy analysis population for Iomervu 300 mgI/mL, 90% of patients for ioversol 320 mgI/mL, 97% of patients for Iomervu 400 mgI/mL, and 95% of patients for iopamidol 370 mgI/mL. Using the 5-point scale, three reader agreement was 27% for Iomervu 300 mgI/mL, 31% for ioversol 320 mgI/mL, 5% for Iomervu 400 mgI/mL, and 2% for iopamidol 370 mgI/mL. Inter-reader agreement appears similar between Iomervu and the comparators.

8.1.3. IOM-104C: Cerebral arteriography

Trial Design

IOM-104C was a prospective, blinded re-read study of two previously conducted prospective, multicenter, randomized, double-blind, active comparator-controlled studies with identical design enrolling adult patients undergoing cerebral arteriography. It was conducted in March 2004. The original imaging studies 48,848-004A and 48,848-004B were conducted from February 1996 to September 1996 at four and six different sites, respectively, all in the United States.

Adult patients referred for cerebral arteriography for diagnostic purposes, preoperative evaluation, or pre-therapeutic evaluation were included in the original phase 3 imaging studies. Exclusion criteria included patients scheduled for or likely to undergo emergency procedures, patients requiring general anesthesia, pregnant patients, patients with serum creatinine >2.5 mg/dL, patients with known sensitivity to iodine containing compounds, and patients with an acute cerebrovascular accident or hemorrhagic event within 48 hours prior to study entry. Certain predisposing risk factors for an adverse reaction from administration of iodinated contrast agents were to be recorded and considered when selecting patients. These included but were not limited to patients with allergic disorders, increased risk of thromboembolism, severe congestive heart failure, sickle cell disease, and diabetes.

In the original studies, patients were randomized to receive either Iomervu 300 mgI/mL or ioversol 320 mgI/mL. The investigator determined the volume per injection and number of injections at each region of interest, which varied according to clinical need. The total procedural dose was limited to the minimum volume required to achieve a diagnostic examination, and a maximum total iodine dose of 60 g was recommended. Vascular areas examined included the internal carotid artery, external carotid artery, common carotid artery, vertebral artery, and intracranial arteries. If multiple images were obtained from a single contrast injection, they were considered together as one image.

Other common design features across the IOM-104 re-read studies are described in Section 8.1.1.

Study Endpoints

A description of study endpoints that were identical across the IOM-104 re-read studies is provided in Section 8.1.1.

The quality of visualization on the 5-point scale for cerebral arteriography in IOM-104C was assessed with similar but varying definitions by vascular area, including the zero order arteries (defined as the common carotid, intracerebral internal carotid, or basilar), first order arteries (defined as the cervical internal and external carotids and the anterior, middle, and posterior cerebral), second order arteries (i.e., major branches of the external carotid, anterior communicating, posterior communicating), and third order or minor arteries. The grading scale for zero order and first order arteries was:

1 = Poor: Little to no opacification preventing any evaluation of vascular margins, plaque, aneurysm, thrombus, or occlusion
2 = Insufficient: Enough opacification versus background for the images to be barely adequate for the evaluation of margins, plaque, thrombus, or occlusion
3 = Fair: Opacification versus background sufficient for the clear evaluation of margins, plaque, aneurysm, thrombus, and occlusion
4 = Good: Complete opacification versus background, allowing rapid and easy evaluation of margins, plaque, aneurysm, thrombus, and occlusion
5 = Excellent: Complete opacification with full demonstration of intraluminal anatomy, down to third order branch arteries and expected minor collaterals, enabling full evaluation of margins, plaque, aneurysm, thrombus, and occlusion

Statistical Analysis Plan

A combined statistical analysis plan was submitted for the IOM-104 re-read studies, described in Section 8.1.1.

Protocol Amendments

No amendments were made to the protocol for the IOM-104C re-read study.

Two amendments were made to the protocols for the original imaging studies 48,848-004A and -004B dated January 23, 1996, and March 22, 1996. Notable amendments consisted of the following:

- The number of clinical sites was changed from six to seven centers to two or more.
- The maximum patient enrollment at each clinical site was changed from 14 to 30 patients.
- The requirements for study participation and postprocedural evaluations was changed from 72 hours to 24 hours after cerebral arteriography.

8.1.4. Study Results

Compliance with Good Clinical Practices

The Applicant indicated that the study was conducted in compliance with GCP and with oversight from the local IRB.

Financial Disclosure

No relevant financial disclosures were reported by the Applicant for the listed clinical investigators.

Patient Disposition

A total of 120 patients were included and randomized to receive either Iomervu or ioversol in the two original phase 3 imaging studies. All randomized patients were dosed. One patient who received ioversol in study 48,848-004A was not included in IOM-104C because the images for this patient could not be located. Therefore, a total of 119 patients received Iomervu or ioversol and were included in the full analysis population of IOM-104C. A total of 61 patients received Iomervu 300 mgI/mL and 58 patients received ioversol 320 mgI/mL.

One (2%) patient who was administered Iomervu discontinued after completion of protocol-defined imaging but prior to study completion due to “surgery within 72 hours”. One (2%) patient who was administered ioversol discontinued due to “administration of non-study contrast agent”.

Protocol Violations/Deviations

A total of eight patients in IOM-104C, five of whom received Iomervu and three of whom received ioversol, did not meet selection criteria.

In study 48,848-004A, three patients who received Iomervu and one patient who received ioversol were not inpatients. One patient who received ioversol had received another non-study contrast agent within 48 hours prior to the study.

In study 48,848-004B, one patient who received Iomervu and one patient who received ioversol had received another non-study contrast agent within 48 hours prior to the study. One patient who received Iomervu entered the study at 17 years of age.

Several minor protocol deviations were documented for patients that received either Iomervu or ioversol in both studies 48,848-004A and -004B, but these were considered unlikely to have had a significant impact on the study results.

Demographic Characteristics

The full analysis population is generally representative of the U.S. population for which cerebral arteriography would be indicated (Table 31). Demographics were similar for patients randomized to receive either Iomervu or ioversol. The proportions of patients above and below age 65 years were generally reflective of the age ranges in which the diseases and conditions that require cerebral arteriography manifest. Patients enrolled were primarily white patients, however drug efficacy or safety is not expected to differ in patients of other races.

Table 31. Demographic Characteristics of Patients in IOM-104C, Safety Population

	48,848-004A and 48,848-004B	
Demographic Parameters	**Iomervu 300 mgI/mL (n=61)**	**Ioversol 320 mgI/mL (n=58)**
Age, years		
Mean (SD)	52 (16)	53 (16)
Median	51	51
Min, max	17, 86	25, 87
Age group, n (%)		
18 to 64 years	47 (77)	42 (73)
≥ 65 years	14 (23)	16 (27)
≥ 75 years	6 (10)	6 (10)
Sex, n (%)		
Male	35 (57)	31 (53)
Female	26 (43)	27 (47)
Race, n (%)[1]		
White	38 (62)	43 (74)
Black or African American	9 (15)	2 (3)
Hispanic	12 (20)	12 (21)
Asian	2 (3)	1 (2)
Other or unknown	0	0

Source: IOM-104C study report, Table E
Abbreviations: n = number of patients, SD = standard deviation
[1] Data on ethnicity were not collected separately from race.

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

Analysis of other baseline characteristics is not necessary given the goal of assessing contrast visualization and the enrollment of patients who received a single type of imaging procedure.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The study drug was administered by study personnel at clinical sites, and therefore drug compliance is not applicable.

Efficacy Results

The primary objective of IOM-104C was to demonstrate non-inferiority of Iomervu to the comparator in the proportion of patients with adequate quality of opacification and anatomic visualization using a 10% non-inferiority margin. For both original imaging studies 48,848-004A and 48,848-004B, 100% (lower bound of 95% CI 94%) of image sets in the Iomervu and comparator groups were rated as having adequate quality visualization, defined as fair, good, or excellent (score of 3-5) on a 5 point scale, by all readers (Table 32). The upper limits of the 2-sided 95% confidence intervals for the difference in the proportion of patients with adequate quality visualization were within the 10% non-inferiority margin for all readers, and the proportion of patients with adequate quality visualization after receiving Iomervu was considered acceptable.

Table 32. Cerebral Arteriography Visualization Score Results in IOM-104C, Efficacy Analysis Population

Reader	% of patients with adequate quality visualization (95% CI)[1]		Difference (95% CI)[2]
48,848-004A and -004B	**Iomervu 300 mgI/mL (n=61)**	**Ioversol 320 mgI/mL (n=58)**	
Reader 1	100 (94, 100)	100 (94, 100)	0 (ND)
Reader 2	100 (94, 100)	100 (94, 100)	0 (ND)
Reader 3	100 (94, 100)	100 (94, 100)	0 (ND)

Source: IOM-104C study report, Table F and Integrated Summary of Effectiveness, Table X
Abbreviations: n = number of patients dosed, CI = confidence interval, ND = not defined
[1] Adequate quality visualization = rated fair, good, or excellent on a 5-point scale
[2] Proportion (%) of patients with visualization rated as adequate in the ioversol group minus Iomervu group

Data Quality and Integrity

No significant data quality issues were identified.

Dose/Dose Response

The concentrations and dose of Iomervu chosen for the original phase 3 imaging studies were based on dosage recommendations of the comparator drugs as well as input from the investigators. The recommended total iodine dose was not to exceed 60 g for cerebral arteriography in adult patients, which is about 200 mL of Iomervu 300 mgI/mL.

The mean total volume of Iomervu 300 mgI/mL administered was 96 ± 42 mL (maximum 198 mL) and the mean total iodine dose administered was 29 ± 13 g (maximum 59 g) (Table 33). Exposure to Iomervu 300 mgI/mL was within the maximum recommended total iodine dose of 60 g.

The proportion of patients who were dosed at each injection site was similar between Iomervu and the active comparator.

Table 33. Volume and Total Iodine Dose Administered in IOM-104C, Safety Population

	48,848-004A and 48,848-004B	
Demographic Parameters	**Iomervu 300 mgI/mL (n=61)**	**Ioversol 320 mgI/mL (n=58)**
Contrast volume, mL		
Mean (SD)	96 (42)	92 (48)
Median	96	94
Min, max	16, 198	10, 242
Total iodine dose administered, grams		
Mean (SD)	29 (13)	29 (15)
Median	29	30
Min, max	5, 59	3, 77
Sites of injections[1], n (% of patients)		
Aortic arch	40 (66)	38 (66)
Common carotid artery	35 (57)	37 (64)
Vertebral artery	33 (54)	32 (55)
Internal carotid artery	31 (51)	29 (50)
Cranial	18 (30)	17 (29)
Other	14 (23)	14 (24)
External carotid artery	13 (21)	11 (19)

Source: IOM-104C study report, Table E; 48-848-004A and -004B study reports, Table 5
Abbreviations: n = number of patients, SD = standard deviation
[1] Patients may have more than one site of injection.

Additional Analyses Conducted on the Individual Trial

A post-hoc analysis of the full analysis population for the inclusion of technically inadequate images was not conducted for IOM-104C and was not necessary, as all image sets for both Iomervu and comparator groups were rated as technically adequate by all readers.

The results of the assessment of images in the re-read study using the full 5-point scale are presented below in Table 34. Two of the three readers evaluated visualization as excellent in all patients or all but one patient for both Iomervu and comparator.

Table 34. Visualization Quality in IOM-104C as Rated on a 5-Point Scale, Efficacy Analysis Population

		48,848-004A and 48,848-004B	
Reader	**Visualization Quality**	**Iomervu 300 mgI/mL**	**Ioversol 320 mgI/mL**
Reader 1	Number of patients	61	58

	Poor	0	0
	Insufficient	0	0
	Fair	3 (5%)	2 (3%)
	Good	27 (44%)	18 (31%)
	Excellent	31 (51%)	38 (66%)
Reader 2	Number of patients	61	58
	Poor	0	0
	Insufficient	0	0
	Fair	0	0
	Good	1 (2%)	0
	Excellent	60 (98%)	58 (100%)
Reader 3	Number of patients	61	58
	Poor	0	0
	Insufficient	0	0
	Fair	0	0
	Good	0	0
	Excellent	61 (100%)	58 (100%)

Source: IOM-104C study report, Table H

All three readers provided the same visualization score on the 2-point scale in 100% of patients in the efficacy analysis population for Iomervu 300 mgI/mL and ioversol 320 mgI/mL. Three reader agreement on the 5-point scale was 51% for Iomervu and 66% for the comparator.

8.1.5. IOM-104D: Visceral and peripheral arteriography

Trial Design

IOM-104D was a prospective, blinded re-read study of two previously conducted prospective, multicenter, randomized, double-blind, active comparator-controlled studies with identical design enrolling adult patients undergoing visceral and peripheral arteriography. It was conducted in April 2004. The original imaging studies 48,848-005A and 48,848-005B were conducted from August 1996 to June 1997 at five different sites each, all in the United States.

Adult patients referred for visceral and peripheral arteriography for diagnostic purposes, preoperative evaluation, or pre-therapeutic evaluation were included in the original phase 3 imaging studies. Exclusion criteria included patients scheduled for or likely to undergo emergency procedures, patients requiring general anesthesia, pregnant patients, patients with serum creatinine >2.5 mg/dL, patients with known sensitivity to iodine containing compounds, and patients requiring a re-examination with the study drug within 24 hours after visceral or peripheral arteriography or within 72 hours after renal arteriography. Certain predisposing risk factors for an adverse reaction from administration of iodinated contrast agents were to be recorded and considered when selecting patients. These included but were not limited to patients with allergic disorders, increased risk of thromboembolism, severe congestive heart failure, sickle cell disease, and diabetes.

In the original studies, patients were randomized to receive either Iomervu 300 mgI/mL or iopamidol 300 mgI/mL. The investigator determined the volume per injection and number of injections at each region of interest which varied according to clinical need. The total procedural dose was limited to the minimum volume required to achieve a diagnostic examination and a maximum total iodine dose of 60 g was recommended. Visceral arteriography included the arterial system of the abdomen and thorax, excluding cardiac examination. Renal arteriography included images of either kidney. Peripheral arteriography included the entire arterial system from the aortic bifurcation to the feet as well as upper extremities. If multiple images were obtained from a single contrast injection, they were considered together as one image.

Other common design features across the IOM-104 re-read studies are described in Section 8.1.1.

Study Endpoints

A description of study endpoints that were identical across the IOM-104 re-read studies is provided in Section 8.1.1.

The quality of visualization on the 5-point scale for visceral and peripheral arteriography in IOM-104D was assessed with similar but varying definitions by vascular area, including the zero order arteries (the aorta for visceral and common iliac artery for peripheral studies), first order arteries (i.e., celiac, superior mesenteric, renal, internal iliac, external iliac, and common femoral), second order arteries (i.e., hepatic, gastric, renal lobar, superficial femoral), and third order or other arteries. The grading scale for zero order and first order arteries was:

1 = Poor: Little to no opacification preventing any evaluation of vascular margins, plaque, aneurysm, thrombus, or occlusion
2 = Insufficient: Enough opacification versus background for the images to be barely adequate for the evaluation of margins, plaque, aneurysm, thrombus, or occlusion
3 = Fair: Opacification versus background sufficient for the clear evaluation of margins, plaque, aneurysm, thrombus, and occlusion
4 = Good: Complete opacification versus background allowing rapid and easy evaluation of margins, plaque, aneurysm, thrombus, and occlusion
5 = Excellent: Complete opacification with full demonstration of intraluminal anatomy, down to third order branch arteries and expected minor collaterals, enabling full evaluation of margins, plaque, aneurysm, thrombus, and occlusion

Statistical Analysis Plan

A combined statistical analysis plan was submitted for the IOM-104 re-read studies, described in Section 8.1.1.

Protocol Amendments

No amendments were made to the protocol for the IOM-104D re-read study.

Two amendments were made to the protocols for the original imaging studies 48,848-005A and -005B dated September 5, 1996, and September 26, 1996. One notable change was an increase in number of clinical sites from one to two centers to five to six centers.

8.1.6. Study Results

Compliance with Good Clinical Practices

The Applicant indicated that the study was conducted in compliance with GCP and with oversight from the local IRB.

Financial Disclosure

No relevant financial disclosures were reported by the Applicant for the listed clinical investigators.

Patient Disposition

A total of 125 patients were included and randomized to receive either Iomervu or iopamidol in the two original phase 3 imaging studies.

Three patients randomized to receive Iomervu were not dosed due to “arteriogram canceled”, “angiogram of renal artery or aorta will not be obtained”, and “contrast agent required dilution”. One patient randomized to receive iopamidol was not dosed due to “cut film was not available at this site”.

A total of 121 patients received Iomervu or iopamidol. Two patients who received Iomervu in studies 48,848-005A and -005B were not included in the blinded read study because the images for these patients from the original study could not be located. Therefore, a total of 119 patients who received Iomervu or iopamidol were included in the full analysis population of the IOM-104D re-read study. A total of 60 patients received Iomervu 300 mgI/mL and 59 patients received iopamidol 300 mgI/mL.

Two (3%) patients who were administered Iomervu discontinued after completion of protocol-defined imaging but prior to study completion due to “another angiographic procedure was performed within 24 hours” and “intra-arterial (intra-operative) angiogram performed during vascular surgery”. One (2%) patient who was administered iopamidol discontinued due to “repeat angiography performed within 24 hours”.

Protocol Violations/Deviations

Several minor protocol deviations were documented for patients that received either Iomervu or iopamidol in both studies 48,848-005A and -005B, but these were considered unlikely to have had a significant impact on the study results.

Demographic Characteristics

The full analysis population is generally representative of the U.S. population for which visceral and peripheral arteriography would be indicated (Table 35). Demographics were similar for patients randomized to receive either Iomervu or iopamidol. The proportions of patients above and below age 65 years were generally reflective of the age ranges in which the diseases and conditions that require visceral or peripheral arteriography manifest. Patients enrolled were primarily white patients, however drug efficacy or safety is not expected to differ in patients of other races.

Table 35. Demographic Characteristics of Patients in IOM-104D, Safety Population

	48,848-005A and 48,848-005B	
Demographic Parameters	**Iomervu 300 mgI/mL (n=60)**	**Iopamidol 300 mgI/mL (n=59)**
Age, years		
Mean (SD)	67 (14)	66 (14)
Median	70	70
Min, max	29, 95	19, 85
Age group, n (%)		
18 to 64 years	23 (38)	22 (37)
≥ 65 years	37 (62)	37 (63)
≥ 75 years	21 (35)	20 (34)
Sex, n (%)		
Male	36 (60)	38 (64)
Female	24 (40)	21 (36)
Race, n (%)[1]		
White	55 (92)	57 (97)
Black or African American	4 (7)	2 (3)
Hispanic	1 (1)	0
Asian	0	0
Other or unknown	0	0

Source: IOM-104D study report, Table E
Abbreviations: n = number of patients, SD = standard deviation
[1] Data on ethnicity were not collected separately from race.

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

Analysis of other baseline characteristics is not necessary given the goal of assessing contrast visualization and the enrollment of patients who received a single type of imaging procedure.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The study drug was administered by study personnel at clinical sites, and therefore drug compliance is not applicable.

Efficacy Results

The primary objective of IOM-104D was to demonstrate non-inferiority of Iomervu to the comparator in the proportion of patients with adequate quality of opacification and anatomic visualization using a 10% non-inferiority margin. For both original imaging studies, 48,848-005A and 48,848-005B, 100% (lower bound 95% CI 94%) of image sets in the Iomervu and comparator groups were rated as having adequate quality visualization, defined as fair, good, or excellent (score of 3-5) on a 5 point scale, by all readers (Table 36). The upper limits of the 2-sided 95% confidence intervals for the difference in the proportion of patients with adequate quality visualization were within the 10% non-inferiority margin for all readers, and the proportion of patients with adequate quality visualization after receiving Iomervu was considered acceptable.

Table 36. Visceral and Peripheral Arteriography Visualization Score Results in IOM-104D, Efficacy Analysis Population

Reader	Patients with adequate quality visualization[1]				Difference (95% CI)[2]
48,848-005A and -005B	Iomervu 300 mgI/mL		Iopamidol 300 mgI/mL		
	n (%)	95% CI	n (%)	95% CI	
Reader 1	59 (100)	(94, 100)	59 (100)	(94, 100)	0 (ND)
Reader 2	59 (100)	(94, 100)	59 (100)	(94, 100)	0 (ND)
Reader 3	59 (100)	(94, 100)	59 (100)	(94, 100)	0 (ND)

Source: IOM-104D study report, Table F and Integrated Summary of Effectiveness, Table GG
Abbreviations: n = number of patients dosed, CI = confidence interval, ND = not defined
[1] Adequate quality visualization = rated fair, good, or excellent on a 5-point scale
[2] Proportion (%) of patients with visualization rated as adequate in the iopamidol group minus Iomervu group

Data Quality and Integrity

No significant data quality issues were identified.

Dose/Dose Response

The concentrations and dose of Iomervu chosen for the original imaging studies were based on dosage recommendations of the comparator drugs as well as input from the investigators. The recommended total iodine dose was not to exceed 60 g for visceral and peripheral arteriography in adult patients, which is about 200 mL of Iomervu 300 mgI/mL.

The mean total volume of Iomervu 300 mgI/mL administered was 161 ± 66 mL (maximum 300 mL) and the mean total iodine dose administered was 48 ± 20 g (maximum 90 g) (Table 37). Approximately 25% of patients exposed to Iomervu 300 mgI/mL received doses that exceeded the maximum recommended total iodine dose of 60 g.

There was less representation of peripheral arteriography procedures than visceral arteriography, in part because most patients in the peripheral arteriography group also received at least an aortic injection. The number of patients receiving peripheral arteriography was considered adequate for evaluation, and visualization quality or safety is not expected to be different with peripheral arteriography.

Table 37. Volume and Total Iodine Dose Administered in IOM-104D, Safety Population

	48,848-005A and 48,848-005B	
Demographic Parameters	**Iomervu 300 mgI/mL (n=60)**	**Iopamidol 300 mgI/mL (n=59)**
Contrast volume, mL		
Mean (SD)	161 (66)	159 (53)
Median	172	159
Min, max	47, 300	55, 253
Total iodine dose administered, grams		
Mean (SD)	48 (20)	48 (16)
Median	50	48
Min, max	14, 90	17, 76
Sites of injections[1], n (% of patients)		
Visceral arteries	58 (97)	57 (97)
Renal artery	19 (32)	17 (29)
Peripheral arteries	22 (37)	21 (36)

Source: IOM-104D study report, Table E; 48-848-005A and -005B study reports, Table D
Abbreviations: n = number of patients, SD = standard deviation
[1] Patients may have more than one site of injection

Additional Analyses Conducted on the Individual Trial

In a post-hoc analysis of the full analysis population, where technically inadequate exams were included in the primary analysis of efficacy by assigning them a score of inadequate, 98% (lower bound of 95% CI 91%) of images in the Iomervu group were rated as having adequate quality visualization by all readers (Table 38). The technically inadequate image set for one patient in the Iomervu group was attributed to poor technique used to acquire the examination, poor copy technique, and/or bad copy of the films. No technically inadequate images were reported for iopamidol.

Table 38. Visualization Quality in IOM-104D, Full Analysis Population

Reader	**% of patients with adequate quality visualization (95% CI)**

48,848-005A and -005B	Iomervu 300 mgI/mL (n=60)	Iopamidol 300 mgI/mL (n=59)
Reader 1	98 (91, 100)	100 (94, 100)
Reader 2	98 (91, 100)	100 (94, 100)
Reader 3	98 (91, 100)	100 (94, 100)

Source: Integrated Summary of Effectiveness, Table HH
Abbreviations: n = number of patients dosed, CI = confidence interval

The results of the assessment of images in the re-read study using the full 5-point scale are presented below in Table 39. Visualization ratings were similar between Iomervu and the active comparator.

Table 39. Visualization Quality in IOM-104D as Rated on a 5-Point Scale, Efficacy Analysis Population

		48,848-005A and 48,848-005B	
Reader	Visualization Quality	Iomervu 300 mgI/mL	Iopamidol 300 mgI/mL
Reader 1	Number of patients	59	59
	Poor	0	0
	Insufficient	0	0
	Fair	0	0
	Good	0	1 (2%)
	Excellent	59 (100%)	58 (98%)
Reader 2	Number of patients	59	59
	Poor	0	0
	Insufficient	0	0
	Fair	0	0
	Good	5 (8%)	1 (2%)
	Excellent	54 (92%)	58 (100%)
Reader 3	Number of patients	59	59
	Poor	0	0
	Insufficient	0	0
	Fair	1 (2%)	0
	Good	14 (24%)	15 (25%)
	Excellent	44 (75%)	44 (75%)

Source: IOM-104D study report, Table H

All three readers provided the same visualization score on the 2-point scale in 100% of patients in the efficacy analysis population for Iomervu 300 mgI/mL and iopamidol 300 mgI/mL. Three reader agreement on the 5-point scale was 73% for Iomervu and 76% for the comparator.

8.1.7. Intra-arterial digital subtraction angiography (DSA) studies

Studies that support the evidence of efficacy of intra-arterial digital subtraction angiography for cerebral, visceral, and peripheral arteriography and aortography are reviewed together here.

PT-28: Cerebral digital subtraction angiography

PT-28 was a prospective, randomized, double-blind, active comparator-controlled study of 92 adult patients undergoing cerebral digital subtraction angiography for diagnostic or pre-operative indications, conducted at a single center in Italy. Patients were randomized to receive either Iomervu 150 mgI/mL or iopamidol 150 mgI/mL.

Images were independently evaluated by two readers blinded to the study drug. Technical adequacy was assessed, and technically inadequate images were excluded from the analysis. Two ratings of technically inadequate were reported for Iomervu and 0 for iopamidol. Quality of visualization was assessed on a 5-point scale (1 = insufficient visualization, 2 = sufficient visualization, 3 = good visualization, 4 = excellent visualization, E = excessive opacification) for each contrast injection. Images assessed as excessively visualized were assigned a score of 2 (sufficient visualization) for analysis. Results were provided as pooled for the two readers.

A total of 47 patients received Iomervu and 45 patients received iopamidol. The cerebral arteries visualized and the number of patients that received Iomervu at each site were the common carotid artery (n=8), vertebral arteries (n=19), external carotid artery (n=1), internal carotid artery (n=44), and upper aortic arch (n=1). The total volumes of Iomervu administered ranged between 4-90 mL, and the injection rates ranged between 2-19 mL/sec. For the arteries visualized by only one patient each, the external carotid artery and upper aortic arch, the volumes and injection rates were similar to and within the range that was administered for other arteries. The proportion of visualization scores of good or excellent (scores of 3 or 4) was 99% (427/432) for Iomervu and 99% (452/458) for iopamidol.

PT-22: Visceral and peripheral digital subtraction angiography

PT-22 was a prospective, randomized, double-blind, active comparator-controlled study of 100 adult patients undergoing visceral and/or peripheral digital subtraction angiography for diagnostic or pre-operative indications, conducted at a single center in Italy. It was identical in design to PT-28 above.

A total of 50 patients received Iomervu and 50 patients received iopamidol. Nine ratings of technically inadequate were reported for Iomervu and 12 for iopamidol. The visceral and peripheral arteries visualized and the number of patients who received Iomervu at each site were the abdominal aorta and its major branches (n=49), iliac-femoral artery (n=50), and femoral and popliteal arteries (n=49). The total volumes administered across the arteries visualized ranged between 20-110 mL, and the injection rates ranged between 10-18 mL/sec. The proportion of visualization scores of good or excellent (scores of 3 or 4) was 91% (454/501) for Iomervu and 82% (412/500) for iopamidol.

PT-23: Visceral digital subtraction angiography

PT-23 was a prospective, randomized, double-blind, active comparator-controlled study of 40 adult patients undergoing visceral digital subtraction angiography for diagnostic or pre-

operative indications, conducted at a single center in Italy. It was identical in design to PT-28 above.

A total of 20 patients received Iomervu and 20 patients received iopamidol. Seven ratings of technically inadequate were reported for Iomervu and 14 for iopamidol. The visceral arteries visualized and the number of patients that received Iomervu at each site were the abdominal aorta (n=20) and renal artery (n=10). The total volumes administered across the arteries visualized ranged between 23-150 mL, and the injection rates ranged between 3-25 mL/sec. The proportion of visualization scores of good or excellent (scores of 3 or 4) was 40% (53/133) for Iomervu and 42% (43/102) for iopamidol. An additional 53% and 54% of scores were sufficient (score of 2) for Iomervu and iopamidol, respectively.

(b) (4)

8.1.9. IOM-104E: CT of the head and body

Trial Design

IOM-104E was a prospective, blinded re-read study of four previously conducted prospective, multicenter, randomized, double-blind, active comparator studies with identical design enrolling adult patients undergoing head and body CT. It was conducted from March to May 2004. The original imaging studies were conducted from August 1996 to July 1997, all in the United States. 48,848-007A and 48,848-008A were both conducted at the same five sites. 48,848-007B and 48,848-008B were both conducted at five other sites that were the same except one from each study.

Adult patients with a documented history or diagnosis that necessitated CT of the brain, head and neck, chest, abdomen, and/or pelvis for diagnostic purposes, preoperative evaluation, or postoperative evaluation, were included in the original imaging studies. Exclusion criteria included patients scheduled for or likely to undergo emergency procedures, patients requiring general anesthesia, pregnant patients, patients with serum creatinine >2.5 mg/dL, and patients with known sensitivity to iodine containing compounds. Certain predisposing risk factors for an adverse reaction from administration of iodinated contrast agents were to be recorded and

considered when selecting patients. These included but were not limited to patients with allergic disorders, increased risk of thromboembolism, severe congestive heart failure, sickle cell disease, and diabetes.

In the original studies, patients were randomized to receive either Iomervu 400 mgI/mL or iopamidol 370 mgI/mL in studies 48,848-007A and -007B, while in studies -008A and -008B, patients were randomized to receive either Iomervu 250 mgI/mL or iopamidol 250 mgI/mL. The concentrations of Iomervu were chosen to bracket the 350 mgI/mL and 300 mgI/mL concentrations. The investigator determined the volume per injection at each anatomical area of interest, which varied according to clinical need. The total procedural dose was limited to the minimum volume required to achieve a diagnostic examination, and a maximum total iodine dose of 60 g was recommended. Most images were acquired by helical CT. The anatomical areas examined included the head, neck, thorax, abdomen, and pelvis.

Source study enrollment was stratified by planned total iodine dose in two categories, 30 to 44 g iodine and 45 to 60 g iodine. Enrollment was controlled such that for every two patients entering the low dose stratum, one patient was to be enrolled into the high dose stratum and similarly for every two high dose patients, one was to be enrolled into the low dose group.

Other common design features across the IOM-104 re-read studies are described in Section 8.1.1.

Study Endpoints

A description of study endpoints that were identical across the IOM-104 re-read studies is provided in Section 8.1.1.

The quality of visualization in IOM-104E was assessed using separate, but related, 5-point scales for each anatomic region including brain, head and neck, chest, abdomen, and pelvis. As an example, the grading scale for pelvic CT was:

1 = Poor:
- No evidence of any significant vascular enhancement leading to:
  - Inability to distinguish the major (common, external, and internal) iliac vessels from lymph nodes and organs
  - Inability to evaluate the lumens of the major iliac vessels
- Contrast-related artifacts prevented any evaluation

2 = Insufficient:
- Some vascular enhancement was present but most images demonstrated:
  - Inadequate distinction of the major iliac vessels from lymph nodes and organs
  - Inadequate ability to evaluate lumens of the major iliac vessels
- Contrast-related artifacts prevented adequate evaluation

3 = Fair:
- Vascular enhancement was present but most images showed no more than

adequate:
    - Distinction of the major iliac vessels from lymph nodes and organs
    - Evaluation of the lumens of major iliac vessels
- Contrast-related artifacts affected image quality enough to make evaluation difficult but did not prevent it

4 = Good:
- Vascular enhancement was present to a level that allowed on most images, proper, though not easy or rapid:
    - Distinction of the major iliac vessels from lymph nodes and organs
    - Evaluation of the lumens of major iliac vessels
- Contrast-related artifacts had no or little effect on image quality and image evaluation

5 = Excellent:
- Marked vascular enhancement leading to clear and easy distinction of the major iliac vessels from lymph nodes and organs and evaluation of lumens of major iliac vessels
- Contrast-related artifacts either were not present or they had no significant effect on image quality or image evaluation

Statistical Analysis Plan

A combined statistical analysis plan was submitted for the IOM-104 re-read studies, described in Section 8.1.1.

Protocol Amendments

No amendments were made to the protocol for the IOM-104E re-read study.

One amendment was made to the protocols for the original imaging studies 48,848-007A, -007B, -008A, and -008B, dated June 5, 1996. Notable changes consisted of the following:
- The number of clinical sites was changed from two to four centers to two to six centers.
- The requirement for each investigator to enroll a minimum of 14 complete and evaluable patients was changed to a minimum of 6 complete and evaluable patients.

8.1.10. Study Results

Compliance with Good Clinical Practices

The Applicant indicated that the study was conducted in compliance with GCP and with oversight from the local IRB.

Financial Disclosure

No relevant financial disclosures were reported by the Applicant for the listed clinical investigators.

Patient Disposition

A total of 233 patients were included and randomized to receive either Iomervu or iopamidol in the four original imaging studies (Table 40).

Two patients randomized to receive Iomervu were not dosed due to "total bilirubin 3.4 mg/dL" and "iodine allergy". One patient randomized to receive iopamidol was not dosed due to "need to have a nuclear medicine study after body CT".

A total of 118 patients received Iomervu and 112 patients received iopamidol and were included in the full analysis population of the IOM-104E re-read study. Iomervu 400 mgI/mL and 250 mgI/mL were administered in 59 patients each. A total of 55 and 57 patients received iopamidol 370 mgI/mL and 250 mgI/mL, respectively.

Four (3%) patients who were administered Iomervu discontinued after completion of protocol-defined imaging but prior to study completion due to withdrawal of consent, withdrawal of consent for 24-hour ECG follow-up, refusal of blood draw, and loss to follow-up. Two (2%) patients who were administered iopamidol discontinued due to withdrawal of consent and loss to follow-up.

Table 40. Patient Disposition in IOM-104E

	48,848-007A and 48,848-007B		48,848-008A and 48,848-008B	
Disposition	**Iomervu 400 mgI/mL**	**Iopamidol 370 mgI/mL**	**Iomervu 250 mgI/mL**	**Iopamidol 250 mgI/mL**
Patients randomized, n (%)	61 (100)	55 (100)	59 (100)	58 (100)
Patients not dosed, n (%)	2 (3)	0	0	1 (2)
Patients dosed, n (%)	59 (97)	55 (100)	59 (100)	57 (98)
Patients discontinued, n (%)	1 (2)	1 (2)	3 (5)	1 (2)

Source: Modified from 48-848-007A, -007B, -008A, and -008B study reports: Table 2.1, Table 2.2, and Table 2.3
Abbreviations: n = number of patients

Protocol Violations/Deviations

In study 48,848-007A, two patients randomized to receive iopamidol were randomized to the low-dose group (30-44 g) but received a dose of ≥45 g iodine.

In study 48,848-007B, one investigator applied a different interpretation of the scoring for diagnostic adequacy than planned in the protocol. Scoring was based on how well this investigator perceived the study agent "enhanced" images in comparison to what was seen as "unenhanced". This protocol deviation was applied to all patients at that site, and these deviations were not listed individually in the clinical study report. Note that this deviation does

not impact the IOM-104E re-read results.

Also in study 48,848-007B, two patients entered the study although they did not meet selection criteria. One patient randomized to receive Iomervu did not have a pregnancy test at the time of screening and one patient randomized to receive iopamidol had severe liver dysfunction (patient's baseline bilirubin was 4.1 mg/dL) identified by laboratory results received after study drug administration.

In study 48,848-008A, one patient entered the study although they did not meet selection criteria. This patient, randomized to receive Iomervu, received another investigational drug within 30 days prior to entering the study.

In study 48,848-008B, one investigator applied a different interpretation of the scoring for diagnostic adequacy for all patients at that site than planned in the protocol, as for study -007B above. Two patients randomized to receive iopamidol entered the study although they did not meet selection criteria. These patients had received other intravascular, oral, or rectal contrast agents prior to the study.

Several minor protocol deviations were documented for patients that received either Iomervu or iopamidol in studies 48,848-007A, -007B, -008A, and -008B, but these were considered unlikely to have had a significant impact on the study results.

Demographic Characteristics

The full analysis population is generally representative of the U.S. population for which CT head and body would be indicated (Table 41). The proportion of female patients was numerically higher in the Iomervu groups than the iopamidol groups, but as will be seen, the primary endpoint result was similar between the drugs. Demographics were otherwise similar for patients randomized to receive either Iomervu or iopamidol. The proportions of patients above and below age 65 years were generally reflective of the age ranges in which the diseases and conditions that require CT head and body manifest. Patients enrolled were primarily white patients, however drug efficacy or safety is not expected to differ in patients of other races.

Table 41. Demographic Characteristics of Patients in IOM-104E, Safety Population

	48,848-007A and 48,848-007B		48,848-008A and 48,848-008B	
Demographic Parameters	**Iomervu 400 mgI/mL (n=59)**	**Iopamidol 370 mgI/mL (n=55)**	**Iomervu 250 mgI/mL (n=59)**	**Iopamidol 250 mgI/mL (n=57)**
Age, years				
Mean (SD)	55 (15)	56 (13)	54 (14)	57 (13)
Median	57	58	54	58
Min, max	19, 79	27, 79	25, 80	21, 82

Age group, n (%)				
18 to 64 years	39 (66)	38 (69)	44 (75)	36 (63)
≥ 65 years	20 (34)	17 (31)	15 (25)	21 (37)
≥ 75 years	2 (3)	2 (4)	5 (8)	4 (7)
Sex, n (%)				
Male	22 (37)	31 (56)	26 (44)	34 (60)
Female	37 (63)	24 (44)	33 (56)	23 (40)
Race, n (%)[1]				
White	46 (78)	46 (83)	46 (78)	46 (80)
Black or African American	11 (19)	7 (13)	8 (13)	7 (12)
Hispanic	2 (3)	1 (2)	3 (5)	2 (4)
Asian	0	0	1 (2)	2 (4)
Other or unknown	0	1 (2)	1 (2)	0

Source: IOM-104E study report, Table F
Abbreviations: n = number of patients, SD = standard deviation
[1] Data on ethnicity were not collected separately from race.

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

Analysis of other baseline characteristics is not necessary given the goal of assessing contrast visualization and the enrollment of patients who received a single type of imaging procedure.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The study drug was administered by study personnel at clinical sites, and therefore drug compliance is not applicable.

Efficacy Results

The primary objective of IOM-104E was to demonstrate non-inferiority of Iomervu to the comparator in the proportion of patients with adequate quality of opacification and anatomic visualization using a 10% non-inferiority margin. For all original imaging studies (48,848-007A and -007B combined; -008A and -008B combined), at least 98% (lower bound of 95% CI at least 91%) of image sets in the Iomervu and comparator groups were rated as having adequate quality visualization, defined as fair, good, or excellent (score of 3-5) on a 5 point scale, by all readers (Table 42). The upper limits of the 2-sided 95% confidence intervals for the difference in the proportion of patients with adequate quality visualization were within the 10% non-inferiority margin for all readers, and the proportion of patients with adequate quality visualization after receiving Iomervu was considered acceptable.

Table 42. CT Head and Body Visualization Score Results in IOM-104E, Efficacy Analysis Population

Reader	% of patients with adequate quality visualization[1]	Difference (95% CI)[2]

48,848-007A and -007B	**Iomervu 400 mgI/mL (n=59)**	**Iopamidol 370 mgI/mL (n=55)**	
Reader 1	98 (91, 100)	100 (93, 100)	1.7 (-1.6, 5.0)
Reader 2	100 (94, 100)	100 (93, 100)	0 (ND)
Reader 3	100 (94, 100)	100 (93, 100)	0 (ND)
48,848-008A and -008B	**Iomervu 250 mgI/mL (n=59)**	**Iopamidol 250 mgI/mL (n=57)**	
Reader 4	100 (94, 100)	100 (94, 100)	0 (ND)
Reader 5	98 (91, 100)	100 (94, 100)	1.7 (-1.6, 5.0)
Reader 6	98 (91, 100)	100 (93, 100)	1.7 (-1.6, 5.0)

Source: IOM-104E study report, Table G and Integrated Summary of Effectiveness, Table H
Abbreviations: n = number of patients dosed, CI = confidence interval, ND = not defined
[1] Adequate quality visualization = rated fair, good, or excellent on a 5-point scale
[2] Proportion (%) of patients with visualization rated as adequate in the iopamidol group minus Iomervu group

Data Quality and Integrity

No significant data quality issues were identified.

Dose/Dose Response

The concentrations and dose of Iomervu chosen for the original imaging studies were based on dosage recommendations of the comparator drugs as well as input from the investigators. The recommended total iodine dose was not to exceed 60 g for head and body CT in adult patients, which is about 150 mL of Iomervu 400 mgI/mL and 240 mL of Iomervu 250 mgI/mL.

The mean total volume of Iomervu 400 mgI/mL administered was 112 ± 18 mL (maximum 150 mL) and the mean total iodine dose administered was 45 ± 7 g (maximum 60 g) (Table 43). The mean total volume of Iomervu 250 mgI/mL administered was 145 ± 20 mL (maximum 191 mL) and the mean total iodine dose administered was 36 ± 5 g (maximum 48 g). Exposure to Iomervu 400 mgI/mL and 250 mgI/mL was within the maximum recommended total iodine dose of 60 g.

Injection rates administered in the studies were injected at or close to the recommended rate, which ranged between 0.9-5 mL/sec.

Although there was less representation of CT head than CT body examinations across all patients, the number of head CTs examined was considered adequate to support the indication. Because nearly all patients receiving Iomervu were assessed as having adequate visualization, formal subgroup analysis by anatomic region would be of limited utility. Of note, in the primary analysis there were two patients who had images scored as less than adequate, one by two readers and one by a single reader. These scores were all for abdominal CT scans.

Table 43. Volume and Total Iodine Dose Administered in IOM-104E, Safety Population

	48,848-007A and 48,848-007B		48,848-008A and 48,848-008B	
Demographic Parameters	**Iomervu 400 mgI/mL (n=59)**	**Iopamidol 370 mgI/mL (n=55)**	**Iomervu 250 mgI/mL (n=59)**	**Iopamidol 250 mgI/mL (n=57)**
Contrast volume, mL				
Mean (SD)	112 (18)	130 (41)	145 (20)	141 (23)
Median	113	122	150	150
Min, max	75, 150	80, 287	100, 191	75, 189
Total iodine dose administered, grams				
Mean (SD)	45 (7)	48 (15)	36 (5)	35 (6)
Median	45	45	38	38
Min, max	30, 60	30, 106	25, 48	19, 47
CT examination[1], n (% of patients)	34 (58)	40 (73)	52 (88)	47 (82)
Abdomen	27 (46)	35 (64)	34 (58)	34 (60)
Pelvis	22 (37)	23 (42)	21 (36)	17 (30)
Thorax	8 (14)	7 (13)	3 (5)	3 (5)
Head	6 (10)	4 (7)	4 (7)	2 (4)
Neck				

Source: IOM-104E study report, Table F; 48-848-007A and -007B study reports, Table D; 48-848-008A and -008B study reports, Table C
Abbreviations: n = number of patients, SD = standard deviation
[1] Patients may have more than one anatomical area examined

Additional Analyses Conducted on the Individual Trial

A post-hoc analysis of the full analysis population for the inclusion of technically inadequate images was not conducted for IOM-104E and was not necessary, as all image sets for both Iomervu and comparator groups were rated as technically adequate by all readers.

The results of the assessment of images in the re-read study using the full 5-point scale are presented below in Table 44. One reader rated one patient's images as insufficient in the Iomervu 400 mgI/mL group, a second reader rated another patient's images as insufficient in the Iomervu 250 mgI/mL group, and a third reader rated one patient's images as poor in the Iomervu 250 mgI/mL group, otherwise all image sets were rated as fair, good, or excellent in keeping with the primary endpoint analysis. Similar observations in IOM-104A are noted in IOM-104E, where there were numerically more images rated as excellent for Iomervu 400 mgI/mL versus comparator for all readers. These findings are not considered likely to have a significant clinical impact.

Table 44. Visualization Quality in IOM-104E as Rated on a 5-Point Scale, Efficacy Analysis Population

Reader[1]	Visualization Quality	48,848-007A and -007B		48,848-008A and -008B	
		Iomervu 400 mgI/mL	Iopamidol 370 mgI/mL	Iomervu 250 mgI/mL	Iopamidol 250 mgI/mL
Readers 1 and 4	Number of patients	59	55	59	57
	Poor	0	0	0	0
	Insufficient	1 (2%)	0	0	0
	Fair	0	3 (6%)	5 (9%)	2 (4%)
	Good	8 (14%)	12 (22%)	18 (31%)	15 (26%)
	Excellent	50 (85%)	40 (73%)	36 (61%)	40 (70%)
Readers 2 and 5	Number of patients	59	54	59	57
	Poor	0	0	0	0
	Insufficient	0	0	1 (2%)	0
	Fair	1 (2%)	0	3 (5%)	1 (2%)
	Good	5 (9%)	12 (22%)	22 (37%)	19 (33%)
	Excellent	53 (90%)	42 (78%)	33 (56%)	37 (65%)
Readers 3 and 6	Number of patients	59	54	59	55
	Poor	0	0	1 (2%)	0
	Insufficient	0	0	0	0
	Fair	1 (2%)	0	4 (7%)	2 (4%)
	Good	4 (5%)	6 (11%)	10 (17%)	12 (22%)
	Excellent	55 (93%)	48 (89%)	44 (75%)	41 (75%)

Source: IOM-104E study report, Table I

[1] Three readers independently assessed images for studies 48,848-007A and -007B and three different readers independently assessed images for studies 48,848-008A and -008B, comprising a total of six different readers

All three readers provided the same visualization score on the 2-point scale in 98% of patients in the efficacy analysis population for Iomervu 250 mgI/mL, 97% of patients for iopamidol 250 mgI/mL, 98% of patients for Iomervu 400 mgI/mL, and 96% of patients for iopamidol 370 mgI/mL. Using the 5-point scale, three reader agreement was 54% for Iomervu 250 mgI/mL, 65% for iopamidol 250 mgI/mL, 80% for Iomervu 400 mgI/mL, and 62% for iopamidol 370 mgI/mL.

8.1.11. Napoli et al. 2011: CT angiography (CTA)

Trial Design

This was a prospective, single-arm study conducted at a single center in Italy.

Patient Population

Patients with symptomatic peripheral arterial disease (Fontaine stages IIa-IV), positive ankle-brachial index, or referral for imaging of abdominal aorta and inflow and runoff arteries after

duplex ultrasound were included. Patients with contraindications to digital subtraction angiography or iodinated contrast agents, acute ischemia that required urgent treatment, or a glomerular filtration rate <30 mL/min/1.73 m^2 were excluded. 168 males (mean age 62 years; age range, 41-84 years) and 44 females (mean age 68 years; age range, 54-88 years) were enrolled. Of the 212 patients who were included, 12 had previously undergone peripheral arterial bypass graft and 7 had an arterial stent placement. The study enrollment took place between July 2005 to December 2007.

Imaging Device and Image Acquisition

CT angiography was performed using a commercially available 64-slice multi-detector CT scanner (Sensation Cardiac 64; Siemens). Bolus tracking software (CARE Bolus; Siemens) was used to determine the delay between administration of Iomervu and imaging for each patient. There was a delay of 8 seconds before start of scanning after an attenuation threshold of 200 Hounsfield units was reached in the proximal abdominal aorta. Reconstructed three-dimensional images included maximum intensity projections, volume rendered images, and curved multiplanar reformations along the longitudinal axis of the artery. After completion of CT angiography, intra-arterial digital subtraction angiography was performed with a standard angiographic unit (Integris V5000; Philips Medical Systems).

Dose

For CT angiography, 130 mL of Iomervu 400 mgI/mL was administered intravenously with an automated injector at a rate of 4 mL/sec. For digital subtraction angiography (reference standard imaging), 25-35 mL of Iomervu 300 mgI/mL was administered at 10-15 mL/sec.

Image Evaluation

The arterial vascular system was divided into 35 segments: the infrarenal aorta; common iliac arteries, external iliac arteries (proximal and distal segments), internal iliac arteries, common femoral arteries, deep femoral arteries, superficial femoral arteries (proximal and distal segments), popliteal arteries (proximal and distal segments), tibiofibular trunks, anterior tibial arteries (proximal and distal segments), peroneal arteries (proximal and distal segments), and posterior tibial arteries (proximal and distal segments).

Vascular regions consisted of the aortoiliac region (distal aorta and common, external, and internal iliac arteries), the femoropopliteal region (common femoral, superficial femoral, deep femoral, and popliteal arteries), and the crural region (anterior and posterior tibial arteries, peroneal arteries, tibiofibular trunks, dorsalis pedis artery, and plantar arch).

The presence and degree of diameter stenosis was scored on a 4-point scale: 1 = none or mild stenosis (≤49% luminal narrowing); 2 = moderate stenosis (50%-69% narrowing); 3 = severe stenosis (70%-99% narrowing); 4 = occlusion (100% lumen blockage). Grades 3 and 4 stenoses

were considered clinically relevant (≥70% stenosis).

Digital subtraction angiography images were reviewed by two readers blinded to CT angiographic and clinical data. Discrepancies in interpretation were resolved by consensus. Of the 7,392 arterial segments and 1,060 regions identified by digital subtraction angiography, 3,113 (42%) and 657 (62%) were positive for significant stenosis, respectively.

For CT angiography, three readers blinded to digital subtraction angiography findings independently evaluated randomized CT angiographic images.

Study Endpoints

The diagnostic performance of CT angiography with Iomervu for the detection of significant stenosis at the arterial segment-, arterial region-, and patient-levels, was assessed in terms of sensitivity, specificity, positive predictive value, and negative predictive value. Digital subtraction angiography was used as the reference standard. All evaluable and non-evaluable segments were included in the analysis. The study was powered for negative predictive value, but formal success criteria were not stated. Inter-reader agreement was calculated using generalized kappa statistics.

Compliance with Good Clinical Practices

The publication indicated that the study was conducted in compliance with GCP and with oversight from the local IRB.

Financial Disclosure

The authors of the publication had no potential conflicts of interest to disclose. No relevant financial disclosures were reported by the Applicant for the listed clinical investigators. A Bracco employee is acknowledged in the publication as having provided editorial assistance with the manuscript, however, the Applicant states he had no role in the design or conduct of the study.

Efficacy Results

A total of 212 patients were evaluated for CT angiography of the peripheral arteries of the lower extremities. Results for the endpoints of regulatory interest were reported as majority read (Table 45). At the segment-level, CT angiography with Iomervu demonstrated 99% sensitivity (95% CI: 98%, 99%) and 97% specificity (95% CI: 96%, 97%) for detection of stenosis ≥70%. Generalized kappa was reported as 0.89 at the segment-level.

Table 45. Sensitivity and Specificity for Detection of ≥70% Stenosis of the Peripheral Arteries of the Lower Extremities in Napoli et al. 2011

	TP	FN	FP	TN	Sensitivity,	Specificity,	PPV,	NPV,

					point estimate % (95% CI)	point estimate % (95% CI)	point estimate % (95% CI)	point estimate % (95% CI)
Segment-level (n=7,392) (infrarenal, iliac, femoral, popliteal, tibiofibular, tibial, peroneal arteries)	3,072	41	138	4,141	99 (98, 99)	97 (96, 97)	96 (95, 96)	99 (99, 99)
Region-level (n=1,060) (aortoiliac, femoropopliteal, crural regions)	646	11	14	389	98 (97, 99)	96 (94, 98)	98 (97, 99)	97 (95, 98)
Patient-level (n=212)	210	0	0	2	100 (98, 100)	100 (16, 100)	100 (98, 100)	100 (16, 100)

Source: Napoli et al. 2011, Table 3
Abbreviations: CI = confidence interval, FN = false negative, FP = false positive, N = number, NPV = negative predictive value, PPV = positive predictive value, TN= true negative, TP = true positive

Limitations of this study include performance at a single center, lack of reporting of results per reader, absence of predefined success thresholds, and enrollment of patients who nearly all had severe peripheral arterial disease, which may limit applicability to patients with less severe disease.

8.1.12. Albrecht et al. 2007: CT angiography (CTA)

Trial Design

This was a prospective, single-arm study conducted at a single center in Germany.

Patient Population

Patients with peripheral arterial disease with chronic ischemia (Fontaine stages IIa-IV) or acute ischemia were included. One patient was excluded for inadequate arterial enhancement due to operator-related technical failure. A total of 34 males and 16 females (mean age 65 years; age range, 36-88 years) were enrolled. Of the 50 patients enrolled, 7 had end-stage renal failure and were being treated with long-term hemodialysis, and the remaining 43 had adequate renal function, which was defined as serum creatinine <1.4 mg/dL. The study enrollment took place between March 2003 and March 2005.

Imaging Device and Image Acquisition

CT angiography was performed using a commercially available 16-slice multi-detector CT scanner (Somatom Sensation 16; Siemens). Bolus tracking software (CARE Bolus; Siemens) was used to determine the delay between administration of Iomervu and imaging for each patient. Scanning began 4 seconds after a threshold attenuation of 250 Hounsfield units was reached in the suprarenal aorta. Reconstructed three-dimensional images included maximum intensity projections and volume rendered images, and curved multiplanar reformations if additional review was needed for sufficient determination of the degree of stenosis.

Intra-arterial digital subtraction angiography was performed with a standard angiographic unit (Integris 3000; Philips Medical Systems). Digital subtraction angiography was performed within 4 weeks after CT angiography. Digital subtraction angiography coverage varied with the clinical indication for each patient as either a bilateral runoff study or unilateral imaging study. The approach for digital subtraction angiography was influenced by the findings on CT angiography and was tailored to each patient.

Dose

For CT angiography, 100 mL of Iomervu 400 mgI/mL was administered intravenously at a rate of 4 mL/sec. For bilateral studies of digital subtraction angiography, 20-40 mL of Iomervu 300 mgI/mL was administered at 20 mL/sec per run. For unilateral studies of digital subtraction angiography, 10-20 mL of Iomervu 300 mgI/mL was administered at 10 mL/sec per run.

Image Evaluation

Images were assessed on the basis of up to 25 arterial segments per patient depending on the available digital subtraction angiography coverage. Segments included the aorta, left and right common and external iliac arteries, common, superficial, and deep femoral arteries, popliteal arteries, tibiofibular trunk, fibular arteries, anterior tibial arteries, posterior tibial arteries above the ankle, dorsalis pedis, and posterior tibial arteries below the ankle.

The degree of diameter stenoses in the segments above the ankle was scored using a 5-point scale: 0 = normal vessel lumen with smooth vessel wall; 1 = wall irregularities or mild circumscript stenosis of ≤50% of vessel diameter; 2 = moderate stenosis of 51-75% of vessel diameter; 3 = severe stenosis of 76-99% of vessel diameter; 4 = occlusion. Lesions scored as grade 2 or higher (>50% stenosis) were considered hemodynamically relevant. Pedal arteries were assessed only for patency or occlusion without grading of stenoses.

Digital subtraction angiography images were reviewed by two readers blinded to CT angiographic and clinical data. Discrepancies in interpretation were resolved by consensus with a third reader. Of the 929 and 933 stenotic lesions identified by two readers on digital subtraction angiography, 312 and 313 (34%) were considered significant (score 2 or higher).

Two readers blinded to digital subtraction angiography findings, patient information, and clinical history independently evaluated CT angiographic images.

Study Endpoints

The diagnostic performance of CT angiography with Iomervu for the detection of lesions with significant stenosis (>50%) in the lower extremities at the arterial segment-level was assessed in terms of sensitivity and specificity. Digital subtraction angiography was used as the reference standard. No predefined statistical hypotheses are stated. Inter-reader agreement was

reported using Cohen kappa.

Compliance with Good Clinical Practices

The publication indicated that the study was conducted in compliance with GCP and with oversight from the independent ethics committee (IEC).

Financial Disclosures

The authors of the publication did not specify whether there were any potential conflicts of interest to disclose. A Bracco employee is listed as an author of this publication. The Applicant stated that this employee provided editorial assistance with the manuscript and that he had no role in the design or conduct of the study. Therefore, no relevant financial disclosures were reported by the Applicant for the listed clinical investigators.

Efficacy Results

Fifty patients were evaluated for CT angiography of the peripheral arteries of the lower extremities. At the segment-level, CT angiography with Iomervu demonstrated 93% sensitivity (95% CI: 91%, 96%) and 97% specificity (95% CI: 95%, 98%) for detection of stenosis >50% for reader 1 and 90% sensitivity (95% CI: 87%, 93%) and 96% specificity (95% CI: 94%, 97%) for reader 2 (Table 46). Inter-reader kappa between readers 1 and 2 was 0.77 for the grading of steno-occlusive lesions on CT angiography.

Table 46. Lesion-Level Sensitivity and Specificity for Detection of >50% Stenosis of the Aortoiliac and Lower Extremity Arteries in Albrecht et al. 2007

	TP	**FN**	**FP**	**TN**	**Sensitivity**, point estimate % (95% CI)	**Specificity**, point estimate % (95% CI)	**PPV**, point estimate % (95% CI)	**NPV**, point estimate % (95% CI)
Reader 1 (n=933)	292	21	22	598	93 (91, 96)	97 (95, 98)	93 (90, 95)	97 (95, 98)
Reader 2 (n=929)	281	31	27	590	90 (87, 93)	96 (94, 97)	91 (88, 94)	95 (93, 96)

Source: Albrecht et al. 2007, Table 4
Abbreviations: CI = confidence interval, FN = false negative, FP = false positive, N = number of lesions, NPV = negative predictive value, PPV = positive predictive value, TN= true negative, TP = true positive

Limitations for this study include performance at a single center, small sample size, no indication of randomization of images, absence of predefined success thresholds, and the influence of CT angiography findings and the individual patient on the approach for digital subtraction angiography.

8.1.13. Additional CT angiography studies

Several studies were submitted as evidence of efficacy for the general CT angiography indication. Napoli et al. 2011 and Albrecht et al. 2007 were selected by the clinical team as most relevant to this application. The remaining studies are briefly reviewed together here.

Iezzi et al. 2008
This was a prospective study of 40 patients with peripheral arterial disease who were referred for angiography of the lower extremities, conducted at a single center in Italy. Patients were randomized to receive CT angiography using either 90 mL of Iomervu 400 mgI/mL or 120 mL of Iomervu 300 mgI/mL at a rate of 3 mL/sec. CT was performed within 48 hours prior to DSA for 33 patients; DSA without endovascular treatment was performed prior to CTA in the remaining patients.

Sensitivity and specificity of CT angiography with Iomervu for the detection of significant stenosis (defined as >70%) of the abdominal aorta and lower extremity arteries at the arterial segment-level (12 segments/patient) was assessed using DSA as the reference standard. DSA images were evaluated by two readers. CT images were independently evaluated by two readers blinded to the study drug and results of DSA, with discrepancies resolved by consensus.

A total of 760 segments were evaluated. Of these, 32 and 6 segments were considered nondiagnostic by DSA and CT angiography, respectively, leaving 722 segments in the sensitivity and specificity analysis. A total of 89 of 365 segments (24%) in 20 patients that received Iomervu 300 mgI/mL were positive for at least 70% stenosis by DSA while 79 of 357 segments (22%) in 20 patients that received Iomervu 400 mgI/mL were positive for stenosis by DSA. Segment-level sensitivity and specificity of CT angiography with Iomervu 300 mgI/mL for the detection of >70% stenosis were 98% and 97%, respectively, and 96% and 96% with Iomervu 400 mgI/mL. Confidence intervals were not provided.

Gruschwitz et al. 2023
This was a retrospective, single-arm study of 109 patients with known or suspected peripheral arterial disease who underwent CT angiography of the lower extremity, conducted at a single center in Germany. Patients were administered 110 mL of Iomervu 350 mgI/mL at a rate of 3 mL/sec for CT angiography and Iomervu 300 mgI/mL for DSA. These procedures were required to be within 30 days of each other for inclusion. CT was performed on a dual energy scanner and multiple reconstructions were evaluated. The results reported here are for the virtual 120 kV images.

Sensitivity and specificity of CT angiography with Iomervu for the detection of significant stenosis (defined as at least 75%) at the arterial segment-level (10 segments per patient) was assessed using DSA as the reference standard. DSA images were evaluated by one reader. CT angiography images were independently evaluated by two readers blinded to clinical information and results of DSA but aware of the affected leg.

Of the 129 patients initially eligible, 18 were excluded due to deviations from the protocol, missing or incomplete datasets, or nondiagnostic CT scans. Additionally, two patients were excluded because of significantly progressed disease between CT scan and DSA. A total of 607 arterial segments were evaluated. The segment-level sensitivity and specificity of CT angiography with Iomervu 350 mgI/mL for the detection of ≥75% stenosis were both 100%. Confidence intervals were not provided.

Millon et al. 2012
This was a retrospective, single-arm study of 73 consecutive patients who were diagnosed with nontraumatic subarachnoid hemorrhage by noncontrast CT. Noncontrast CT was immediately followed by CT angiography of the cerebral arteries. The study was conducted at a single center in France. Patients were administered 25 mL of Iomervu 400 mgI/mL at a rate of 5 mL/sec.

Patient-level sensitivity and specificity of CT angiography with Iomervu for the detection of intracranial vascular lesions (aneurysms, dural arteriovenous fistula, arteriovenous malformations, and arterial dissections) that could explain the subarachnoid hemorrhage was assessed using three-dimensional DSA as the reference standard, or surgical results for patients who could not undergo three-dimensional DSA. CT angiography images were independently evaluated by two readers blinded to information about the patients' therapeutic management.

A total of 56 patients had DSA for reference, and in this subgroup, 45 patients (80%) were positive for at least one lesion. The patient-level sensitivity and specificity of CT angiography with Iomervu 400 mgI/mL for the detection of bleeding lesions were both 100%. Confidence intervals were not provided but can be calculated; the lower bounds of the 95% exact CIs were 92% for sensitivity and 72% for specificity. In the remaining 17 patients in whom three-dimensional DSA was not performed, seven patients died before any angiography or surgery could be performed, and 10 patients had emergency surgery. Surgical findings for the latter 10 patients were in agreement with the results of CT angiography.

Kim et al. 2020
This was a retrospective, single-arm study of 128 patients with 143 cerebral aneurysms treated using titanium clips who underwent postoperative CT angiography of the cerebral arteries. The study was conducted at a single center in Korea. For CT angiography, patients were administered 80-100 mL of Iomervu 400 mgI/mL at a rate of 3-4 mL/sec. All patients were required to have DSA and three-dimensional rotational angiography for inclusion. These studies were performed within 28 days before or after the CT angiography.

Lesion-level sensitivity and specificity of CT angiography with Iomervu for the detection of residual or recurrent aneurysm and of significant stenosis (defined as at least 70%) of the aneurysm parent artery was assessed using three-dimensional rotational angiography as the reference standard. Confidence intervals were not provided but are calculated (95% exact CIs).

Three-dimensional rotational angiography and CT angiography images were independently evaluated by four readers, two for each modality.

Of the 143 clipped aneurysms, 24 residual or recurrent aneurysms were identified by three-dimensional rotational angiography and 2 parent arteries were positive for stenosis. The sensitivity and specificity of CT angiography with Iomervu 400 mgI/mL for the detection of residual or recurrent aneurysm were 83% (95% CI: 63%, 95%) and 100% (95% CI: 97%, 100%), respectively, for reader 1 and 79% (95% CI: 58%, 93%) and 100% (95% CI: 97%, 100%), respectively, for reader 2. Sensitivity and specificity for >70% stenosis of the parent artery were both 100% for both readers with lower bounds of the confidence intervals being 16% and 97%, respectively.

Schaefer et al. 2013
This was a prospective, single-arm study of 52 patients with asymptomatic aortoiliac aneurysms or penetrating atherosclerotic ulcers that were to be treated by endovascular prosthesis placement. The study was conducted at a single center in Germany. Patients were administered Iomervu 350 mgI/mL for preoperative CT angiography (volume and rate not specified) and 20 mL of Iomervu 300 mgI/mL at a rate of 14 mL/sec per sequence for DSA.

Sensitivity and specificity of CT angiography with Iomervu for the detection of relevant stenosis (defined as at least 50%) of the celiac trunk and superior mesenteric artery was assessed using DSA as the reference standard. Confidence intervals were not provided but are calculated (95% exact CIs). DSA and CT images were randomized and evaluated by two readers in consensus with 4 weeks between reading different modalities.

One patient was not included in the analysis of CT angiography due to lost images. Therefore, a total of 51 patients were included in the analysis. Thirteen and two significant arterial stenoses were detected in the celiac trunk and superior mesenteric artery, respectively, by DSA. The sensitivity and specificity of CT angiography with Iomervu 350 mgI/mL for the detection of ≥50% stenosis of the celiac trunk were 100% (95% CI: 74%, 100%) and 95% (83%, 99%), respectively. For the superior mesenteric artery, the sensitivity was 100% (95% CI: 16%, 100%) and specificity was 98% (95% CI: 89%, 100%).

Stueckle et al. 2004
This was a retrospective, single-arm study of 52 patients who underwent CT angiography and DSA of the abdominal vessels for suspicion of aortic dissection, aortic aneurysm, or stenosis of the mesenteric or iliac arteries before surgical treatment. The study was conducted at a single center in Germany. For CT angiography, patients were administered 100 mL of Iomervu 350 mgI/mL at a rate of 3 mL/sec.

Sensitivity and specificity of CT angiography with Iomervu for the detection of high-grade stenosis (defined as at least 85%) of the abdominal arteries was assessed at the patient-level

using DSA as the reference standard. Confidence intervals were not provided. CT images were evaluated by two readers in consensus.

Eleven patients (21%) were positive for high grade stenosis by digital subtraction angiography. The sensitivity and specificity of Iomervu 350 mgI/mL with CT angiography in axial projections, three-dimensional volume reconstruction, and multiplanar projections for the detection of ≥85% stenosis were 100% and at least 85%, respectively.

8.1.14. Andreini et al. 2010: Coronary CT angiography (CCTA)

Trial Design

This was a prospective, single-arm study conducted at a single center in Italy. The objective of this study was to compare the diagnostic performance of coronary CT angiography between patients with and without diabetes.

Patient Population

Patients referred for invasive coronary angiography for suspected coronary artery disease because of chest pain or inconclusive stress test were included and grouped by those with and without a history of diabetes mellitus. Patients with previous invasive coronary angiography, history of coronary artery disease, contraindication to the administration of iodinated contrast agents, creatinine clearance <60 mL/min, inability to sustain a 15-second breath hold, cardiac arrhythmias, or patients who were pregnant were excluded. A total of 184 males and 26 females (mean age 64 years) were enrolled, of whom 105 (50%) had diabetes. Study enrollment took place between January 2007 to December 2008.

Imaging Device and Image Acquisition

Coronary CT angiography was performed using a 64-slice multi-detector CT scanner (LightSpeed VCT; GE Healthcare). Bolus tracking software was used to determine the delay between administration of Iomervu and imaging for each patient. Reconstructed images were analyzed using volume rendering, multi-planar reconstruction, and vessel analysis software packages. Invasive coronary angiography was analyzed with quantitative coronary angiography software (QantCor QCA; Pie Medical Imaging). Coronary CT angiography was performed approximately three days prior to invasive coronary angiography.

Dose

For coronary CT angiography, 80 mL of Iomervu 400 mgI/mL was administered intravenously at a rate of 5 mL/sec. Invasive coronary angiography was performed according to the institution's standard technique.

Image Evaluation

Coronary artery segments were classified according to the 15-segment American Heart Association classification and all segments with a diameter of at least 1.5 mm were included.

Invasive coronary angiography images were evaluated by two readers blinded to the coronary CT angiography findings. Of the 2,532 arterial segments identified by invasive coronary angiography, 559 (22%) were positive for significant stenosis, defined as at least 50%.

Coronary CT angiography images were evaluated independently by two readers blinded to invasive coronary angiography and clinical findings. Discrepancies in interpretation were resolved by consensus.

Study Endpoints

The diagnostic performance of coronary CT angiography with Iomervu for the detection of significant stenosis (>50%) of the coronary arteries at the arterial segment- and patient-levels, was assessed in terms of sensitivity, specificity, positive predictive value, and negative predictive value. Invasive coronary angiography was used as the reference standard. No predefined statistical hypotheses were stated. Patients with and without diabetes were separately analyzed in the study, but combined results are reported here. Inter-reader agreement was analyzed using kappa statistics.

Compliance with Good Clinical Practices

The publication indicated that the study was conducted in compliance with GCP and with oversight from an IEC.

Financial Disclosures

The authors of the publication did not specify whether there were any potential conflicts of interest to disclose. No relevant financial disclosures were reported by the Applicant for the listed clinical investigators.

Efficacy Results

All 210 patients were evaluable at coronary CT angiography. A total of 2532 of 2652 (95%) segments were considered evaluable. At the segment-level, coronary CT angiography with Iomervu demonstrated 84% sensitivity (95% CI: 81%, 87%) and 94% specificity (95% CI: 92%, 95%) for detection of stenosis >50% for evaluable segments (Table 47). At patient-level, sensitivity was higher and specificity was lower than at segment-level, as expected for the analysis in which positive segment-level results took precedence over negative segment-level

results at the patient-level. Inter-reader kappa was reported as 0.74 for diabetic patients and 0.78 for non-diabetic patients at the segment-level.

Table 47. Sensitivity and Specificity for Detection of >50% Stenosis of the Coronary Arteries in Andreini et al. 2010

	TP	**FN**	**FP**	**TN**	**Sensitivity**, point estimate % (95% CI)	**Specificity**, point estimate % (95% CI)	**PPV**, point estimate % (95% CI)	**NPV**, point estimate % (95% CI)
Segment-level (n=2,532)	469	90	128	1,845	84 (81, 87)	94 (92, 95)	79 (76, 81)	95 (94, 96)
Patient-level (n=210)	170	10	12	18	94 (90, 97)	60 (41, 77)	93 (90, 96)	64 (48, 78)

Source: Andreini et al. 2010, Table 6
Abbreviations: CI = confidence interval, FN = false negative, FP = false positive, N = number, NPV = negative predictive value, PPV = positive predictive value, TN= true negative, TP = true positive

Limitations for this study include performance at a single center, lack of reporting of results per reader, and absence of predefined success thresholds.

8.1.15. Pontone et al. 2014: Coronary CT angiography (CCTA)

Trial Design

This was a prospective, single-arm study conducted at a single center in Italy. The objective of this study was to compare the diagnostic performance of coronary CT angiography performed using standard spatial resolution (0.625 mm) and high spatial resolution (0.23 mm).

Patient Population

Patients at high risk for coronary artery disease, assessed by Diamond-Forrester risk score, who were scheduled for invasive coronary angiography were included. Patients with contraindications to iodinated contrast agents, impaired renal function, inability to sustain a breath hold, heart rate >65 beats per minute despite IV beta-blockade during coronary CT angiography, cardiac arrhythmias, previous history of percutaneous coronary intervention or coronary artery bypass graft surgery, body mass index >35 kg/m^2, or patients who were pregnant were excluded. Of the 197 patients randomized to undergo standard or high-resolution CT, 13 patients did not achieve a target heart rate of ≤65 beats per minute and were excluded.

After exclusion, 150 males and 34 females (mean age 63 years) were enrolled with 91 patients randomized to the standard resolution protocol and 93 patients randomized to the high-resolution protocol. The study enrollment took place between January 2010 to September 2010.

Imaging Device and Image Acquisition

Coronary CT angiography was performed using a 64-slice multi-detector CT scanner (LightSpeed VCT XTe; GE Healthcare) for standard resolution images. Bolus tracking software was used to determine the delay between administration of Iomervu and imaging for each patient. Prospective electrocardiogram triggering was performed. An iterative reconstruction algorithm was used.

High resolution coronary CT angiography was performed using a different scanner, Discovery CT750 HD (GE Healthcare), but otherwise the same acquisition protocol. Although image acquisition with high spatial resolution has been introduced within the last decade and its utility has been compared with standard resolution CT in the literature, the evaluation of coronary artery disease with high resolution coronary CT angiography is not considered to be routine clinical practice at this time. Therefore, the high resolution results are not discussed in this review.

Invasive coronary angiography was analyzed with quantitative coronary angiography software (QantCor QCA; Pie Medical Imaging).

Dose

For coronary CT angiography, 90 mL of Iomervu 400 mgI/mL was administered intravenously at a rate of 5 mL/sec. Invasive coronary angiography was performed according to the institution's standard technique.

Image Evaluation

Coronary arteries were segmented according to the 15-segment American Heart Association classification. The degree of diameter stenosis was graded on a 5-point scale: 0 = 0% stenosis; 1 = 1%-24% stenosis; 2 = 25%-49% stenosis; 3 = 50%-69% stenosis; 4 = ≥70%-99% stenosis; 5 = 100% stenosis.

Invasive coronary angiography images were evaluated independently by two readers blinded to coronary CT angiographic data. Discrepancies in interpretation were resolved by a third reader. Of the 1,456 arterial segments identified by invasive coronary angiography, 266 (18%) were positive for significant stenosis, defined as at least 50%.

Coronary CT angiography was performed approximately seven days prior to invasive coronary angiography. Coronary CT angiography images were independently evaluated by two readers blinded to invasive coronary angiography, clinical findings, and scanner type. Discrepancies in interpretation were resolved by a third reader.

Study Endpoints

The diagnostic performance of coronary CT angiography with Iomervu for the detection of significant stenosis (≥50%) of the coronary arteries, at the arterial segment- and patient-levels, was assessed in terms of sensitivity, specificity, positive predictive value, and negative predictive value. Invasive coronary angiography was used as the reference standard. No predefined statistical hypotheses were stated. Inter-reader agreement was analyzed using kappa statistics.

Compliance with Good Clinical Practices

The publication indicated that the study was conducted in compliance with GCP and with oversight from an IEC.

Financial Disclosures

The authors of the publication had no potential conflicts of interest to disclose. No relevant financial disclosures were reported by the Applicant for the listed clinical investigators.

Efficacy Results

All 91 patients in the standard resolution group who received coronary CT angiography were evaluable, and 1383 of 1456 (95%) segments were considered evaluable. At the segment-level, coronary CT angiography with Iomervu demonstrated 97% sensitivity (95% CI: 94%, 99%) and 95% specificity (95% CI: 93%, 96%) for detection of stenosis ≥50% (Table 48). At patient-level, sensitivity was numerically higher and specificity was lower than at segment-level, as expected for the analysis in which positive segment-level results took precedence over negative segment-level results at the patient-level. Inter-reader kappa was reported as 0.77 at the segment-level.

Table 48. Sensitivity and Specificity for Detection of ≥50% Stenosis of the Coronary Arteries for Standard Resolution Images in Pontone et al. 2014

	TP	**FN**	**FP**	**TN**	**Sensitivity**, point estimate % (95% CI)	**Specificity**, point estimate % (95% CI)	**PPV**, point estimate % (95% CI)	**NPV**, point estimate % (95% CI)
Segment-level (n=1,383)	236	8	60	1,079	97 (94, 99)	95 (93, 96)	80 (75, 84)	99 (99, 99)
Patient-level (n=91)	78	0	7	6	100 (95, 100)	46 (19, 75)	91 (84, 97)	100 (54, 100)

Source: Pontone et al. 2014, Table 1
Abbreviations: CI = confidence interval, FN = false negative, FP = false positive, N = number, NPV = negative predictive value, PPV = positive predictive value, TN= true negative, TP = true positive

Limitations for this study include performance at a single center, lack of reporting of results per reader, and absence of predefined success thresholds.

8.1.16. Additional coronary CT angiography studies

Four studies were submitted as evidence of efficacy for the coronary CT angiography indication. Andreini et al. 2010 and Pontone et al. 2014 were selected by the clinical team as most relevant to this application. The remaining studies are briefly reviewed together here.

Andreini et al. 2017
This was a prospective study of 166 patients without known coronary artery disease, including 83 patients with chronic atrial fibrillation and 83 patients with sinus rhythm, who were scheduled for invasive coronary angiography. This study was conducted at a single center in Italy. Each patient was imaged with coronary CT angiography 3 to 10 days prior to invasive coronary angiography. Patients with a body mass index ≤25 kg/m^2 were administered 50 mL of Iomervu 400 mgI/mL at a rate of 5 mL/sec for the coronary CT angiography and patients with BMI >25 kg/m^2 were administered 60 mL.

Sensitivity and specificity of coronary CT angiography with Iomervu for the detection of significant stenosis (defined as >50%) of the coronary arteries at the arterial segment- and patient-levels were assessed using invasive coronary angiography as the reference standard. Combining the atrial fibrillation and sinus rhythm groups, 98% of the 2622 coronary artery segments were evaluable. Non-evaluable segments were imputed as positive. CT images were independently evaluated by two readers blinded to invasive coronary angiography and clinical findings, with discrepancies resolved by consensus.

The sensitivity and specificity of coronary CT angiography with Iomervu 400 mgI/mL for the detection of >50% stenosis at the segment-level were 97% (95% CI: 93, 100) and 98% (95% CI: 96, 99), respectively, in the atrial fibrillation group and 96% (95% CI: 93, 99) and 98% (95% CI: 97, 99), respectively, in the sinus rhythm group. Sensitivity and specificity at the patient-level were 95% (95% CI: 84, 99) and 98% (95% CI: 87, 100), respectively, in the atrial fibrillation group and 98% (95% CI: 88, 100) and 95% (95% CI: 82, 99) in the sinus rhythm group, respectively.

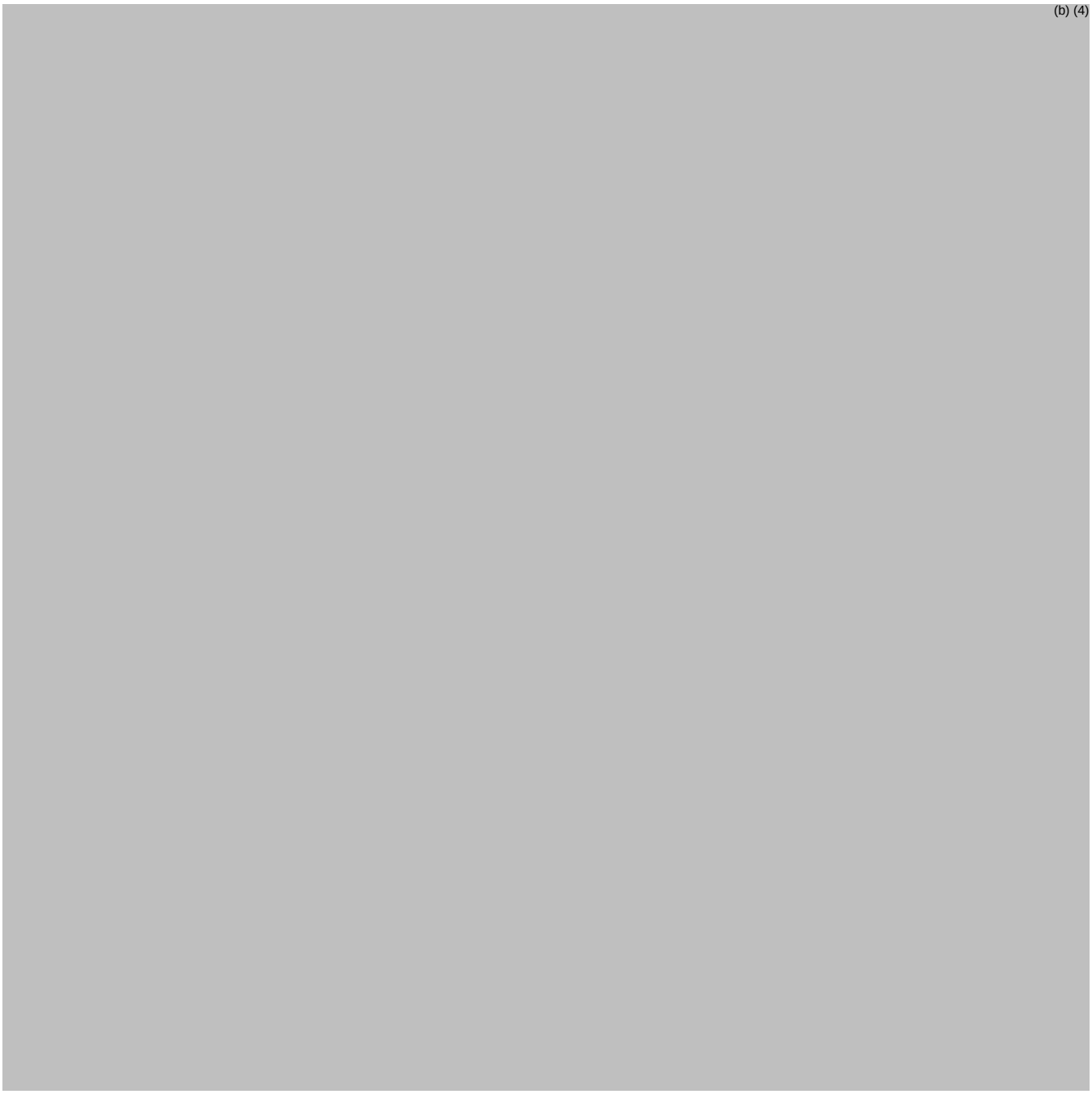
Brodoefel et al. 2008
This was a prospective, single-arm study of 125 patients with suspected coronary artery disease or suspected progression of known coronary artery disease who were scheduled for invasive coronary angiography. This study was conducted at a single center in Germany. Patients received a coronary CT angiogram using 80 mL Iomervu 400 mgI/mL at a rate of 5 mL/sec.

Sensitivity and specificity of coronary CT angiography with Iomervu for the detection of significant stenosis (defined as at least 50%) of the coronary arteries at the arterial segment- and patient-levels were assessed using invasive coronary angiography as the reference standard. Invasive coronary angiography was evaluated by a single reader blinded to CT results.

CT images were evaluated in consensus by two readers blinded to clinical information and the results of invasive coronary angiography.

A total of 1,540 arterial segments were evaluated, and 85 segments were excluded from the analysis because of stent graft placement. The sensitivity and specificity of coronary CT angiography with Iomervu 400 mgI/mL for the detection of ≥50% stenosis were 92% and 93% at the segment-level and 100% and 78% at the patient-level.

(b) (4)



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8.1.19. Portnoy et al. 2011: CT urography (CTU)

Trial Design

This was a retrospective study conducted at a single center in Israel. The objective of this study was to compare the image quality of the urinary collecting system and radiation dose associated with three-phase and split-bolus dual-phase CT urographic protocols.

Patient Population

A total of 156 consecutive patients who underwent CT urography for assessment of hematuria or other urologic diseases were evaluated for inclusion. Patients with one-sided urinary collecting system due to nephroureterectomy (n=3), image artifacts due to the presence of

surgical clips (n=1), or error in effective dose measurement (n=2) were excluded. Of the 150 patients included, two were scanned twice during the study period, each time with a different imaging protocol. A total of 104 males and 46 females (mean age 59 years; age range, 20-89 years) were included. Patients underwent CT urography between February 2008 and September 2009.

Imaging Device and Image Acquisition

CT urography was performed using a 64-slice multi-detector CT scanner (LightSpeed VCT; GE Healthcare). Images were reconstructed in the axial, coronal, and sagittal planes.

Noncontrast scans were obtained for all patients before administration of Iomervu.

In the single bolus three-phase scan protocol, patients were administered a single IV bolus injection of 90 mL of Iomervu 350 mgI/mL at a rate of 2.5 mL/sec. Nephrourographic phase scans were obtained 100 seconds post-injection, then urographic phase scans were obtained at 600 seconds post-injection. Two variants of this protocol were used with different noise indices.

In the split-bolus dual-phase protocol, patients were administered a bolus of 80 mL of Iomervu 350 mgI/mL at a rate of 2.5 mL/sec followed by a second bolus of 40 mL at the same rate after a delay of 360 seconds. Nephrourographic phase scans were obtained 120 seconds after the second bolus.

Image Evaluation

Each urinary collecting system was divided into six regions for evaluation: the upper intrarenal collecting system, lower intrarenal collecting system, intrarenal collecting system including the renal pelvis, proximal ureter (ureteropelvic junction to iliac crest), mid ureter (iliac crest to inferior margin of the sacroiliac joint), and distal ureter (inferior margin of the sacroiliac joint to the ureterovesical junction). Each segment was scored for opacification as 0 for incomplete or 1 for complete.

For parenchymal image quality, qualitative assessment of the nephrographic or nephrourographic phase scans was scored on a 3-point scale: 0 = inadequate image quality; 1 = diagnostic quality; 2 = very good or excellent quality.

Images were evaluated by two readers, with blinding and independence unstated, for parenchymal image quality.

Study Endpoints

CT urography with Iomervu was evaluated for number of urinary collecting system segments opacified and renal parenchymal image quality. No predefined statistical hypotheses were

stated.

Compliance with Good Clinical Practices

The publication indicated that the study was conducted in compliance with GCP and with oversight from the local IRB. Informed consent from the participants was waived due to the retrospective nature of the study.

Financial Disclosures

The authors of the publication did not specify whether there were any potential conflicts of interest to disclose. No relevant financial disclosures were reported by the Applicant for the listed clinical investigators.

Efficacy Results

Among the 150 patients included in this study, 100 underwent the single bolus contrast protocol and 50 underwent the split-bolus protocol. Parenchymal image quality was scored as 2 (very good or excellent) for 97 of 100 patients receiving the single bolus protocol and 32 of 50 patients receiving the split bolus protocol. The remaining patients were scored as 1 (diagnostic). The mean number of opacified urinary collecting system segments (out of 12) was 10.9 among patients receiving the single bolus protocol and 11.4 in patients receiving the split-bolus protocol.

Limitations of this study include retrospective design, performance at a single center, methods of image assessment, lack of per-reader results, uncertainty of whether there was blinding of the readers, and absence of predefined success thresholds.

8.1.20. Martingano et al. 2013: CT urography (CTU)

Trial Design

This was a retrospective, single-arm study conducted at a single center in Italy.

Patient Population

Patients who underwent both CT urography and MR urography for assessment of hematuria were included. Information on exclusion criteria and description of patients excluded, if any, were not provided. A total of 26 males and 9 females (mean age 67 years; age range, 41-87 years) were included. Patients underwent CT urography between January 2009 and October 2010.

Imaging Device and Image Acquisition

CT urography was performed using a 64-slice multi-detector CT scanner (Aquilion 64; Toshiba Medical Systems). Reconstructed three-dimensional images included maximum intensity projections.

Noncontrast scans were obtained before administration of Iomervu. In a split-bolus dual-phase protocol, patients were administered an IV bolus of 400 mgI/kg of Iomervu 350 mgI/mL at a rate of 2 mL/sec followed by a second bolus of 200 mgI/kg at the same rate after a delay of 420 seconds. Nephrourographic phase scans were obtained 100 seconds after the second bolus.

Image Evaluation

For evaluation of visualization quality, images of the urinary tract and bladder were divided into 11 regions which consisted of the upper calyces, middle calyces, and lower calyces, renal pelvis, and ureter on each side as well as the urinary bladder.

The qualitative assessment of the nephrourographic phase scans was scored on a 6-point scale: 0 = absence of visualization; 1 = poor visualization; 2 = fair visualization; 3 = moderate visualization; 4 = good visualization; 5 = excellent visualization.

CT urography images of the urinary tract and bladder were evaluated independently by two blinded readers for image quality.

Study Endpoints

CT urography with Iomervu was evaluated for visualization quality of the urinary collecting system and bladder, assessed as a mean image quality rating on a 6-point scale. No predefined statistical hypotheses were stated. Inter-reader agreement was calculated using weighted kappa statistics. Reader confidence for diagnosis of urothelial malignancy was also assessed, however the results are not reviewed here due to limited detail regarding the reference standard data for malignancy and the small number of patients available for analysis.

MR urographic images were analyzed similarly to CT urographic images. The MR urogram results are not discussed in this review as they are not directly relevant to the performance of Iomervu.

Compliance with Good Clinical Practices

Although the study was retrospective, it describes collection of informed consent for each patient after the nature of the procedures had been fully explained.

Financial Disclosures

The authors of the publication had no potential conflicts of interest to disclose. No relevant financial disclosures were reported by the Applicant for the listed clinical investigators.

Efficacy Results

Of the 35 patients included in this study, one had been treated with surgical removal of the left kidney and ureter, and 2 patients had a cystectomy with removal of the pelvic ureter on one side, resulting in a total of 378 segments that were present for evaluation. The mean image quality score for the urinary tract overall on a scale of 0 to 5 was 4.2 ± 1.4 and 4.1 ± 1.5 for readers 1 and 2, respectively (Table 49). The calyces and renal pelvis tended to be scored higher than the ureters and bladder. Inter-reader kappa was 0.85.

Table 49. Mean Visualization Score of Different Portions of the Urinary Tract on a 6-Point Scale (n=378 Segments of Urinary Tract) in Martingano et al. 2013

	All Sites	Calyces	Renal pelvis	Ureters	Bladder
Reader 1	4.15 ± 1.44	4.33 ± 1.32	4.17 ± 1.49	3.81 ± 1.72	3.63 ± 1.19
Reader 2	4.12 ± 1.51	4.32 ± 1.40	4.11 ± 1.68	3.69 ± 1.68	3.75 ± 1.17

Source: Martingano et al. 2013, Table 2

Limitations of this study include the retrospective design, small sample size, performance at a single center, absence of predefined success thresholds, and lack of information on criteria for exclusion of patients.

8.1.21. Additional CT urography studies

Four studies were submitted as evidence of efficacy for the CT urography indication. Portnoy et al. 2011 and Martingano et al. 2013 were selected by the clinical team as most relevant to this application. The remaining studies are briefly reviewed together here.

Bretlau et al. 2014
This was a retrospective study of 771 patients with hematuria who were referred for CT urography, conducted at a single center in Denmark. Noncontrast scans were obtained before administration of Iomervu in a split-bolus dual-phase protocol. Patients were administered an IV bolus of 25 mL of Iomervu 400 mgI/mL followed by a second bolus of 50 mL after a delay of 600 seconds. Injection rate was not stated. CT scans were obtained 50 seconds after the start of the injection.

This was a study to estimate the prevalence of common urologic diseases or pathology in patients with hematuria and to compare CT urography to clinical follow up, and it did not assess endpoints for adequacy of visualization.

Kahn et al. 2022

This was a retrospective, single-arm study of 15 patients with and without hydronephrotic kidneys, conducted at a single center in Israel. Noncontrast scans were obtained before administration of Iomervu in a four-phase protocol. Patients were administered a single IV bolus of 90-120 mL of Iomervu 300 mgI/mL. Nephrourographic phase scans were obtained at 100 seconds post-injection, first excretory phase scans were obtained at 570-690 seconds post-injection, and second excretory phase scans were obtained at 840-1,020 seconds post-injection.

The primary objective was to evaluate an image processing algorithm for assessing renal obstruction with CT urography. It included an assessment of sensitivity and specificity of the algorithm for the detection of hydronephrotic kidneys, however the reference standard was derived from reader analysis of the images.

8.1.22. Integrated Assessment of Effectiveness

The Applicant has submitted substantial evidence for the effectiveness of Iomervu for use in the following adult indications:

- Cerebral arteriography, including IA-DSA
- Visceral and peripheral arteriography and aortography, including IA-DSA
- Coronary arteriography and cardiac ventriculography
- CT of the head and body
- CT angiography of intracranial, visceral, and lower extremity arteries
- Coronary CT angiography
- CT urography

These indications can be divided into structure delineation claims and disease detection claims. The structure delineation claims include cerebral arteriography, visceral and peripheral arteriography and aortography, coronary arteriography and cardiac ventriculography, CT of the head and body, and CT urography. With the exception of CT urography, the studies that provided evidence of effectiveness for these indications assessed the quality of opacification and anatomic visualization on images obtained with Iomervu and with comparator iodinated contrast drugs using three blinded, independent readers. This paradigm is consistent with the data that supported approval of other drugs in class.

The IOM-104 re-read studies (for coronary arteriography and cardiac ventriculography, cerebral arteriography, visceral and peripheral arteriography, and CT head and body) were designed to demonstrate non-inferiority of Iomervu to an active comparator. During pre-NDA discussions, FDA communicated that the review would be focused on the results of the efficacy of Iomervu itself in the form of visualization results per reader, even in the absence of related pre-specified endpoints. Because of the nature of the underlying visualization quality scoring, non-inferiority comparisons to approved drugs, while of interest for the review, are difficult to interpret. Therefore, the proportions of patients that were rated as having images with adequate quality visualization are reported for the IOM-104 re-read studies in the prescribing information for Iomervu. The observed proportions were sufficiently high for all IOM-104 studies to support

clinical utility of Iomervu for the associated indications.

For two indications, coronary arteriography and cardiac ventriculography and CT head and body, the Applicant proposed use of Iomervu concentrations that were not studied in IOM-104A and IOM-104E, respectively. However, both of those studies included concentrations higher and lower than the desired untested concentration. This bracketing approach is reasonable from a clinical perspective and is further discussed in the clinical pharmacology review (Section 6).

For CT urography, the assessment of image quality differed between the two studies, although both studies conducted imaging protocols for the evaluation of the urinary collecting system. Study 1 (Portnoy et al. 2011) assessed parenchymal image quality on a 3-point scale, while Study 2 (Martingano et al. 2013) assessed the visualization quality of the urinary system overall on a 6-point scale. Limitations of these studies include the methods of image assessment in Study 1 and small sample size in Study 2. However, these weaknesses were not considered to significantly impact the ability of these studies to demonstrate adequate visualization of the urinary system.

The remaining indications, CT angiography of intracranial, visceral, and lower extremity arteries and coronary CT angiography are considered disease detection claims. Studies providing evidence for such claims typically measure diagnostic performance of a test for detecting a specified condition, in this case vascular stenosis, against a reference standard. The Applicant relied on literature data for these indications and was not able to provide source data. The non-coronary CT angiography studies utilized thresholds of either 50% or 70% for defining significant stenosis, and both of these thresholds have been used in studies supporting other imaging drug marketing approvals and are considered reasonable. None of the studies compared their performance to pre-defined success thresholds, however, the observed sensitivity and specificity results were considered clinically relevant.

For all of the above indications, the mechanism of action of Iomervu, relying on the interaction of the drug with x-rays and the distribution of iomeprol through the vascular system and into the extracellular space, is the same. Therefore, it is reasonable to consider the potential for studies intended to provide evidence of effectiveness for a given indication to provide confirmatory evidence for other related indications. Such an approach must consider potential differences in effectiveness between modalities (radiography and CT) and in some cases between body parts. For example, the coronary arteries have more motion than some other vascular structures. Nonetheless, the submitted studies were considered provide sufficient mutual support for their intended indications. For example, among the structure delineation claims, IOM-104A, IOM-104C, and IOM-104D are considered mutually supportive, and IOM-104E is mutually supportive of the studies of CT urography.

During pre-NDA discussions, FDA asked the Applicant to consider whether sufficient data were available for CT urography (b) (4) indications. The Applicant agreed to conduct a

literature search and submit relevant studies. As discussed above, we found the provided evidence adequate for CT urography. (b) (4)

After considering the above issues and limitations, we find that the Applicant has submitted substantial evidence of effectiveness to meet the regulatory standards for approval in the form of adequate and well-controlled studies that also provide mutually supportive confirmatory evidence for the proposed indications. (b) (4) .

8.2. Review of Safety

8.2.1. Safety Review Approach

Safety data for Iomervu used in intra-arterial (IA) and intravenous (IV) procedures for adults and pediatric patients were collected from 88 clinical studies that constitute the pooled safety population and the primary source for analysis of safety. Clinical studies not included in the Applicant's pooled safety population and data from postmarketing surveillance in countries where iomeprol is marketed were also reviewed.

Clinical studies included in the pooled safety analysis collected information on adverse events (AEs), serious adverse events (SAEs), and fatal outcomes, with causality assessment. Studies in the safety database that varied in completeness of safety reporting but collected information on SAEs and fatal outcomes were not included in the pooled safety analysis and were separately reviewed. Phase 2 studies, clinical pharmacology studies, clinical development studies conducted in other countries, and observational studies were not included in the pooled safety analysis.

The safety review evaluated all sources of safety data but was focused on the assessment of clinical studies that were included in the pooled safety analysis.

8.2.2. Review of the Safety Database

Overall Exposure

The overall pooled safety population (n=4,923) consists of 4,739 adult patients and 184 pediatric patients who were administered Iomervu intra-arterially or intravenously in clinical trials. Because the administered volume and concentration can vary significantly by indication, exposure is expressed as the total iodine dose throughout, which is calculated from the concentration of the solution (mass of organically bound iodine/mL; mgI/mL) and total volume (mL) administered during the radiographic procedure.

The data for the pooled safety population was further analyzed for adult and pediatric patients who received only up to the maximum recommended total iodine dose of 86 g (n=4,804) to account for the possibility of a different adverse event profile with administration of doses higher than recommended (Table 50). A total of 119 patients in the overall population were exposed to total iodine dose greater than 86 g, including 1 patient for whom an AE was reported but whose total iodine dose administered was unknown.

Table 50. Demographic and Baseline Characteristics of the Pooled Safety Population

Parameter	Overall Safety Population n=4,923	≤86 g Population n=4,804
Sex, n %		
Male	3,261 (66%)	3,165 (66%)
Female	1,659 (34%)	1,636 (34%)
Unspecified	3 (0%)	3 (0%)
Age, years		
Mean (SD)	58 (17)	58 (17)
Median	61	61
Min, max	0.03, 99	0.03, 99
Age group, n %		
≤17 years	184 (4%)	184 (4%)
<65 years	2,897 (59%)	2,823 (59%)
≥65 years	2,021 (41%)	1,976 (41%)
≥75 years	637 (13%)	628 (13%)
Missing	5 (<0.1%)	5 (<0.1%)
Race/Ethnicity, n %		
White	4,138 (84%)	4,031 (84%)
Asian	442 (9%)	442 (9%)
Black or African American	56 (1%)	54 (1%)
Hispanic	26 (1%)	26 (1%)
Other or Unknown	261 (5%)	251 (5%)
Intra-arterial procedures, n %	1,802 (37%)	1,712 (36%)
Coronary arteriography	1,002 (20%)	927 (19%)
Visceral/peripheral DSA	318 (7%)	313 (7%)
Cerebral DSA	137 (3%)	137 (3%)
Visceral/peripheral arteriography	136 (3%)	129 (3%)
Cerebral arteriography	105 (2%)	104 (2%)
General arteriography	104 (2%)	102 (2%)
Intravenous procedures, n %	3,121 (63%)	3,092 (64%)
CT body	1,161 (24%)	1,135 (24%)
Excretory urography	657 (13%)	657 (14%)
CT visceral/peripheral angiography	483 (10%)	482 (10%)
Coronary CT angiography	295 (6%)	295 (6%)
CT head	210 (3%)	210 (4%)
Chest DSA	114 (2%)	112 (2%)
Phlebography	73 (2%)	73 (2%)
CT head and neck	46 (1%)	46 (1%)
CT cerebral angiography	42 (1%)	42 (1%)
CT pulmonary angiography	40 (1%)	40 (1%)
History of hypersensitivity or allergies, n %		
Absent	3,559 (71%)	3,517 (73%)

Present	425 (9%)	422 (9%)
Not assessed	939 (20%)	865 (18%)
Region, n %		
Europe	4,132 (84%)	4,018 (84%)
Asia	432 (9%)	432 (9%)
United States	359 (7%)	354 (7%)
Concentration (mgI/mL), n %		
150	269 (5%)	269 (6%)
200	125 (3%)	125 (3%)
250	153 (3%)	153 (3%)
300	1,567 (32%)	1,556 (32%)
350	590 (12%)	581 (12%)
400	2,218 (45%)	2,120 (44%)
Unknown	1 (<0.1%)	0
Total iodine dose, grams[1]		
Mean (SD)	40 (22)	39 (18)
Median	37	36
Min, max	1.5, 260	1.5, 86

Source: Integrated Summary of Safety, Table V, Table W, Table X, Table OOO, and Table PPP
Abbreviations: DSA = digital subtraction angiography, NA = not available, SD = standard deviation
[1] For one patient included in the overall safety population, an AE was reported but total iodine dose administered was unknown.

Iomervu was administered during one procedure in all studies, though in some cases it was delivered in divided doses. In the overall safety population, 2,457 patients (50%) were exposed to one injection with total iodine doses not exceeding 86 g. A total of 2,466 patients (50%) were exposed to more than one injection, with a maximum number of up to 31, which also includes patients with an unknown number of injections. All patients who were exposed to total iodine doses exceeding 86 g were administered more than one injection, primarily in coronary arteriography and cardiac ventriculography studies and body CT studies.

Adequacy of the safety database:

The size, Iomervu exposure, and demographics of the safety database are adequate.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Categorization of Adverse Events

AE collection for 88 studies began after the informed consent form was signed and lasted until at least 24 hours after Iomervu administration. In 13 of these studies that collected laboratory and physical exam findings and assessed for lab-related AEs, AE data collection lasted up to 72 hours after administration. AEs assessed as having an unknown or missing relationship were considered related to the administration of Iomervu, in addition to those assessed as having a definite, probable, possible, reasonable possibility, or doubtful relationship to Iomervu. AEs with an unknown onset time were considered post-administration AEs. The Applicant states that in some crossover studies (crossover of two concentrations of Iomervu, or crossover of Iomervu and comparator), study drugs were administered within a short period of time and the causality of AEs was difficult to assess. The Applicant's approach conservatively attributed all

AEs reported in these studies to the administration of Iomervu.

Verbatim descriptions of the AEs observed in clinical trials were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1. All AEs reported after the first injection of the study drug, regardless of relationship, were tabulated by MedDRA system organ class and preferred term. Postmarketing AEs were coded using MedDRA version 26.0.

The severity of AEs was categorized as mild, moderate, or severe, but in some studies the severity was not assessed for SAEs or laboratory AEs for reasons that were not further described by the Applicant.

Routine Clinical Tests

The collection of data for physical examinations, laboratory tests, vital signs, ECGs, hemodynamic monitoring, and neurological and mental status examinations was limited to select studies in the pooled safety analysis.

Complete physical examination data were collected in 13 studies within 24 hours before and after the procedure. In cerebral arteriography studies, physical exams were also conducted within 1 hour after the procedure. Neurological and mental status examinations were performed in two cerebral arteriography studies (48,848-004A and -004B) within 24 hours before and 1 hour after the procedure. The exam evaluated the patients' gait, speech, coordination, cranial nerves, sensory and motor reflexes, and overall mental status.

Hematology and chemistry laboratory data were collected in the same 13 studies as above within 24 hours before (up to 7 days before for pediatric patients) and 24 hours after the procedure. Serum creatinine and blood urea nitrogen were measured at 48- and 72-hours post-procedure in certain arteriography studies. Any laboratory changes from pre-procedure to post-procedure considered by the investigator to be an AE was included in the recording of AEs.

Vital sign data (blood pressure, heart rate, and body temperature) were collected in 9 of the 13 studies and were measured within 24 hours before the procedure and at specific time points up to 24 hours after injection. Any vital sign changes from pre-procedure to post-procedure considered by the investigator to be an AE was included in the recording of AEs. Hemodynamic monitoring was also conducted in the four coronary arteriography and cardiac ventriculography studies. For coronary artery injections, hemodynamic measurements (aortic systolic and diastolic pressure and heart rate) were obtained immediately prior to and at 5, 10, 15, 30, 40, 50, 60, 90, 120, 150, and 180 seconds after the first injection of Iomervu. For ventriculography, hemodynamic measurements of left ventricular end diastolic pressure and left ventricular peak systolic pressure were obtained 10 minutes prior to, immediately prior to, and at 5, 30, 60, and 120 seconds after the first injection of Iomervu.

Twelve-lead ECGs were collected from 13 studies within 24 hours before and 1-, 4-, and 24-hours post-procedure. In four coronary arteriography and cardiac ventriculography studies,

continuous ECG monitoring was performed throughout the procedure. Twelve- and 2-lead ECGs in the coronary arteriography and cardiac ventriculography studies were evaluated in an off-site blinded read analysis in IOM-103. Two-lead rhythm strip ECG data were obtained within 10 minutes before the first injection and continuously for up to 180 seconds after each coronary artery injection, or up to 120 seconds after each left ventricular injection. Any change in ECG parameters from pre-procedure to post-procedure considered by the investigator to be an AE was included in the recording of AEs.

8.2.4. Safety Results

Deaths

Seven deaths were reported for adult patients in the pooled population, none of which were considered related to Iomervu by the investigator. Seven other deaths were reported for adult patients in studies not included in the pooled safety analysis population.

Deaths reported in the pooled safety population
An 80-year-old female with cirrhosis, type 1 diabetes, rectal cancer, and bleeding esophageal varices for many years underwent CT urography. The patient experienced melena and died one day after the procedure. The investigator considered the event to be severe and not related to Iomervu.

A 71-year-old male with heart failure, left bundle branch block, respiratory insufficiency, bladder cancer with hematuria, and renal insufficiency underwent CT urography for staging of urinary bladder cancer. Two weeks prior to the procedure, the patient was hospitalized for eight days because of respiratory insufficiency. The patient completed the procedure with no reported adverse events. Approximately two weeks later, the patient received blood transfusions because of hematuria. The patient's general condition worsened, and the patient lost consciousness 21 days after administration of Iomervu. One day later, the patient died. The cause of death was attributed to cardiac failure. The investigator described this event as severe and not related to the administration of Iomervu.

A 70-year-old male with severe aortoiliac arteritis, oropharyngeal cancer, and lung cancer with widespread metastases underwent abdominal CT for staging of liver metastasis. Three hours prior to the examination, the patient had mottling on the skin of the lower extremities, abdominal pain, and the patient was unable to walk. Approximately seven hours after the abdominal CT, the patient experienced intestinal mesenteric infarction and died. The investigator considered the event to be unrelated to the administration of Iomervu and attributed the death to intestinal ischemia caused by the patient's underlying arteritis.

A 52-year-old male with renal cancer with widespread metastases, impaired renal function, and hepatomegaly underwent excretory urography. Approximately three weeks after receiving Iomervu, the patient experienced cardiorespiratory arrest and died. The investigator considered

the cardiorespiratory arrest to be severe and not related to the administration of Iomervu. The cause of death was attributed to progressive underlying disease.

A 63-year-old female with hypertension, type 2 diabetes, and coronary artery disease underwent coronary arteriography. Two weeks after the procedure, the patient underwent coronary artery bypass graft surgery. Four days later, the patient experienced severe acute kidney injury that was resistant to extracorporeal dialysis and died. The cause of death was attributed to cardiac arrest. The investigator did not attribute the acute kidney injury to the administration of Iomervu.

A 69-year-old male with hypertension and peripheral vasculopathy underwent coronary arteriography for coronary artery disease. Nineteen days after the coronary arteriography procedure, the patient underwent coronary artery bypass surgery. The patient experienced a severe stroke approximately one day after surgery and died four days later. An autopsy was performed and confirmed the cause of death to be a stroke. The investigator considered the event unrelated to the administration of Iomervu.

A 56-year-old male with hypertension, peripheral vasculopathy, coronary artery disease, unstable angina, and severe reduction of left ventricular function underwent coronary arteriography. Eight days after the procedure, the patient underwent coronary artery bypass graft surgery. Three hours after the surgery, the patient experienced severe cardiogenic shock and died 70 minutes later. The investigator considered the event unrelated to the administration of Iomervu.

Deaths reported in studies not included in the pooled safety population

A 69-year-old male with cardiovascular disease, history of coronary artery bypass surgery, and anterior myocardial infarction was admitted because of coronary artery bypass occlusion and underwent coronary arteriography. Following successful recanalization at the end of the procedure, the patient lost consciousness and subsequently died. Although the assessment of relationship to Iomervu was not collected, the investigator considered the cause of death to be cardiogenic shock due to the patient's underlying cardiovascular disease. Fatal cardiovascular reactions including shock are known to occur with iodinated contrast agents and class-wide warning language for cardiovascular adverse reactions has been included in labeling. This event is not a signal of new serious risk related to Iomervu.

A 63-year-old male with bronchial carcinoma and suspected pulmonary embolism underwent intravenous DSA. Approximately 60 minutes after administration of Iomervu, the patient experienced bronchial hemorrhage causing acute respiratory insufficiency and died. Autopsy showed that the pulmonary hemorrhage was caused by a tumor-induced vasobronchial fistula. There were no signs of a catheter-induced perforation. The investigator considered the cause of death to be attributed to metastatic lung carcinoma and not related to the administration of Iomervu or the angiographic procedure.

A 62-year-old male with stomach cancer, liver and lymphatic metastases, and diabetes underwent body CT. Seven days after the procedure, the patient died due to asphyxia. The investigator considered the patient's death to be unrelated to Iomervu.

A 65-year-old female with lung cancer underwent body CT. Two days after the procedure, the patient died due to cardiac tamponade. The investigator considered the patient's death to be unrelated to Iomervu.

A 63-year-old male with advanced cancer of the pancreatic tail, accompanied by extension to the stomach and liver metastasis, underwent body CT. No adverse event was reported at the time of the procedure. Twenty days after the procedure, the patient died due to disease progression and respiratory failure. The investigator considered the patient's death to be unrelated to Iomervu.

A 60-year-old male with unstable angina, hypertension, and renal failure underwent coronary angiography. Three days after the procedure, the patient underwent coronary artery bypass surgery. One day later, the patient died as a result of ventricular fibrillation. The investigator considered the patient's death to be unrelated to Iomervu.

A 66-year-old male with lung cancer, pneumonia, and hydrothorax underwent chest angiography. Sixteen days after the procedure, the patient died due to respiratory insufficiency. The investigator considered the patient's death to be unrelated to Iomervu.

Serious Adverse Events

A total of 37 SAEs were reported for 28 patients (0.6%) in the overall safety population, of whom 3 patients received a total iodine dose exceeding 86 g (Table 51). These latter patients experienced pulmonary embolism (90 g), ventricular fibrillation (120 g), and myocardial infarction (200 g). Seven fatal AEs were observed in seven patients (0.1%), as described in the previous section. Thirteen SAEs in seven patients (0.1%) were considered related to Iomervu by the investigator.

Neither a significant difference in incidence or trend for higher SAEs was observed between the population exposed up to and over the recommended maximum dose, though analysis is limited by the small number of SAEs and low proportion of patients dosed at >86 g iodine. The rank order of AEs by system organ class remained the same for both populations.

No SAEs were reported in pediatric patients in the pooled safety population.

Table 51. Treatment Emergent Serious Adverse Events in Adult and Pediatric Patients

	Overall Safety Population n=4,923		**≤86 g Population n=4,804**	
MedDRA System Organ Class	n SAEs	n (%) Patients	n SAEs	n (%) Patients

At least one SAE	37	28 (0.6)	34	25 (0.5)
Cardiac disorders	14	13 (0.3)	12	11 (0.2)
Atrial fibrillation	1	1 (<0.1)	1	1 (<0.1)
Atrioventricular block complete	2	2 (<0.1)	2	2 (<0.1)
Cardiac failure congestive	1*	1 (<0.1)*	1*	1 (<0.1)*
Cardio-respiratory arrest	1	1 (<0.1)	1	1 (<0.1)
Cardiogenic shock	1	1 (<0.1)	1	1 (<0.1)
Left ventricular dysfunction	1	1 (<0.1)	1	1 (<0.1)
Myocardial infarction[1]	4*	4 (<0.1)*	3*	3 (<0.1)*
Ventricular fibrillation	3*	3 (<0.1)*	2*	2 (<0.1)*
Nervous system disorders	6	5 (0.1)	6	5 (0.1)
Aphasia	1	1 (<0.1)	1	1 (<0.1)
Cerebral ischemia	1	1 (<0.1)	1	1 (<0.1)
Cerebrovascular accident	1	1 (<0.1)	1	1 (<0.1)
Cerebrovascular disorder	1*	1 (<0.1)*	1*	1 (<0.1)*
Hemiplegia	2	2 (<0.1)	2	2 (<0.1)
Vascular disorders	5	5 (0.1)	5	5 (0.1)
Circulatory collapse	2	2 (<0.1)	2	2 (<0.1)
Hypertension	1*	1 (<0.1)*	1*	1 (<0.1)*
Hypertensive crisis	1	1 (<0.1)	1	1 (<0.1)
Peripheral artery thrombosis	1	1 (<0.1)	1	1 (<0.1)
Respiratory, thoracic and mediastinal disorders	5	4 (<0.1)	4	3 (<0.1)
Dyspnea	1	1 (<0.1)	1	1 (<0.1)
Hypoxia	1	1 (<0.1)	1	1 (<0.1)
Pulmonary embolism	1	1 (<0.1)	0	0
Respiratory arrest	1*	1 (<0.1)*	1*	1 (<0.1)*
Respiratory failure	1	1 (<0.1)	1	1 (<0.1)
Gastrointestinal disorders	3	3 (<0.1)	3	3 (<0.1)
Intestinal ischemia	1	1 (<0.1)	1	1 (<0.1)
Melena	1	1 (<0.1)	1	1 (<0.1)
Nausea	1	1 (<0.1)	1	1 (<0.1)
Renal and urinary disorders	2	2 (<0.1)	2	2 (<0.1)
Acute kidney injury[2]	2*	2 (<0.1)*	2	2 (<0.1)*
General disorders and administrative site conditions	1	1 (<0.1)	1	1 (<0.1)
Pain	1*	1 (<0.1)*	1*	1 (<0.1)*
Infections and infestations	1	1 (<0.1)	1	1 (<0.1)
Pneumonia	1	1 (<0.1)	1	1 (<0.1)

Source: Integrated Summary of Safety, Table AA
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, SAE = serious adverse event
* Indicates an event that was assessed as related to Iomervu administration by the investigator in at least one patient. Related AEs include definite, probable, possible, reasonable possibility, doubtful, unknown, or missing relationship to study agent.
[1] Acute myocardial infarction was combined with myocardial infarction.
[2] Includes an event that the Applicant coded as "chronic kidney disease"

Nine SAEs in seven patients (0.1%) were considered related to Iomervu by the investigator. The majority of these events are consistent with those observed with other iodinated contrast agents and have been observed in postmarketing surveillance of Iomervu. Brief narratives and assessment of the SAEs considered related to the administration of Iomervu by the investigator are provided below.

- A 71-year-old female with left upper lobe chest nodule, small bowel obstruction, hysterectomy, and axillary lipoma underwent body CT. The patient's blood pressure increased from 124/82 mm Hg at 10 minutes prior to administration of Iomervu to 240/120 mm Hg at one-hour post-administration. The investigator considered the event to be definitely related to Iomervu.

- A 56-year-old male with coronary artery disease underwent coronary arteriography. The patient experienced ventricular fibrillation after the last injection of Iomervu in the right coronary artery and was immediately treated with electrical cardioversion. The investigator described the event as probably related to Iomervu.

- A 55-year-old male with hypertension underwent coronary arteriography. The patient experienced ventricular fibrillation after the second injection in the left coronary artery and was immediately treated with electrical cardioversion. The investigator described the event as probably related Iomervu.

- A 61-year-old male with chronic renal insufficiency (baseline serum creatinine 3.5 mg/dL), hypertension, claudication, anemia, pneumonia, and hyperuricemia underwent peripheral and visceral arteriography. The patient experienced right heart failure, abnormal kidney function, and pneumonia with fever and chills two days following the first injection of Iomervu. Hospitalization was prolonged and all three events required treatment. The patient's serum creatinine was 4.8, 5.7, and 5.7 mg/dL at 24, 48, and 72 hours, respectively, after Iomervu administration. All three adverse events were still present at the last recorded evaluation of this patient. No further follow-up was available. The investigator considered the heart failure and abnormal kidney function to be definitely related to Iomervu and the pneumonia to be unrelated to Iomervu.
  Although the verbatim term for this event was chronic renal insufficiency, the narrative describes an acute increase in serum creatinine in a patient with chronic renal insufficiency. Therefore, the reviewer considers the event to be acute kidney injury.

- A 47-year-old male with left anterior descending (LAD) coronary artery partial occlusion and ischemic cardiomyopathy underwent coronary arteriography for recurring angina. During the second injection of Iomervu, an occlusion of the proximal LAD occurred resulting in myocardial infarction. Percutaneous transluminal coronary angioplasty was performed, and the event resolved after two hours. The investigator described the event as possibly related to Iomervu.

- A 52-year-old male with dysarthria, ataxic gait, lower left facial paresis, and diplopia underwent cerebral DSA. A previous CT scan showed multiple areas of bilateral, subtentorial hypodensity with the appearance of ischemic lesions. The patient experienced severe apneic episodes starting 5 minutes after injection of Iomervu and lasting for three hours. After the procedure, the patient experienced respiratory arrest and worsening cerebrovascular status (verbatim term cerebral vasculopathy). The investigator concluded

that the events resulted from the patient's pathologic condition and the brief ischemia was "naturally associated" with injection of the contrast agent.

- A 69-year-old male with heart failure, cardiomegaly, coronary artery disease, hypertension, angina, myocardial infarction, and a motor vehicle accident in which he sustained multiple contusions and fractured hip, pelvis, and ribs, underwent coronary arteriography. The patient experienced moderate generalized pain approximately two hours after the first injection. The investigator considered the event to be of unknown relationship to Iomervu. The reviewer considers this SAE attributable to the multiple injuries, but relatedness to Iomervu could not be ruled out due to lack of details regarding pain symptoms prior to administration of Iomervu.

A total of 28 SAEs in 23 patients (0.5%) were considered unrelated to Iomervu by the investigator, including seven leading to death (described previously). The narratives were reviewed for relatedness of the events to Iomervu, and the reviewer concurs with the assessment by the investigator that they were attributable to patients' comorbidities or other procedures after completion of the radiographic procedure. The events lacked temporal association to radiographic procedures, occurred before administration of Iomervu, or had confirmation of disease causality at autopsy.

AEs with no information on investigator assessment of seriousness were also reviewed. All were changes in various laboratory and vital sign assessments from pre- to post-procedure.

One patient experienced a non-treatment emergent SAE of left ventricular dysfunction during a coronary arteriography procedure in study 48,848-001B.

<u>SAEs reported in studies not included in the pooled safety population</u>
In four pharmacokinetic studies of 108 patients with renal impairment, patients undergoing hemodialysis, pediatric patients, and elderly patients, two SAEs were reported for two patients. One SAE of infection was reported in a study of patients with severe renal impairment, and one SAE of chest pain six days post-procedure was reported in a study in elderly patients. Both were considered unrelated to the administration of Iomervu by the investigator.

In phase 2 studies of 181 patients with intra-arterial drug administration and 131 patients with intravenous administration, no SAEs or deaths were reported.

In 40 studies conducted in Japan, 2,578 patients and healthy volunteers were administered Iomervu and adverse reaction data were available for 2,384 patients. SAEs were reported for six patients, the most frequent being hypotension in three patients. Five deaths were reported (described above), including one reported outside of the study period at 20 days. None of the fatal cases reported in the Japanese clinical development studies were considered related to Iomervu.

In other observational studies conducted in Germany (n=9), Korea (n=1), and Japan (n=4) of 108,045 patients, SAEs were reported in 28 patients. Hypersensitivity reactions and nausea were the most frequent SAEs observed that were considered related to Iomervu by the investigator. SAEs of dyspnea, mucosal edema, nausea, and paresthesia that were considered related to Iomervu were attributed to hypersensitivity. SAEs for which relatedness could not be ruled out that were similar to those observed in the pooled safety analysis were cardiac arrest, nausea, increased blood pressure, dyspnea, respiratory failure, vomiting, increased heart rate, syncope, cough, pulmonary edema, wheezing, erythema, and circulatory collapse.

SAEs for which relatedness could not be ruled out that were observed in postmarketing reports were convulsion, tremor, and hyperhidrosis.

In the pediatric population, a study that was not included in the pooled analysis reported one SAE considered unrelated by the investigator. A 3-year-old male with congenital heart defect and pulmonary edema underwent coronary arteriography for postoperative assessment of surgical correction of cardiac defects. Two seconds after receiving a 20 mL intra-arterial injection, the patient experienced cardiac arrest which lasted for eight seconds and atrioventricular block which lasted for 170 seconds. Although the relationship was not collected on the case report form, the investigator considered the events related to the catheterization process and not the administration of Iomervu. Due to the timing and nature of the events, relatedness to Iomervu cannot be ruled out.

No new significant safety signal was identified from the reporting of SAEs in studies not included in the pooled safety population.

Dropouts and/or Discontinuations Due to Adverse Effects

Seven patients (0.1%) in the overall safety population discontinued due to one or more AEs. Two patients discontinued from the study due to SAEs after intra-arterial administration, neither event was considered related to Iomervu administration. The first patient experienced cerebral ischemia at the beginning of a selective coronary arteriography procedure, following the first 5 mL test injection of Iomervu. The other patient experienced circulatory collapse (reported as vasovagal syncope) during a technically challenging femoral arteriography procedure.

Patients who discontinued due to AEs considered probably related to Iomervu experienced malaise, erythema, severe rhinitis (described by the investigator as spasmodic sneezing that lasted for two minutes), and back pain. For one patient who experienced cough, dyspnea, hypertension, and erythema, there was no assessment of causality by the investigator and these AEs were considered related to Iomervu. For another patient who discontinued from the study, the AE was not specified, with no further available information and assessment of causality.

The discontinuations that occurred due to the AEs described do not suggest an important safety issue.

Significant Adverse Events

A total of 29 severe AEs were reported in 23 patients (0.5%), 2 of which were reported for 2 patients who received doses exceeding 86 g. Seventeen severe and serious AEs were reported in 14 patients (0.3%), all of which were discussed above. Of note, severity was not collected for serious AEs or laboratory AEs in older studies, and 10 SAEs did not have severity information.

Twelve severe AEs not considered serious by the investigator were reported in nine patients (0.2%). Those considered related by the investigator consisted of three AEs of vomiting in three patients (most frequent), headache, nausea, sneezing, and urticaria. Those that were not considered related were atrial fibrillation, bradycardia, cardiac arrest, neurological exam abnormal, and pain in extremity.

Treatment Emergent Adverse Events and Adverse Reactions

A total of 854 TEAEs were experienced by 486 patients in the overall safety population (Table 52). There was one AE with no information on whether the event was treatment emergent for a patient who received a total iodine dose of 35 g, which was included as a TEAE. A total of 28 AEs were experienced by 13 patients who were administered total iodine doses exceeding 86 g. After excluding these patients administered doses exceeding 86 g, 826 AEs were experienced by 473 patients in the population that received doses compatible with those recommended in labeling (n=4,804).

No significant difference in incidence or specific trend for higher AEs was observed between the overall safety population and the ≤86 g iodine population. The rank order of AEs by system organ class remained the same for both populations. The most notable difference between the two populations was a higher incidence of cardiac AEs in patients who received doses exceeding 86 g (94 AEs in 81 patients versus 86 AEs in 75 patients). These preferred terms were chest pain, bradycardia, defect conduction intraventricular, sinus bradycardia, myocardial infarction, and ventricular fibrillation.

The overall safety population experienced 488 mild (57%), 255 moderate (30%), and 29 severe (3%) AEs. Severity information was not collected for 82 (10%) AEs in older studies for SAEs or laboratory AEs.

Table 52. Treatment Emergent Adverse Events in Adult and Pediatric Patients

	Overall Safety Population n=4,923		**≤86 g Population n=4,804**	
MedDRA System Organ Class	n AEs	n (%) Patients	n AEs	n (%) Patients
At least one AE	854	486 (9.9)	826	473 (9.8)

General disorders and administrative site conditions	190	156 (3.3)	188	155 (3.4)
Nervous system disorders	126	107 (2.2)	124	106 (2.2)
Gastrointestinal disorders	124	87 (1.8)	121	84 (1.7)
Investigations	98	65 (1.4)	90	63 (1.4)
Cardiac disorders	94	81 (1.6)	86	75 (1.6)
Vascular disorders	57	56 (1.1)	55	54 (1.1)
Musculoskeletal and connective tissue disorders	50	49 (1.0)	49	48 (1.0)
Skin and subcutaneous tissue disorders	41	38 (0.8)	41	38 (0.8)
Respiratory, thoracic, and mediastinal disorders	31	27 (0.5)	30	26 (0.5)
Psychiatric disorders	15	13 (0.3)	15	13 (0.3)
Injury, poisoning, and procedural complications	7	6 (0.1)	7	6 (0.1)
Renal and urinary disorders	6	6 (0.1)	6	6 (0.1)
Eye disorders	4	4 (0.1)	4	4 (0.1)
Ear and labyrinth disorders	3	3 (0.1)	3	3 (0.1)
Infections and infestations	2	2 (0.1)	2	2 (0.1)
Surgical and medical procedures	3	3 (0.1)	3	3 (0.1)
Metabolism and nutrition disorders	2	2 (<0.1)	1	1 (<0.1)
Uncoded	1	1 (<0.1)	1	1 (<0.1)

Source: Integrated Summary of Safety Appendix 3, Table B and Table E
Abbreviations: AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities

Out of 119 patients (2%) in the overall safety population that received doses exceeding 86 g or an unknown dose, 13 patients (10.9%) experienced 28 AEs. The incidence of AEs for the proportion of patients who received 86 g iodine or less was similar at 9.8%. However, the available clinical data are not adequate to support safety of administration of doses exceeding 86 g.

The most common AEs assessed as related by the Applicant are listed by preferred term in Table 53. The most frequent adverse reactions reported after Iomervu administration for 4,621 adult patients who received doses ranging from 1.5 g to 86 g were feeling hot, headache, nausea, chest pain, back pain, and vomiting. Iomervu was not shown to be associated with new adverse reactions relative to other iodinated contrast agents.

Table 53. Adverse Events Assessed as Related to Iomervu Occurring in ≥0.2% Adult and Pediatric Patients

	Overall Safety Population n=4,923		**≤86 g Population n=4,804**	
MedDRA Preferred Term	n AEs	n (%) Patients	n AEs	n (%) Patients
Feeling hot	93	91 (1.8%)	93	91 (1.9%)
Headache	60	56 (1.1%)	58	55 (1.1%)
Nausea	51	49 (1.0%)	50	48 (1.0%)
Extrasystoles[1]	35	29 (0.6%)	35	29 (0.6%)
Chest pain[2]	32	30 (0.6%)	27	27 (0.6%)
Back pain	26	26 (0.5%)	25	25 (0.5%)
Vomiting	25	25 (0.5%)	24	24 (0.5%)
Hematoma[3]	21	21 (0.4%)	21	21 (0.4%)
Dysgeusia[4]	19	18 (0.4%)	19	18 (0.4%)

Blood pressure increased[5]	17	17 (0.3%)	17	17 (0.3%)
Injection site pain[6]	16	16 (0.3%)	15	15 (0.3%)
Dizziness	15	15 (0.3%)	15	15 (0.3%)
Urticaria	14	14 (0.3%)	14	14 (0.3%)
Flushing[7]	13	13 (0.3%)	13	13 (0.3%)
Electrocardiogram T wave abnormal	11	11 (0.2%)	11	11 (0.2%)
Hypotension	11	11 (0.2%)	10	10 (0.2%)
Pain	10	10 (0.2%)	10	10 (0.2%)
Diarrhea	9	9 (0.2%)	9	9 (0.2%)
Dyspnea	8	8 (0.2%)	8	8 (0.2%)
Ecchymosis	8	8 (0.2%)	8	8 (0.2%)
Pain in extremity	8	8 (0.2%)	8	8 (0.2%)

Source: Pooled safety data from Iomervu clinical studies, FDA clinical reviewer
Abbreviations: AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities
[1] Includes preferred term ventricular extrasystoles
[2] Includes preferred terms angina pectoris and chest discomfort
[3] Includes preferred terms catheter site hematoma and injection site hematoma
[4] Includes preferred term taste disorder
[5] Includes preferred term hypertension
[6] Includes preferred terms catheter site pain, infusion site pain, and injection site discomfort
[7] Includes preferred term hot flush

In the prescribing information for Iomervu, the preferred term “tension” was reworded as “anxiety” to provide a more consistent description of the adverse reaction as described in other labels for iodinated contrast agents.

Of the 486 patients who experienced at least one TEAE in the overall safety population of 4,923 patients (total 854 AEs), 485 AEs were reported for 216/359 patients (60%) in studies conducted in the U.S., and 369 AEs were reported for 270/4,564 patients (6%) in studies conducted outside the U.S. This may reflect differences in the assessment and reporting of AEs, but further review was difficult due to lack of specific details provided on the nature of data collection other than the information discussed in the initial sections of the safety review. However, major discrepancies in the types of AEs reported between the U.S. and non-U.S. studies were not identified. The most frequent AEs observed for Iomervu were similar across all studies without regard to U.S. versus outside U.S. locations.

Pediatric adverse events

In the pediatric population, 40 AEs were observed in 29 of the 184 patients who received total iodine doses ranging from 1.8 g to 76 g. All AEs reported in the pediatric population were treatment emergent and assessed as related by the investigator. The most frequent adverse reaction was 22 reports of extrasystoles in 17 patients (9%). All cases of extrasystole originated from one study of patients undergoing cardioangiography, and in 10 of the 17 patients they were reported before administration of Iomervu. The relationship of these extrasystoles to Iomervu was not assessed by the investigator and the Applicant considered all AEs for the 17 patients to be TEAEs, using a conservative approach. We consider it reasonable to exclude the extrasystole cases that occurred prior to drug administration and the incidence of extrasystoles in pediatric patients was assessed as 4% rather than 9%. The other AEs experienced in pediatric patients were hypotension, hypertension, erythema, tachycardia, vomiting, cough, dyspnea,

bronchospasm, headache, nausea, and urticaria. All AEs observed in pediatric patients were also reported for adults and occurred with similar incidence. No serious adverse reactions or deaths were reported in the pediatric population in the pooled safety analysis.

AEs reported in studies not included in the pooled safety population
In four pharmacokinetic studies of 108 patients with renal impairment, patients undergoing hemodialysis, pediatric patients, and elderly patients, the most frequently reported AE was vasodilation in 21 patients. In the study of patients with renal impairment, headache was also reported in three patients. In the study of patients undergoing hemodialysis, four patients experienced sensation of warmth that was considered related. In the study of pediatric patients, six patients experienced 15 AEs, with the most frequent AEs being pain, diarrhea, nausea, and vasodilation, all mild or moderate in intensity. In the study of elderly patients, 10 patients experienced vasodilation, 9 of which were considered related to Iomervu.

In phase 2 studies of 312 patients, AEs were reported in 21 patients. In a cerebral arteriography study, four patients experienced scotoma. Other AEs reported in this study include headache, trembling, paresthesia of the hand and face, distress during catheter positioning, and bradyarrhythmia. In a coronary arteriography study, five patients experienced cutaneous erythema, dizziness, angina, and nausea. In a urography study, six patients experienced headache, hypertension, tachycardia, distress, and pruritus.

In 40 clinical development studies conducted in Japan, 2,578 patients and healthy volunteers were administered Iomervu and adverse reaction data were available for 2,384 patients. The most frequently reported adverse reactions consisted of heat sensation, nausea, rash, vomiting, and itching.

In other observational studies conducted in Germany (n=9), Korea (n=1), and Japan (n=4) of 108,045 patients, AEs were reported in 1,446 patients. Review of the AEs collected during these studies did not identify any inconsistencies with the AE profile observed in the overall safety population.

No new significant safety signal was identified from the reporting of AEs in studies not included in the pooled safety population.

Laboratory Findings

Laboratory findings were assessed for changes of potential clinical importance, which the Applicant predefined for each hematology and chemistry parameter. The majority of adult patients had laboratory values within the normal range at baseline (within 24 hours prior to procedure). A total of 39 laboratory findings were reported as TEAEs in 27 patients (0.5%), 31 of which occurred in 20 patients (0.4%) and were considered related to Iomervu, as shown in Table 54. Eight TEAEs were experienced by two patients (<0.1%) who received doses exceeding 86 g, which mostly consisted of blood gas abnormalities.

Table 54. Laboratory Adverse Reactions in Adult Patients

MedDRA Preferred Term	Overall Safety Population n=4,923	
	n AEs	n (%) Patients
At least one AE	31	20
Hematology	11	8 (0.2%)
Activated partial thromboplastin time prolonged	5	5 (0.1%)
Prothrombin time prolonged	3	3 (0.1%)
Activated partial thromboplastin time shortened	1	1 (<0.1%)
Eosinophil count increased	1	1 (<0.1%)
Neutrophil count increased	1	1 (<0.1%)
Chemistry	20	12 (0.2%)
Alanine aminotransferase increased[1]	6	6 (0.1%)
Blood creatinine increased	3	3 (0.1%)
Aspartate aminotransferase increased[2]	3	3 (0.1%)
Blood bilirubin increased	2	2 (<0.1%)
Blood urea increased	2	2 (<0.1%)
Blood creatine phosphokinase MB increased	1	1 (<0.1%)
Blood creatine phosphokinase increased	1	1 (<0.1%)
Blood lactate dehydrogenase increased	1	1 (<0.1%)
Blood potassium decreased	1	1 (<0.1%)

Source: Pooled safety data from Iomervu clinical studies, FDA clinical reviewer
Abbreviations: AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities
[1,2] Includes the preferred term "liver function test abnormal" for the verbatim term "AST and ALT increased".

Screening of the laboratory findings for Hy's Law cases did not identify any signal for potential drug-induced liver injury.

Serum creatinine was assessed in greater detail for findings suggestive of acute kidney injury, a known risk of iodinated contrast agents. The Kidney Disease Improving Global Outcomes (KDIGO) criteria provide a consensus definition for intrinsic acute kidney injury and are also used to define contrast-associated acute kidney injury (KDIGO Acute Kidney Injury Work Group, 2012; American College of Radiology, 2024). The guidelines define acute kidney injury as an absolute increase of ≥0.3 mg/dL or relative increase of ≥50% in serum creatinine at 48 to 72 hours from baseline (or nephrotoxic event). Although glomerular filtration rate is a more accurate measure of renal function, data analysis was driven by serum creatinine.

Serum creatinine data at baseline and at 24-, 48-, and 72-hours post-administration were assessed for absolute and relative increases that meet the KDIGO definition of acute kidney injury. Out of 1,228 patients who had data at baseline and at least one post-administration time point, 96 patients had complete records at 24, 48, and 72 hours. The median baseline serum creatinine for 1,228 patients was 0.9 mg/dL.

A slight shift imbalance towards an increase in serum creatinine was observed consistently at all time points after administration of Iomervu (Table 55). Potentially clinically meaningful increases in serum creatinine were observed at 48- and 72-hours post-administration in 2% of

patients (23 of 1,228 patients) using the criterion of relative increase of ≥50% from baseline, and 5% of patients (61 of 1,228 patients) using the criterion of absolute increase of ≥0.3 mg/dL.

Although the collection of creatinine data was incomplete and serum creatinine has limitations for detection of acute kidney injury, the available data demonstrate a potential risk. These observations are generally consistent with experience from intra-arterial or intravenous administration of other iodinated contrast agents. The potential risk of renal impairment is adequately addressed in the prescribing information with the inclusion of the class-wide warning for acute kidney injury in Section 5.4 and the inclusion of acute kidney injury as an adverse reaction in Section 6.1.

Table 55. Relative Change in Serum Creatinine After Administration of Iomervu Among 1,228 Patients with Baseline and Post-Administration Measurements

Relative Change from Baseline	24 Hours Post-Administration (n=537)	48 Hours Post-Administration (n=790)	72 Hours Post-Administration (n=104)
≤-50%	0	3 (<1%)	2 (2%)
>-50% to ≤-25%	10 (2%)	30 (4%)	2 (2%)
>-25 to <0%	134 (25%)	217 (27%)	22 (21%)
0%	140 (26%)	182 (23%)	27 (26%)
>0% to <25%	189 (35%)	273 (35%)	32 (31%)
≥25% to <50%	50 (9%)	68 (9%)	13 (13%)
≥50%	14 (3%)	17 (2%)	6 (6%)

Source: Pooled safety data from Iomervu clinical studies, FDA clinical reviewer
The dataset has one record per patient per post-administration time point.

As was observed in the adult population, the majority of laboratory findings for pediatric patients were within the normal range at baseline (within seven days prior to procedure) and remained within the normal range post-administration. Mean changes in hematology and chemistry parameters from baseline and at 24 hours post-administration did not reveal any clinically meaningful trends.

Vital Signs

Vital signs were assessed for changes of potential clinical importance, which the Applicant predefined for blood pressure, heart rate, and temperature. The majority of adult patients had vital signs within the normal range at baseline within 24 hours prior to procedure. Thirteen patients (0.3%) experienced 14 vital sign-related TEAEs. These included six AEs of increases in blood pressure experienced in six patients, of which five were considered related to Iomervu by the investigator. Other vital sign-related AEs were decreases in blood pressure, increases in body temperature, increases in heart rate, and decreases in heart rate, all of which were assessed as related to Iomervu except one AE of blood pressure decrease and one AE of heart rate increase.

For the pediatric population, the majority of patients' vital signs were within the normal range at baseline immediately prior to procedure and remained within the normal range post-procedure. Mean changes in blood pressure, heart rate, and body temperature from baseline and at multiple time points post-administration up to two hours post-procedure did not indicate any clinically meaningful trends.

No significant safety signal was identified from the collected vital sign data.

Electrocardiograms (ECGs)

ECGs were assessed for changes of potential clinical importance, which the Applicant predefined for each ECG parameter. The majority of ECG parameters for adult patients were within the normal range at baseline within 24 hours prior to procedure. Shift tables were used to present changes from baseline in ECG parameters at each post-administration time point. Post-administration shifts to outside the normal range appeared similar between Iomervu and the comparator. No significant safety signal was identified from the collected ECG data.

Twenty patients (0.4%) experienced 21 ECG-related TEAEs. The most commonly reported were 11 AEs of T wave abnormal experienced in 11 patients, all from a study of coronary arteriography and cardiac ventriculography. Other ECG-related AEs were ST segment depression, T wave inversion, ST segment elevation, ST-T change, ECG abnormal, and ECG change. All AEs except ST segment elevation were considered related to Iomervu by the investigator.

For pediatric patients, the majority of ECG parameters at baseline within seven days prior to procedure, four to six hours post-procedure, and 24 hours post-procedure were within normal range. None of the changes in ECG evaluations from baseline to post-administration time points were assessed as clinically significant by the investigator. One patient experienced right intraventricular conduction abnormalities one day after a urography procedure and one patient experienced repolarization abnormalities one day after CT of the brain. As was described previously, 17 patients in one cardioangiography study (PT-27) experienced transient and sporadic extrasystoles, the majority of which were present only at baseline, and one patient experienced ST segment decreases post-administration. The majority of patients in this cardioangiography study demonstrated abnormal ECGs at baseline (within 24 hours prior to procedure), with most showing signs of hypertrophy of one or both ventricles and some conduction or rhythm abnormalities.

Arrhythmias are known to occur with other iodinated contrast agents and use of class-wide warning language is adequate to address this issue.

QT

The Interdisciplinary Review Team for Cardiac Safety Studies (IRT) was consulted for assessment of the Applicant's QTc evaluation. A thorough QT study was not conducted, and the IRT did not identify an adequate substitute in the application.

Cardiac arrhythmias are known adverse reactions for iodinated contrast agents. Like other iodinated contrast, Iomervu will be administered by health care professionals in monitored settings with availability of emergency resuscitation equipment and trained personnel. Therefore, class warning language is expected to mitigate the risk.

Immunogenicity

Clinical immunogenicity studies were not needed or conducted.

8.2.5. Analysis of Submission-Specific Safety Issues

Hypersensitivity Reactions

Hypersensitivity reactions are a known class-wide risk with iodinated contrast agents, with most severe hypersensitivity reactions occurring shortly after administration of the first or subsequent doses. AEs with preferred terms of hypersensitivity reaction or anaphylaxis were not specifically reported in clinical trials of Iomervu, however, it is very likely that some of the observed adverse reactions such as urticaria occurred due to hypersensitivity.

The Applicant's summary of postmarketing data identified 25,620 patients (0.02%) from over 160 million exposed patients who experienced hypersensitivity reactions as defined by Standardized MedDRA Query. Of the patients with hypersensitivity reactions, 7,847 (31%) had serious reactions. Anaphylactic reactions after administration of Iomervu were reported in 6,689 patients (0.004%).

The data demonstrate there is risk for hypersensitivity reactions with administration of Iomervu as for other iodinated contrast agents. The proposed labeling for Iomervu related to hypersensitivity in Sections 5.2 and 6.2 is similar to that of other marketed iodinated contrast agents.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions are another known class-wide risk with iodinated contrast agents that manifest most commonly as delayed reactions. Severe dermatologic AEs were not observed in clinical trials of Iomervu.

As discussed in more detail in Section 8.2.9, the Division of Pharmacovigilance (DPV) was consulted for review of Iomervu postmarketing safety data. Several reports were identified for severe cutaneous reactions that are described in the class-wide warnings for iodinated contrast agents. These included preferred terms "drug reaction with eosinophilia and systemic

symptoms" (n=161), "acute generalized exanthematous pustulosis" (n=80), "toxic skin eruption" (n=79), "eosinophilia" (n=71), "toxic epidermal necrolysis" (n=15), and "Stevens-Johnson syndrome" (n=11). The Applicant's summary of postmarketing data also identified reports of the same preferred terms: "drug reaction with eosinophilia and systemic symptoms" (n=46), "acute generalized exanthematous pustulosis" (n=62), "toxic skin eruption" (n=53), "eosinophilia" (n=84), "toxic epidermal necrolysis" (n=3), and "Stevens-Johnson syndrome" (n=8).

The risk of severe cutaneous reactions with administration of Iomervu is demonstrated in the postmarketing data. Severe cutaneous reactions are described in labeling for Iomervu in Sections 5.11 and 6.2 similarly as for other marketed iodinated contrast agents.

Acute Kidney Injury

The risk of acute kidney injury with Iomervu was discussed with the laboratory findings in Section 8.2.4. In addition to adverse reactions of acute kidney injury that occurred for two patients (<0.1%) in clinical trials, the Applicant's summary of postmarketing data also identified reports of preferred terms "acute kidney injury" (n=214), "renal failure" (n=38), and "renal injury" (n=2).

The review of the data did not identify inconsistencies with the description of the risk of acute kidney injury in the proposed labeling for Iomervu in Sections 5.3, 6.1, 8.5, and 8.6. The proposed language is similar to that used for other marketed iodinated contrast agents.

(b) (4)

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

Clinical outcome assessment data were not collected for analysis of safety.

8.2.7. Safety Analyses by Demographic Subgroups

As shown in Table 56 and Table 57, the proportion of patients with at least one AE or SAE and the proportion of AEs or SAEs in each age range were reasonably similar to the proportion of patients of that age.

Table 56. Treatment Emergent Adverse Events by Patient Age in the ≤86 g Population

Age Group	Patients (n=4,804)	AEs (n=826)	Patients with at least one AE (n=473)
≤17 years	184 (4%)	40 (5%)	29 (6%)
18 to 64 years	2,639 (55%)	505 (61%)	283 (60%)
65 to 74 years	1,348 (28%)	197 (24%)	117 (25%)
≥75 years	628 (13%)	84 (10%)	44 (9%)
Missing	5 (0%)		

Source: Pooled safety data from Iomervu clinical studies, FDA clinical reviewer
Abbreviations: AE = adverse event

Table 57. Treatment Emergent Serious Adverse Events by Patient Age in the ≤86 g Population

Age Group	Patients (n=4,804)	SAEs (n=34)	Patients with at least one SAE (n=25)
≤17 years	184 (4%)	0	0
18 to 64 years	2,639 (55%)	19 (56%)	13 (52%)
65 to 74 years	1,348 (28%)	12 (35%)	10 (40%)
≥75 years	628 (13%)	3 (9%)	2 (8%)
Missing	5 (0%)		

Source: Pooled safety data from Iomervu clinical studies, FDA clinical reviewer
Abbreviations: SAE = serious adverse event

As shown in Table 58, the proportion of females with at least one AE and proportion of AEs reported by females was greater than the fraction of females in the analysis, indicating that females were more likely to experience AEs. This trend was not observed for SAEs (Table 59). Males experienced higher incidence of cardiac disorders at the system organ class level (7% versus 3%) and higher incidence of chest pain (3% versus 1%) and extrasystoles (3% versus 1%). However, this may relate to the increased incidence of coronary artery disease in males with resulting increased use of Iomervu for coronary arteriography. Because of the relatively modest effect size and because the types of AEs overall experienced by both sexes were similar, the clinical significance of the observed differences is doubtful.

Table 58. Treatment Emergent Adverse Events by Patient Sex in the ≤86 g Population

Sex	Patients (n=4,804)	AEs (n=826)	Patients with at least one AE (n=473)
Male	3,165 (66%)	442 (54%)	266 (56%)
Female	1,636 (34%)	384 (46%)	207 (44%)

Unspecified	3 (0%)		

Source: Pooled safety data from Iomervu clinical studies, FDA clinical reviewer
Abbreviations: AE = adverse event

Table 59. Treatment Emergent Serious Adverse Events by Patient Sex in the ≤86 g Population

Sex	Patients (n=4,804)	SAEs (n=34)	Patients with at least one SAE (n=25)
Male	3,165 (66%)	23 (68%)	18 (72%)
Female	1,636 (34%)	11 (32%)	7 (28%)
Unspecified	3 (0%)		

Source: Pooled safety data from Iomervu clinical studies, FDA clinical reviewer
Abbreviations: AE = adverse event

A subgroup analysis for AE incidence by race was not performed due to enrollment of predominantly white patients.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

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

Human Reproduction and Pregnancy

The Applicant received 21 spontaneous reports of exposure to mostly single doses of Iomervu during pregnancy. Exposure occurred during the first trimester in five cases, during the second trimester in three cases, and during the third trimester in nine cases. In the remaining four patients, gestational age at the time of exposure was unknown. Among these patients, seven AEs were reported for worsening skin rash (n=1), extravasation (n=1), mild discomfort (n=1), itching and redness (n=1), contrast agent reaction (n=1), spontaneous abortion (n=1), and pre-eclampsia and early onset of delivery (n=1). The report of pre-eclampsia occurred 21 days after administration, and therefore was assessed as unrelated to Iomervu. The pregnancy outcomes were full-term birth (n=5), premature birth (n=2), elective termination of the pregnancy (n=1), and spontaneous abortion (n=1). In the case of spontaneous abortion, causality to Iomervu was assessed as unlikely. No information on pregnancy outcome was available for 12 other cases. Stillbirths, congenital anomalies, or perinatal complications were not reported in any of the 21 cases.

The Applicant received seven reports of exposure to Iomervu during lactation. Six reports were not associated with AEs in the mother or child. There was one report of transient neonatal hypothyroidism for a 17-day-old pre-term child after the lactating mother underwent a CT exam with Iomervu.

The available clinical data are insufficient to draw robust conclusions regarding safety in pregnancy or during lactation.

Pediatrics and Assessment of Effects on Growth

A total of 184 pediatric patients up to age 17 years were included in clinical trials. All adverse reactions observed in pediatric patients (extrasystoles, hypotension, hypertension, erythema, tachycardia, vomiting, bronchospasm, cough, dyspnea, headache, nausea, and urticaria) were also reported for adults and occurred with similar incidence.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The highest dose of Iomervu administered in clinical trials was a total iodine dose of 260 g, which is 3-fold the recommended dose. No potential for drug abuse, withdrawal, or rebound is expected.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Iomervu has been marketed for intra-arterial and intravenous use for adults and pediatrics outside the U.S. since its initial approval in 1992 in the United Kingdom, with subsequent authorization in 50 countries to date. The Applicant estimates that over 160 million patients, including 1.2 million pediatric patients, have been exposed to Iomervu worldwide between July 1, 1997, and June 30, 2023. Of the estimated patients exposed, a total of 35,953 patients (0.02%) reported 68,638 adverse events for which the relationship to Iomervu could not be ruled out by the reporter or the Applicant. Serious cases of contrast-induced acute kidney injury and cardiovascular reactions were reported in ≤0.0002% of exposed patients. The 305 fatal adverse reactions (0.0002%) reported spontaneously and described in the literature most frequently involved cardiac and/or respiratory symptoms related to serious hypersensitivity reactions, including anaphylactic shock.

DPV was consulted for an assessment of adverse events reported with Iomervu from available postmarketing data. The evaluation of the FDA Adverse Event Reporting System database, published medical literature, and VigiBase did not identify any safety signals unrepresented in the proposed labeling.

Expectations on Safety in the Postmarket Setting

Based on the available safety database including extensive foreign postmarketing experience, the postmarketing safety profile in the U.S. is expected to be similar to other marketed iodinated contrast drugs.

8.2.10. Integrated Assessment of Safety

Intravascular use of Iomervu was not found to be associated with significant new adverse reactions compared to currently marketed iodinated contrast agents. The major safety issues for Iomervu are the potential for hypersensitivity reactions, severe cutaneous adverse reactions, acute kidney injury, and cardiovascular adverse reactions. The most frequent adverse reactions for Iomervu are feeling hot, headache, nausea, chest pain, back pain, and vomiting. The overall safety profile of Iomervu is acceptable.

8.3. Statistical Issues

8.3.1. NDA 216017 – Intravenous Administration

Study IOM-104E formed the basis for the evaluation of efficacy of Iomervu in CT imaging of the head and body in adults.

8.3.1.1. Study IOM-104E (head and body CT)

Study IOM-104E was an off-site blinded reading of images obtained from patients enrolled in four head or body CT studies (48848-007A, 48848-007B, 48848-008A, and 48848-008B), which were all phase 3, multicenter, double-blind, parallel, randomized control studies with balanced designs. The aim of IOM-104E was to compare the efficacy of Iomervu (400 mgI/mL and 250 mgI/mL) with iopamidol (370 mgI/mL and 250 mgI/mL) regarding quality of enhancement and anatomic visualization in various body CT applications. Off-site assessment occurred from March 2004 to May 2004, and the IOM-104E Clinical Trial Report was dated February 4, 2005. As explained on page 5 of the reviewers guide for IOM-104E, the Applicant decided not to proceed with NDA submission due to commercial reasons at the end of 2005. Image sets for all 230 patients who had received Iomervu or iopamidol in the four original CT studies were included in IOM-104E (Table 60).

Table 60. Patients Included in IOM-104E from Original Studies

Original Study No.	Iomervu 400 mgI/mL	Iomervu 250 mgI/mL	iopamidol 370 mgI/mL	iopamidol 250 mgI/mL	Total
48848-007A	29	-	25	-	54
48848-007B	30	-	30	-	60
48848-008A	-	28	-	28	56

48848-008B	-	31	-	29	60
Total	59	59	55	57	230

Source: Synopsis of IOM-104E CSR.

Quality of enhancement and anatomic visualization of the images were assessed off-site by independent board-certified radiologists according to a 5-point score: 1 = Poor; 2 = Insufficient; 3 = Fair; 4 = Good; 5 = Excellent. Specific criteria were defined for each score and body region as described in Section 8.1. This 5-point ordinal scale was collapsed to a 3-point ordinal scale (1 = Poor/Insufficient; 2 = Fair; 3 = Good/Excellent) and to a 2-point ordinal scale (1 = Inadequate Quality = Poor/Insufficient; 2 = Adequate Quality = Fair/Good/Excellent).

The derived 2-point ordinal scale was used in the primary analyses of non-inferiority comparison between Iomervu and the active control iopamidol for the proportion of patients with adequate quality (AQ) rating of opacification and anatomic visualization for combined studies (48,848-007A + 007B combined: Iomervu 400 mgI/mL vs. iopamidol 370 mgI/mL; 008A + 008B combined: Iomervu 250 mgI/mL vs. iopamidol 250 mgI/mL). The testing procedure involved a two-sided 95% CI for the treatment difference between the active control iopamidol and Iomervu for the 2-point scale AQ rating proportion described above. The upper limit of the two-sided 95% CI for the difference (comparator - Iomervu) in percentage was calculated and compared with the non-inferiority margin of 10% (Table 61).

Table 61. Study IOM-104E (Head and Body CT) Primary Efficacy Analysis: Quality of Opacification and Anatomic Visualization (Derived 2-Point Scale) – Combined Studies (Efficacy Population)

Reader [a]	Study Agent/ Concentration	Adequate Quality [b]		Difference [c] iopamidol – Iomervu	
		n/N (%)	(95% CI) [e]	(%)	95% CI [d] (%)
Combined Studies: 48,848-007A and 48,848-007B					
Reader 1	Iomervu 400 mgI/mL iopamidol 370 mgI/mL	58/59 (98.3) 55/55 (100.0)	(91.00, 99.70) (93.47, 100.00)	1.7	(-1.6, 5.0)
Reader 2	Iomervu 400 mgI/mL iopamidol 370 mgI/mL	59/59 (100.0) 54/54 (100.0)	(93.89, 100.00) (93.36, 100.00)	0.0	Not Defined (SE=0)
Reader 3	Iomervu 400 mgI/mL iopamidol 370 mgI/mL	59/59 (100.0) 54/54 (100.0)	(93.89, 100.00) (93.36, 100.00)	0.0	Not Defined (SE=0)
Combined Studies: 48,848-008A and 48,848-008B					
Reader 4	Iomervu 250 mgI/mL iopamidol 250 mgI/mL	59/59 (100.0) 57/57 (100.0)	(93.89, 100.00) (93.69, 100.00)	0.0	Not Defined (SE=0)

Reader 5	Iomervu 250 mgI/mL iopamidol 250 mgI/mL	58/59 (98.3) 57/57 (100.0)	(91.00, 99.70) (93.69, 100.00)	1.7	(-1.6, 5.0)
Reader 6	Iomervu 250 mgI/mL iopamidol 250 mgI/mL	58/59 (98.3) 55/55 (100.0)	(91.00, 99.70) (93.47, 100.00)	1.7	(-1.6, 5.0)

a. Three independent readers separately assessed the image sets from the combination of studies 48,848-007A and 48,848-007B in blinded fashion, and three different independent readers separately assessed the image sets from the combination of studies 48,848-008A and 48,848-008B in blinded fashion, comprising a total of six different independent readers.
b. Adequate Quality = Fair + Good + Excellent; expressed as n/N (%), where n = the number of patients with image sets of Adequate Quality and N = number of patients with technically adequate image sets.
c. Percentage of patients with an overall fair, good, or excellent rating in the iopamidol group minus the percentage of patients with an overall fair, good, or excellent rating in the Iomervu group.
d. Two-sided confidence interval of the difference between study agents (iopamidol minus Iomervu) in the percentage of patients with an overall fair, good, or excellent rating.
e. CI generated in response to FDA request, therefore numbers are not included in final CSR for Study IOM-104E.

Source: Table G (derived from *End-of-Text Tables 2.2 and 3.2*) on Page 39/95 of IOM-104E CSR and Table Q (CSR for IOM-104E *End-of-Text Tables 2.2 and 3.2*) on Page 60/235 of IOM-104E Clinical Overview.

FDA's comments dated September 2, 2021, regarding the SAP pointed out the concern that the proposed efficacy population included technically adequate images only and may exclude images that were considered technically inadequate. In response, the Applicant re-calculated efficacy data by reader including any exams considered technically inadequate (TI), imputing the lowest efficacy rating for those cases. For Study IOM-104E, since 100% of image sets with Iomervu were rated as technically adequate by all blinded readers, the result of the post-hoc efficacy analysis for Iomervu were identical to the results of the original analysis as presented in Table 61.

From Table 61 above, it appeared the performance of Iomervu itself was good with point estimates and 95% CIs for proportion of patients with adequate quality images of 98.3% [95% CI: 91% - 99.7%], 100% [95% CI: 93.89% - 100%], and 100% [95% CI: 93.89% - 100%] for combined studies 48,848-007A and 48,848-007B, and point estimates and 95% CIs of 100% [95% CI: 93.89% - 100%], 98.3% [95% CI: 91% - 99.7%], and 98.3% [95% CI: 91% - 99.7%] for combined studies 48,848-008A and 48,848-008B.

The quality of enhancement and anatomic visualization were also assessed using the original 5-point score as a secondary analysis and the results were consistent with those observed for the primary efficacy endpoint based on the derived 2-point scale. For the 5-point scale, the proportions of patients with image sets rated as excellent varied among the readers; however, the overall good/excellent rates were high in the Iomervu group for all off-site blinded readers in each of the combined studies. As shown in Table 62, there were just two patients receiving Iomervu rated as having insufficient and one patient rated as having poor enhancement and anatomic visualization.

Table 62. Study IOM-104E (Head and Body CT) Secondary Efficacy Analysis: Quality of Opacification and Anatomic Visualization (5-Point Scale) – Combined Studies (Efficacy Population)

Characteristic		Combined Studies: 48,848-007A and 48,848-007B		Combined Studies: 48,848-008A and 48,848-008B	
		IOMERON 400 mgI/mL N (%)	ISOVUE 370 mgI/mL N (%)	IOMERON 250 mgI/mL N (%)	ISOVUE 250 mgI/mL N (%)
Reader 1[a]	Number of Patients	59	55	59	57
	Poor	0	0	0	0
	Insufficient	1 (1.7)	0	0	0
	Fair	0	3 (5.5)	5 (8.5)	2 (3.5)
	Good	8 (13.6)	12 (21.8)	18 (30.5)	15 (26.3)
	Excellent	50 (84.7)	40 (72.7)	36 (61.0)	40 (70.2)
Reader 2[a]	Number of Patients	59	54	59	57
	Poor	0	0	0	0
	Insufficient	0	0	1 (1.7)	0
	Fair	1 (1.7)	0	3 (5.1)	1 (1.8)
	Good	5 (8.5)	12 (22.2)	22 (37.3)	19 (33.3)
	Excellent	53 (89.8)	42 (77.8)	33 (55.9)	37 (64.9)
Reader 3[a]	Number of Patients	59	54	59	55
	Poor	0	0	1 (1.7)	0
	Insufficient	0	0	0	0
	Fair	1 (1.7)	0	4 (6.8)	2 (3.6)
	Good	3 (5.1)	6 (11.1)	10 (16.9)	12 (21.8)
	Excellent	55 (93.2)	48 (88.9)	44 (74.6)	41 (74.5)

a. Three independent readers separately assessed the image sets from the combination of studies 48,848-007A and 48,848-007B in blinded fashion, and three different independent readers separately assessed the image sets from the combination of studies 48,848-008A and 48,848-008B in blinded fashion, comprising a total of six different independent readers.

Source: Table I (derived from *End-of-Text Tables 2.4 and 3.4*) on Page 41/95 of IOM-104E CSR.

8.3.2. NDA 216016 – Intraarterial Administration

Studies IOM-104A, IOM-104C, and IOM-104D form the basis for evaluation of efficacy of Iomervu in angiographic indications requiring IA administration in adult patients.

8.3.2.1. Study IOM-104A (cardioangiography)

Study IOM-104A was an off-site blinded reading of images obtained from patients enrolled in four cardioangiography studies (48848-001A, 48848-001B, 48848-002A, and 48848-002B), which were all phase 3, multicenter, double-blind, parallel, randomized control studies with balanced designs that enrolled patients with documented cardiac history or diagnosis who required cardioangiography for diagnostic purposes or preoperative evaluation. The aim of IOM-104A was to compare the efficacy of Iomervu 400 mgI/mL with iopamidol 370 mgI/mL, and Iomervu 300 mgI/mL with ioversol 320 mgI/mL regarding quality of enhancement and anatomic visualization of vessels in cardioangiography applications. Off-site assessment occurred from March 2004 to May 2004, and the IOM-104A Clinical Trial Report was dated

February 3, 2005. As explained on page 5 of the NDA 216016 reviewers guide, the Applicant decided not to proceed with NDA submission due to commercial reasons at the end of 2005. Image sets for all 237 patients who had received Iomervu, iopamidol, or ioversol in the 4 original cardioangiography studies were included in the IOM-104A study as shown in Table 63.

Table 63. Patients Included in IOM-104A from Original Studies

Original Study No.	Iomervu 400 mgI/mL	Iomervu 300 mgI/mL	iopamidol 370 mgI/mL	ioversol 320 mgI/mL	Total
48848-001A	30	-	27	-	57
48848-001B	29	-	31	-	60
48848-002A	-	31	-	29	60
48848-002B	-	28	-	32	60
Total	59	59	58	61	237

Source: Synopsis of IOM-104A CSR.

Quality of enhancement and anatomic visualization of the images were assessed off-site by independent board-certified radiologists according to a 5-point score: 1 = Poor; 2 = Insufficient; 3 = Fair; 4 = Good; 5 = Excellent. Specific criteria were defined for each score as described in Section 8.1. This 5-point ordinal scale was collapsed to a 3-point ordinal scale (1 = Poor/Insufficient; 2 = Fair; 3 = Good/Excellent) and to a 2-point ordinal scale (1 = Inadequate Quality = Poor/Insufficient; 2 = Adequate Quality = Fair/Good/Excellent).

The derived 2-point ordinal scale was used in the primary analyses of non-inferiority comparison between Iomervu and the active controls iopamidol and ioversol for proportion of patients with AQ rating of opacification and anatomic visualization for combined studies (48,848-001A + 001B combined: Iomervu 400 mgI/mL vs. iopamidol 370 mgI/mL; 002A + 002B combined: Iomervu 300 mgI/mL vs. ioversol 320 mgI/mL). The testing procedure involved a two-sided 95% CI for the treatment difference between the active controls iopamidol and ioversol versus Iomervu for the 2-point scale AQ rating proportion described above. The upper limit of the two-sided 95% CI for the difference (comparator - Iomervu) in percentage was calculated and compared with the non-inferiority margin of 10% (Table 64).

Table 64. Study IOM-104A (Cardioangiography) Primary Efficacy Analysis: Quality of Opacification and Anatomic Visualization (Derived 2-Point Scale) – Combined Studies (Efficacy Population)

		Adequate Quality	Difference [d] Comparator – Iomervu (%)

Reader [a]	Study Agent/ Concentration	n/N (%) [b]	95% CI (%) [c]	(%)	95% CI [e] (%)
Combined Studies: 48,848-001A and 48,848-001B					
Reader 1	Iomervu 400 mgI/mL iopamidol 370 mgI/mL	59/59 (100.0) 57/57 (100.0)	(93.89, 100.00) (93.69, 100.00)	0.0	Not Defined (SE=0)
Reader 2	Iomervu 400 mgI/mL iopamidol 370 mgI/mL	57/57 (100.0) 55/55 (100.0)	(93.69, 100.00) (93.47, 100.00)	0.0	Not Defined (SE=0)
Reader 3	Iomervu 400 mgI/mL iopamidol 370 mgI/mL	58/58 (100.0) 58/58 (100.0)	(93.79, 100.00) (93.79, 100.00)	0.0	Not Defined (SE=0)
Combined Studies: 48,848-002A and 48,848-002B					
Reader 4	Iomervu 300 mgI/mL ioversol 320 mgI/mL	59/59 (100.0) 61/61 (100.0)	(93.89, 100.00) (94.08, 100.00)	0.0	Not Defined (SE=0)
Reader 5	Iomervu 300 mgI/mL ioversol 320 mgI/mL	59/59 (100.0) 60/60 (100.0)	(93.89, 100.00) (93.98, 100.00)	0.0	Not Defined (SE=0)
Reader 6	Iomervu 300 mgI/mL ioversol 320 mgI/mL	55/56 (98.2) 55/56 (98.2)	(90.55, 99.68) (90.55, 99.68)	0.0	(-4.91, 4.91)

a. Three independent readers separately assessed the image sets from the combination of studies 48,848-001A and 48,848-001B in blinded fashion, and three different independent readers separately assessed the image sets from the combination of studies 48,848-002A and 48,848-002B in blinded fashion, comprising a total of six different independent readers.
b. Adequate Quality = Fair + Good + Excellent; expressed as n/N (%), where n = the number of patients with image sets of Adequate Quality and N = number of patients with technically adequate image sets.
c. Two-sided 95% confidence interval by the Wilson score method for the proportion of adequately (Sufficient/Good/Excellent) and inadequately (Poor/Insufficient) opacified exams by reader. Data generated using derived 2-point scale in response to FDA request, therefore numbers are not included in IOM-104A CSR.
d. Percentage of patients with an overall fair, good, or excellent rating in the control agent group minus the percentage of patients with an overall fair, good, or excellent rating in the Iomervu group.
e. Two-sided confidence interval of the difference between study agents (control agent minus Iomervu) in the percentage of patients with an overall fair, good or excellent rating.

Source: Table G (derived from *End-of-Text Tables 2.2 and 3.2*) on Page 35/91 of IOM-104A CSR and Table S (CSR for IOM-104A *End-of-Text Tables 2.2 and 3.2*) on Page 62/203 of NDA 216016 Clinical Overview.

FDA's comments dated September 2, 2021, regarding the SAP pointed out the concern that the proposed efficacy population included technically adequate images only and may exclude images that were considered technically inadequate (TI). In response, the Applicant re-calculated efficacy data by reader including any exams considered TI, imputing the lowest efficacy rating for those cases. Specifically, TI exams not assessed by the blinded readers were included in the primary efficacy analyses by imputing a rating of Poor for those cases (Table 65). In this post-hoc analysis, the proportion of patient exams with AQ after Iomervu 400 mgI/mL was 100% (95% CI: 93.89, 100.00) for Reader 1, 96.6% (95% CI: 88.46, 99.07) for Reader 2, and 98.3% (95% CI: 91.00, 99.70) for Reader 3 in combined study 48,848-001A and 48,848- 001B. The proportion of patient exams with AQ after Iomervu 300 mgI/mL was 100% (95% CI: 93.89, 100.00) for Readers 4 and 5, and was 93.2% (95% CI: 83.82, 97.33) for Reader 6 in combined study 48,848-002A and 48,848-002B.

Table 65. Study IOM-104A (Cardioangiography) Post-Hoc Efficacy Analysis Including Technically Inadequate Exams: Quality of Opacification and Anatomic Visualization (Derived 2-Point Scale) – Combined Studies (Including All Dosed Patients)

Reader [a]	Study Agent/ Concentration	Adequate Quality Exams	
		n/N (%) [b]	95% CI (%) [c]
Combined Studies: 48,848-001A and 48,848-001B			
Reader 1 Including TI exams	Iomervu 400 mgI/mL iopamidol 370 mgI/mL	59/59 (100.0) 57/58 (98.3)	(93.89, 100.00) (90.86, 99.69)
Reader 2 Including TI exams	Iomervu 400 mgI/mL iopamidol 370 mgI/mL	57/59 (96.6) 55/58 (94.8)	(88.46, 99.07) (85.86, 98.23)
Reader 3 Including TI exams	Iomervu 400 mgI/mL iopamidol 370 mgI/mL	58/59 (98.3) 58/58 (100.0)	(91.00, 99.70) (93.79, 100.00)
Combined Studies: 48,848-002A and 48,848-002B			
Reader 4 Including TI exams	Iomervu 300 mgI/mL ioversol 320 mgI/mL	59/59 (100.0) 61/61 (100.0)	(93.89, 100.00) (94.08, 100.00)
Reader 5 Including TI exams	Iomervu 300 mgI/mL ioversol 320 mgI/mL	59/59 (100.0) 60/61 (98.4)	(93.89, 100.00) (91.28, 99.71)
Reader 6 Including TI exams	Iomervu 300 mgI/mL ioversol 320 mgI/mL	55/59 (93.2) 55/61 (90.2)	(83.82, 97.33) (80.16, 95.41)

a. Three independent readers separately assessed the image sets from the combination of studies 48,848-001A and 48,848-001B in blinded fashion, and three different independent readers separately assessed the image sets from the combination of studies 48,848-002A and 48,848-002B in blinded fashion, comprising a total of six different independent readers.
b. Adequate Quality = Fair + Good + Excellent; expressed as n/N (%), where n = the number of patients with image sets of Adequate Quality and N = number of patients dosed with Iomervu or control agent. Results are from a post-hoc analysis in which images sets graded as technically inadequate and therefore excluded by the readers were included by imputing the lowest score (Poor) for quality of enhancement and anatomic visualization.
c. Two-sided 95% confidence interval by the Wilson score method for the proportion of adequately (Sufficient/Good/Excellent) and inadequately (Poor/Insufficient) opacified exams by reader. Data generated using derived 2-point scale in response to FDA request, therefore numbers are not included in IOM-104A CSR.

Abbreviations: CI = confidence interval, TI = technically inadequate
Source: Post-hoc efficacy analysis requested by FDA. Table T on Page 63/203 of NDA 216016 Clinical Overview.

The quality of enhancement and anatomic visualization were also assessed using the original 5-point score as a secondary analysis and the results were consistent with those observed for the primary efficacy endpoint based on the derived 2-point scale. For the 5-point scale, the proportions of patients with image sets rated as excellent varied among the readers; however, the overall good/excellent rates were high in the Iomervu group for all off-site blinded readers in each of the combined studies. As shown in Table 66, there was just one patient rated as having insufficient enhancement and anatomic visualization by Reader 3 in the Iomervu 300 mgI/mL group. However, there would be an additional six patients with poor enhancement and

anatomic visualization when imputing the lowest efficacy rating for those six cases that were considered TI and excluded from the original analysis.

Table 66. Study IOM-104A (Cardioangiography) Secondary Efficacy Analysis: Quality of Opacification and Anatomic Visualization (5-Point Scale) – Combined Studies (Efficacy Population)

Characteristic		Combined Studies: 48,848-001A and 48,848-001B		Combined Studies: 48,848-002A and 48,848-002B	
		IOMERON 400 mgI/mL N (%)	ISOVUE 370 mgI/mL N (%)	IOMERON 300 mgI/mL N (%)	OPTIRAY 320 mgI/mL N (%)
Reader 1[a]	Number of Patients	59	57	59	61
	Poor	0	0	0	0
	Insufficient	0	0	0	0
	Fair	11 (18.6)	5 (8.8)	5 (8.5)	4 (6.6)
	Good	45 (76.3)	51 (89.5)	27 (45.8)	19 (31.1)
	Excellent	3 (5.1)	1 (1.8)	27 (45.8)	38 (62.3)
Reader 2[a]	Number of Patients	57	55	59	60
	Poor	0	0	0	0
	Insufficient	0	0	0	0
	Fair	0	2 (3.6)	1 (1.7)	1 (1.7)
	Good	4 (7.0)	4 (7.3)	21 (35.6)	10 (16.7)
	Excellent	53 (93.0)	49 (89.1)	37 (62.7)	49 (81.7)
Reader 3[a]	Number of Patients	58	58	56	56
	Poor	0	0	0	0
	Insufficient	0	0	1 (1.8)	1 (1.8)
	Fair	0	0	10 (17.9)	8 (14.3)
	Good	8 (13.8)	11 (19.0)	29 (51.8)	22 (39.3)
	Excellent	50 (86.2)	47 (81.0)	16 (28.6)	25 (44.6)

a. Three independent readers separately assessed the image sets from the combination of studies 48,848-001A and 48,848-001B in blinded fashion, and three different independent readers separately assessed the image sets from the combination of studies 48,848-002A and 48,848-002B in blinded fashion, comprising a total of six different independent readers.

Source: Table I (derived from *End-of-Text Tables 2.4 and 3.4*) on Page 37/91 of IOM-104A CSR.

8.3.2.2. Study IOM-104C (cerebral angiography)

Study IOM-104C was an off-site blinded reading of images obtained from patients enrolled in two cerebral angiography studies: 48848-004A and 48848-004B which were phase 3, multicenter, double-blind, parallel, randomized control studies with balanced designs that enrolled patients with documented history or diagnosis that necessitated cerebral angiography for diagnostic purposes or preoperative evaluation. The aim of IOM-104C was to compare the efficacy of Iomervu 300 mgI/mL with ioversol 320 mgI/mL regarding quality of enhancement and anatomic visualization of vessels in cerebral angiography applications. Off-site assessment was in March 2004, and the IOM-104C Clinical Trial Report was dated January 27, 2005. (b) (4) Image sets for 119 of the 120 patients who had received Iomervu or ioversol in the 2 original cerebral angiography

studies were included in the IOM-104C study. One patient who received ioversol in study 48,848-004A was not included in IOM-104C because the patient's images from the original study could not be located. A summary of the number of patients is in Table 67.

Table 67. Patients Included in IOM-104C from Original Studies

Original Study No.	Iomervu 300 mgI/mL	ioversol 320 mgI/mL	Total
48848-004A	30	27	57
48848-004B	31	31	62
Total	61	58	119

Source: Synopsis of IOM-104C CSR.

As for Study IOM-104A, a derived 2-point ordinal scale was used in the primary analyses of non-inferiority comparison between Iomervu and the active control ioversol for proportion of patients with AQ rating of opacification and anatomic visualization for combined studies (48,848-004A + 004B combined: Iomervu 300 mgI/mL vs. ioversol 320 mgI/mL). The same non-inferiority testing procedure with non-inferiority margin of 10% was carried out and two-sided 95% CI for the difference (ioversol - Iomervu) in percentage was calculated (Table 68).

Table 68. Study IOM-104C (Cerebral Angiography) Primary Efficacy Analysis: Quality of Opacification and Anatomic Visualization (Derived 2-Point Scale) – Combined Studies (Efficacy Population)

Reader [a]	Study Agent/ Concentration	Adequate Quality [b] n/N (%) [c]	Adequate Quality [b] 95% CI (%) [d]	Difference [e] ioversol – Iomervu (%) (%)	Difference [e] ioversol – Iomervu (%) 95% CI [f] (%)
Combined Studies: 48,848-004A and 48,848-004B					
Reader 1	Iomervu 300 mgI/mL ioversol 320 mgI/mL	61/61 (100.0) 58/58 (100.0)	(94.08, 100.00) (93.79, 100.00)	0.0	Not Defined (SE=0)
Reader 2	Iomervu 300 mgI/mL ioversol 320 mgI/mL	61/61 (100.0) 58/58 (100.0)	(94.08, 100.00) (93.79, 100.00)	0.0	Not Defined (SE=0)
Reader 3	Iomervu 300 mgI/mL ioversol 320 mgI/mL	61/61 (100.0) 58/58 (100.0)	(94.08, 100.00) (93.79, 100.00)	0.0	Not Defined (SE=0)

a. Three independent blinded readers separately assessed the image data from combined studies 48,848-004A and 48,848-004B.
b. Adequate Quality = combined levels 3-5 (Fair, Good, or Excellent) of the 5-point scale.
c. n = the number of patients with image sets of Adequate Quality and N = number of patients with technically adequate image sets.
d. Two-sided 95% confidence interval by the Wilson score method for the proportion of adequately (Sufficient/Good/Excellent) and inadequately (Poor/Insufficient) opacified exams by reader. Data generated using derived 2-point scale in response to FDA request, therefore numbers are not included in IOM-104C CSR.
e. Percentage of patients with an overall fair, good, or excellent rating in the ioversol group minus the percentage of patients with an overall fair, good, or excellent rating in the Iomervu group.

f. Two-sided confidence interval of the difference between study agents (ioversol minus Iomervu) in the percentage of patients with an overall fair, good or excellent rating.

Source: Table F (derived from *End-of-Text Tables 2.2*) on Page 30/62 of IOM-104C CSR and Table EE (CSR for IOM-104C *End-of-Text Tables 2.2*) on Page 99/203 of NDA 216016 Clinical Overview.

As described for IOM-104A, the Applicant re-calculated efficacy data by reader including any exams considered TI and imputing the lowest efficacy rating for those cases. For Study IOM-104C, since 100% of image sets with Iomervu were rated as technically adequate by all blinded readers, the results of the post-hoc efficacy analysis for Iomervu were identical to the results of the original analysis as presented above.

From Table 68, it appeared the performance of Iomervu itself was good with 95% CI of 94.08%-100% for proportion of patients with adequate quality images for all three blinded readers for the combined studies 48,848-004A and 48,848-004B. The quality of enhancement and anatomic visualization were also assessed using the original 5-point score as a secondary analysis and the results were consistent with those observed for the primary efficacy endpoint based on the derived 2-point scale. For the 5-point scale, the majority (>=98.4%) of patients had image sets rated as excellent by Readers 2 and 3 in the Iomervu groups. Reader 1 rated image sets as excellent for 50.8% and as good for 44.3% of the patients in the Iomervu groups. As shown in Table 69, there were no patients receiving Iomervu rated as having poor or insufficient enhancement and anatomic visualization.

Table 69. Study IOM-104C (Cerebral Angiography) Secondary Efficacy Analysis: Quality of Opacification and Anatomic Visualization (5-Point Scale) – Combined Studies (Efficacy Population)

Characteristic		Combined Studies: 48,848-004A and 48,848-004B	
		IOMERON 300 mgI/mL N (%)	OPTIRAY 320 mgI/mL N (%)
Reader 1	Number of Patients	61	58
	Poor	0	0
	Insufficient	0	0
	Fair	3 (4.9)	2 (3.4)
	Good	27 (44.3)	18 (31.0)
	Excellent	31 (50.8)	38 (65.5)
Reader 2	Number of Patients	61	58
	Poor	0	0
	Insufficient	0	0
	Fair	0	0
	Good	1 (1.6)	0
	Excellent	60 (98.4)	58 (100.0)
Reader 3	Number of Patients	61	58
	Poor	0	0
	Insufficient	0	0
	Fair	0	0
	Good	0	0
	Excellent	61 (100.0)	58 (100.0)

Source: Table H (derived from *End-of-Text Tables 2.4*) on Page 32/62 of IOM-104C CSR.

8.3.2.3. Study IOM-104D (visceral/peripheral angiography)

Study IOM-104D was an off-site blinded reading of images obtained from patients enrolled in two visceral and peripheral angiography studies: 48848-005A and 48848-005B which were phase 3, multicenter, double-blind, parallel randomized control studies with balanced designs which enrolled patients with documented history or diagnosis that necessitated peripheral or visceral angiography for diagnostic purposes or preoperative evaluation. The aim of IOM-104D was to compare the efficacy of Iomervu 300 mgI/mL with iopamidol 300 mgI/mL regarding quality of enhancement and anatomic visualization in visceral/peripheral angiography applications. Off-site assessment was in April 2004, and the IOM-104D Clinical Trial Report was dated February 1, 2005. As explained on Page 5 of the NDA 216016 reviewers guide, the Applicant decided not to proceed with NDA submission due to commercial reasons at the end of 2005. Image sets for 119 of the 121 patients who had received Iomervu or iopamidol in the 2 original studies were included in the IOM-104D (Table 70) blinded reading study. Image data for two patients who received Iomervu (one in study 48,848-005A and one in study 48,848-005B) were not included in study IOM-104D because the patient's images from the original study could not be located.

Table 70. Patients Included in IOM-104D from Original Studies

Original Study No.	Iomervu 300 mgI/mL	iopamidol 300 mgI/mL	Total
48848-005A	28	30	58
48848-005B	32	29	61
Total	60	59	119

Source: Synopsis of IOM-104D CSR.

As for Study IOM-104A, a derived 2-point ordinal scale was used in the primary analyses of non-inferiority comparison between Iomervu and the active control iopamidol for proportion of patients with adequate quality (AQ) rating of opacification and anatomic visualization for combined studies (48,848-005A + 005B combined: Iomervu 300 mgI/mL vs. iopamidol 300 mgI/mL). The same non-inferiority testing procedure with non-inferiority margin of 10% was carried out and two-sided 95% CI for the difference (iopamidol - Iomervu) in percentage was calculated (Table 71).

Table 71. Study IOM-104D (Visceral/Peripheral Angiography) Primary Efficacy Analysis: Quality of Opacification and Anatomic Visualization (Derived 2-Point Scale) – Combined Studies (Efficacy Population)

Reader [a]	Study Agent/ Concentration	Adequate Quality [b]		Difference [e] iopamidol – Iomervu (%)	
		n/N (%) [c]	95% CI (%) [d]	(%)	95% CI [f] (%)

Combined Studies: 48,848-005A and 48,848-005B					
Reader 1	Iomervu 300 mgI/mL iopamidol 300 mgI/mL	59/59 (100.0) 59/59 (100.0)	(93.89, 100.00) (93.89, 100.00)	0.0	Not Defined (SE=0)
Reader 2	Iomervu 300 mgI/mL iopamidol 300 mgI/mL	59/59 (100.0) 59/59 (100.0)	(93.89, 100.00) (93.89, 100.00)	0.0	Not Defined (SE=0)
Reader 3	Iomervu 300 mgI/mL iopamidol 300 mgI/mL	59/59 (100.0) 59/59 (100.0)	(93.89, 100.00) (93.89, 100.00)	0.0	Not Defined (SE=0)

a. Three independent blinded readers separately assessed the image data from combined studies 48,848-005A and 48,848-005B.
b. Adequate Quality = combined levels 3-5 (Fair, Good, or Excellent) of the 5-point scale.
c. n = the number of patients with image sets of Adequate Quality and N = number of patients with technically adequate image sets.
d. Two-sided 95% confidence interval by the Wilson score method for the proportion of adequately (Sufficient/Good/Excellent) and inadequately (Poor/Insufficient) opacified exams by reader. Data generated using derived 2-point scale in response to FDA request, therefore numbers are not included in IOM-104D CSR.
e. Percentage of patients with an overall fair, good, or excellent rating in the iopamidol group minus the percentage of patients with an overall fair, good, or excellent rating in the Iomervu group.
f. Two-sided confidence interval of the difference between study agents (iopamidol minus Iomervu) in the percentage of patients with an overall fair, good or excellent rating.

Source: Table F (derived from *End-of-Text Tables 2.2*) on Page 31/63 of IOM-104D CSR and/or Table RR (CSR for IOM-104D *End-of-Text Tables 2.2*) on Page 122/203 of NDA 216016 Clinical Overview.

As described for IOM-104A, the Applicant re-calculated efficacy data by reader including any exams considered TI and imputing the lowest efficacy rating for those cases. Specifically, the one TI exam not assessed by the blinded readers was included in the primary efficacy analyses by imputing a rating of "Poor" for that case (Table 72). In this post-hoc analysis, the proportion of patient exams with AQ after Iomervu 300 mgI/mL was 98.3% (95% CI: 91.14, 99.71) for all three off-site readers.

Table 72. Study IOM-104D (Visceral/Peripheral Angiography) Post-Hoc Efficacy Analysis Including Technically Inadequate Exams: Quality of Opacification and Anatomic Visualization (Derived 2-Point Scale) – Combined Studies (Including All Dosed Patients)

Reader [a]	Study Agent/ Concentration	Adequate Quality Exams [b]	
		n/N (%) [b]	95% CI (%) [c]
Combined Studies: 48,848-005A and 48,848-005B			
Reader 1 Including TI exams	Iomervu 300 mgI/mL iopamidol 300 mgI/mL	59/60 (98.3) 59/59 (100.0)	(91.14, 99.71) (93.89, 100.00)
Reader 2 Including TI exams	Iomervu 300 mgI/mL iopamidol 300 mgI/mL	59/60 (98.3) 59/59 (100.0)	(91.14, 99.71) (93.89, 100.00)
Reader 3 Including TI exams	Iomervu 300 mgI/mL iopamidol 300 mgI/mL	59/60 (98.3) 59/59 (100.0)	(91.14, 99.71) (93.89, 100.00)

a. Three independent readers separately assessed the image sets from the combination of studies 48,848-005A and 48,848-005B in blinded fashion.

b. Adequate Quality = Fair + Good + Excellent; expressed as n/N (%), where n = the number of patients with image sets of Adequate Quality and N = number of patients dosed with Iomervu or control agent. Results are from a post-hoc analysis in which images sets graded as technically inadequate and therefore excluded by the readers were included by imputing the lowest score (Poor) for quality of enhancement and anatomic visualization.
c. Two-sided 95% confidence interval by the Wilson score method for the proportion of adequately (Sufficient/Good/Excellent) and inadequately (Poor/Insufficient) opacified exams by reader. Data generated using derived 2-point scale in response to FDA request, therefore numbers are not included in IOM-104D CSR.

Abbreviations: CI = confidence interval, TI = technically inadequate
Source: Post-hoc efficacy analysis requested by FDA. Table SS on Page 123/203 of NDA 216016 Clinical Overview.

The quality of enhancement and anatomic visualization were also assessed using the original 5-point score as a secondary analysis and the results were consistent with those observed for the primary efficacy endpoint based on the derived 2-point scale. For the 5-point scale, the majority (>=91.5%) of patients in the Iomervu group had image sets rated as excellent by Readers 1 and 2, while 74.6% of patients had image sets rates as excellent by Reader 3 (Table 73). The overall good/excellent rates were high in Iomervu group for all off-site blinded readers. There were no patients receiving Iomervu rated as having poor or insufficient enhancement and anatomic visualization. However, there would be one patient with poor enhancement and anatomic visualization when imputing the lowest efficacy rating for the case that was considered TI and excluded from the original analysis.

Table 73. Study IOM-104D (Visceral/Peripheral Angiography) Secondary Efficacy Analysis: Quality of Opacification and Anatomic Visualization (5-Point Scale) – Combined Studies (Efficacy Population)

Characteristic		Combined Studies: 48,848-005A and 48,848-005B	
		IOMERON 300 mgI/mL N (%)	ISOVUE 300 mgI/mL N (%)
Reader 1	Number of Patients	59	59
	Poor	0	0
	Insufficient	0	0
	Fair	0	0
	Good	0	1 (1.7)
	Excellent	59 (100.0)	58 (98.3)
Reader 2	Number of Patients	59	59
	Poor	0	0
	Insufficient	0	0
	Fair	0	0
	Good	5 (8.5)	1 (1.7)
	Excellent	54 (91.5)	58 (98.3)
Reader 3	Number of Patients	59	59
	Poor	0	0
	Insufficient	0	0
	Fair	1 (1.7)	0
	Good	14 (23.7)	15 (25.4)
	Excellent	44 (74.6)	44 (74.6)

Source: Table H (derived from *End-of-Text Tables 2.4*) on Page 33/63 of IOM-104D CSR.

8.4. Conclusions and Recommendations

Results from adequate and well-controlled studies of Iomervu for coronary, cerebral, visceral, and peripheral arteriography and aortography, intra-arterial digital subtraction angiography, as well as CT head and body and CT urography, demonstrated adequate image quality of the vessels and anatomical structures visualized. Results from adequate and well-controlled studies of Iomervu for CT angiography including coronary CT angiography demonstrated adequate diagnostic performance for the detection of significant stenosis in the peripheral, cerebral, visceral, and coronary arteries.

The important safety issues identified for Iomervu are similar to those for other iodinated contrast agents. No new safety signals are identified.

The benefit-risk balance for Iomervu is favorable. The Applicant has presented sufficient evidence to support approval of Iomervu for use in intra-arterial administration in arteriography and intravenous administration in CT imaging.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held, and no external consultations were requested for this NDA.

10 Pediatrics

As per the agreed pediatric study plan, the primary evidence of efficacy for intra-arterial and intravenous administration of Iomervu in pediatric patients is provided by extrapolation from data in adult patients. Of note, the indication for radiographic evaluation of cardiac chambers and related arteries is supported by the adult indication for coronary arteriography and cardiac ventriculography and is adapted to reflect the pathological conditions most frequently imaged in pediatric patients. Similar language is used in the labeling of related iodinated contrast drugs.

The Applicant conducted an open-label, multicenter study (48,848-010) of the pharmacokinetics of Iomervu in 19 pediatric patients 3 to 17 years of age. A population pharmacokinetic simulation of Iomervu in pediatric patients younger than 3 years of age was also conducted. As discussed in Section 6, the results were sufficient to establish that no dose adjustment is necessary for pediatric patients of all ages. The data from the pharmacokinetic study and pharmacokinetic simulation in pediatric patients supported extrapolation of efficacy established in adults to pediatric patients 0 to 17 years of age. In combination with the safety of Iomervu obtained in 184 pediatric patients, Iomervu is recommended for approval for use in pediatric patients 0 to 17 years of age.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

The following points related to the proposed prescribing information were recommended.

- Indications and Usage
  - (b) (4)
  - The term (b) (4) replaced with "radiographic evaluation of cardiac chambers and related arteries". This descriptive term was also used in another iodinated contrast media (ICM) labeling (i.e., Ultravist).
  - Editorial revisions were recommended to improve readability as well as for consistency with other recently revised ICM labeling:
    - Intra-arterial procedures are presented before intravenous procedures for consistency with other ICM labeling.
    - Age group is indicated for each procedure instead of presenting pediatric procedures separately to minimize redundancy.
    - Within the same route of administration procedures, imaging procedures are listed in an order of adults and pediatric patients, adults, and pediatric patients.
    - Specific iodine concentrations indicated for each procedure are removed to avoid redundancy with the DOSAGE AND ADMINISTRATION section; the following statement is added at the end of the section to address concern for removing the iodine concentrations in association with imaging procedures, "*Specific concentrations of IOMERVU are recommended for each type of imaging procedure [see Dosage and Administrations (2.2, 2.3, 2.4, 2.5)].*"
    - Consistent terminology and order for imaging procedures are used between the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections.
  - The agreed upon indication statement reads as follows:

    1.1 Intra-arterial Procedures†

    IOMERVU is indicated for:

    - *Cerebral arteriography, including intra-arterial digital subtraction angiography (IA-DSA), in adults and pediatric patients*
    - *Visceral and peripheral arteriography and aortography, including IA-DSA, in adults and pediatric patients*
    - *Coronary arteriography and cardiac ventriculography in adults*
    - *Radiographic evaluation of cardiac chambers and related arteries*

in pediatric patients

1.2 Intravenous Procedures†

IOMERVU is indicated for:

- *Computed tomography (CT) of the head and body in adults and pediatric patients*
- *CT angiography of intracranial, visceral, and lower extremity arteries in adults and pediatric patients*
- *Coronary CT angiography in adults and pediatric patients*
- *CT urography in adults and pediatric patients*

†Specific concentrations of IOMERVU are recommended for each type of imaging procedure [see Dosage and Administration (2.2, 2.3, 2.4, 2.5)].

- Dosage and Administration
  - For pediatric intra-arterial procedure dosing, the maximum total dose was capped to 5 mL/kg and no more than adult maximum total dose for all intra-arterial procedures.
  - The following editorial revisions were recommended:
    - Dosing instructions are presented with the same terminology and order used in the INDICATIONS AND USAGE section.
    - Pediatric dosing instructions are presented separately from adults to avoid confusion with adult dosing and to be easily identified in the Full Prescribing Information: Contents (Table of Contents).
    - In each dosing table, iodine concentration(s) and volumes to administer, injection sites, and injection rate range when applicable for each imaging procedure are included in a consistent manner.
    - Maximum dose is indicated in terms of volume of each iodine concentration instead of the maximum amount of iodine to avoid dosing error from miscalculation.
- Contraindications
  - The proposed (b) (4) was deleted for consistency with other ICM labeling.
- Warnings and Precautions
  - A proposed warning (b) (4) was deleted because there was not enough evidence to determine clinical significance and recommendations. (b) (4)
  - This section was revised to be consistent with other recently revised ICM labeling in PLR/PLLR format (e.g., Ultravist).
- Adverse Reactions
  - Adverse Reactions in Adults

- The proposed adverse reaction table was modified:
  - to exclude [redacted] (b) (4) in order to avoid implying an unapproved dose per 21 CFR 201.57(c)(3)(ii).
  - to include the rate of an identified adverse reaction from all reported adverse events of that type without omitting events from the rate calculation based on the judgement of individual investigators as recommended in the final FDA guidance, "Adverse Reactions Section of Labeling".
- The agreed upon adverse reaction table reads as follows:

Table 5: Adverse Reactions Reported in ≥0.5% of 4,621 Adult Patients Receiving Intra-arterial or Intravenous Administration of IOMERVU in Clinical Trials	
Adverse Reaction	**Incidence (%)**
Feeling hot	2
Headache	1.2
Nausea	1
Chest pain	0.6
Back pain	0.5
Vomiting	0.5

- Adverse reactions <0.5% were categorized by body system and within each category, the adverse reactions were listed in decreasing order of severity per 21 CFR 201.57(c)(7)(ii).

  - Adverse Reactions in Pediatric Patients
    - Safety findings in 184 pediatric patients were included.
  - Postmarketing Experience: Adverse reactions identified from foreign spontaneous reports were included to be consistent with 21 CFR 201.57(c)(7)(ii)(B).

- Drug Interactions
  - This section was revised to be consistent with other recently revised ICM labeling in PLR/PLLR format (e.g., Ultravist, Omnipaque).
- Use in Specific Populations
  - Pregnancy and Lactation: Revisions recommended by the Division of Pediatric and Maternal Health (DPMH) were implemented.
  - Pediatric Use
    - Pediatric use statements were revised to be consistent with those in the Indications and Usage section according to the standard sentence structure, "The safety and effectiveness of {drug name} {for indication Y} have been established in pediatric patients" recommended in the FDA final guidance, "Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling".
    - The following basis of approval of iomeprol in pediatric patients was included:

        - Efficacy studies in adults with a cross-reference to section 14 Clinical Studies
        - Pharmacokinetic data in patients aged 3 years to 17 years and pharmacokinetic simulation in pediatric patients younger than 3 years of age with a cross-reference to subsection 12.3 Pharmacokinetics
        - Safety data of 140 pediatric patients for intravenous use and 44 patients for intra-arterial use with a cross reference to the *Clinical Trials Experiences* subsection
      - Pediatric risks including thyroid dysfunction were included to be consistent with other ICM labeling.
  - Geriatric Use
    - The verbatim statement for drugs that are excreted by the kidney as required by 21 CFR 201.57(c)(9)(v)(C)(2) was added with cross references to the *Acute Kidney Injury* and *Renal Impairment* subsections.
- Clinical Studies
  - Data presentation was revised to emphasize the primary endpoints used to demonstrate effectiveness, i.e., visualization scores for structure delineation indications and sensitivity and specificity for disease detection indications, and for consistency with other ICM.
  - Presentation of the studies was reordered to be consistent with the order of the indications.
- Strength Designation
  - ICM labeling uses the concentration of bound iodine in mg/mL for strengths and dosing instructions instead of the amount of the drug substance (i.e., iomeprol). The iodine atoms covalently bound to the contrast molecule provide attenuation of X-rays in direct proportion to the concentration of the contrast agent and using the iodine amount for strength and dosing allows dose comparison among different ICMs. Therefore, (b) (4) the concentration of bound iodine in mg/mL was used as strength throughout the labeling. The amount of iomeprol was included in the statement of ingredients (i.e., each mL contains) in the DESCRIPTION section to meet the regulation 21 CFR 201.57(c)(12)(i)(C), and the equivalent amount of bound iodine was included in parentheses to show relationship between the amount of iomeprol and bound iodine, similar to the equivalency statement recommended in drug products containing salt drug substances.

12 Risk Evaluation and Mitigation Strategies (REMS)

A risk evaluation and mitigation strategy was not needed for this NDA.

13 Postmarketing Requirements and Commitment

Each NDA has one CMC post marketing commitment (PMC) for environmental assessment. NDA 216016 has PMC 4662-1 and NDA 216017 has PMC 4661-1. The PMCs are identical in content.

PMC Description	Submit a final environmental assessment report
Final Report Submission Date	01/31/2025
Explain the review issue and the goal of the study	The applicant submitted an environmental assessment (EA) for the active ingredient iomeprol. As approval of this drug application will lead to an increased use of iomeprol and the expected introduction concentration of iomeprol is (b) (4) ppb, exceeding the categorical exclusion (from an EA) level of 1 ppb per 21 CFR 25.31(b), an EA is needed in accordance with 21 CFR 25.40(a). The CDER EA team's read-across analysis indicates that iomeprol could have the potential for causing toxic effects on fish embryos at an environmentally relevant level. Therefore, the EA team recommended the applicant conduct a fish early life-stage assay such as OECD 210, so as to enable the Agency to meet the requirement to determine whether approval of this drug application would significantly affect the quality of the human environment in the US, per 21 CFR 25.15(a). The applicant agreed to conduct an OECD 210 assay and submit preliminary data including the no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC) by September 23, 2024, to allow the Agency to complete the EA review within the review timeline and determine whether the EA is acceptable. The final EA report will be finished and submitted later via this PMC.
What type of study is agreed upon?	☒ Quality CMC study for Environmental Assessment

14 Division Director (Clinical) Comments

The Product Quality reviewers' recommendation for approval of the two NDAs is noted.

The Pharmacology and Toxicology reviewers have determined that no drug-related toxicities that might preclude approval have been identified. I concur with their assessment.

The Clinical Pharmacology reviewers have determined that the proposed dosing regimens in adult and pediatric patients are acceptable. I concur with their recommendation for approval of the applications.

Regarding the clinical and statistical reviews, I concur with the review approach for the two Iomervu marketing applications. The Applicant submitted two NDAs for Iomervu, one NDA with indications for the intra-arterial route of administration and the other NDA with indications for the intravenous route. The clinical reviewers note that visualization of vasculature and tissue perfusion with Iomervu by the two routes of administration depends on the same mechanism of action and has similar clinical meaningfulness. Therefore, direct evidence of effectiveness of the drug for intra-arterial indications also provides confirmatory evidence of effectiveness for the intravenous indications and vice versa. Moreover, the adverse reaction profile of Iomervu is generally similar for the two routes of administration. Therefore, the approach of combining the clinical data in the two NDAs in a single review is justified.

I also concur with the criteria for identifying the 19 key primary efficacy studies with visualization or diagnostic performance endpoints. Eleven of these studies were conducted by the Applicant and eight were studies published in the scientific literature. The efficacy of Iomervu was evaluated in adequate and well-controlled clinical studies for each proposed indication. The studies that supported efficacy of Iomervu for use in cerebral arteriography, visceral and peripheral arteriography and aortography, coronary arteriography and cardiac ventriculography, intra-arterial digital subtraction angiography, CT head and body, and CT urography demonstrated adequate visualization of the intended portions of the vascular system and anatomical structures based on the use of qualitative visualization scales. The studies that supported efficacy of Iomervu for use in CT angiography including coronary CT angiography demonstrated adequate diagnostic performance against a reference standard for the detection of clinically important stenosis at the arterial segment-level.

The clinical reviewers note that the success criteria for the original Iomervu studies and the re-read studies conducted by the Applicant required that the upper limits of the 2-sided 95% confidence intervals for the difference in the proportion of patients with adequate visualization for Iomervu are within the 10% non-inferiority margin to the active comparator. The criteria are met and the proportion of patients with adequate visualization quality after receiving Iomervu is considered acceptable. However, it should be considered that non-inferiority testing for qualitative visualization score endpoints has important shortcomings. The assessments are

subjective and discontinuous and are not validated against a reference standard. It is generally not clear how to assess the meaningfulness of the non-inferiority margin for a visualization score. For these reasons, I agree that presentation of efficacy data for Iomervu alone be presented in the labeling.

Regarding the use of Iomervu in pediatric patients, I concur with the recommendation for approval in patients 0 to 17 years of age. The data from a pharmacokinetic study and a pharmacokinetic simulation support extrapolation of efficacy from adults to pediatric patients of all ages and the safety data are adequate.

The number of study subjects and their demographics, the levels of Iomervu exposure, and the comprehensiveness of clinical evaluations in the NDA safety database are adequate. The important safety issues attributable to Iomervu are similar to the issues for other marketed iodinated contrast agents. No new safety signals are identified. The prescribing information and package and container labels are acceptable in their present form.

In summary, I concur with the unanimous recommendation by the NDA review team for approval of the two applications. The Applicant has provided substantial evidence of effectiveness for use of Iomervu for intra-arterial administration in arteriography and intravenous administration in CT imaging. The clinical benefit-risk balance for Iomervu is favorable.

15 Office Director (or designated signatory authority) Comments

In reviewing the NDAs 216016 and 216017, I agree with the assessment by the Division of Imaging and Radiation Medicine and the multidisciplinary review team that the substantial evidence of effectiveness in the eight of the proposed indications has been met and that the benefit of Iomervu outweighs its risks. I further note that the two of the eight indications (CT Angiography and CT Urography) are new labeled indications for an iodinated contrast agent marketed in this country. I agree with the recommendation for marketing approval of this drug as provided in the approved labeling.

16 Appendices

16.1. References

Albrecht T, Foert E, Holtkamp R, Kirchin MA, Ribbe C, Wacker FK, et al. 16-MDCT angiography of aortoiliac and lower extremity arteries: comparison with digital subtraction angiography. Am J Roentgenol. 2007; 189:702-711.

American College of Radiology Committee on Drugs and Contrast Media. ACR Manual on Contrast Media. https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Published July 2024. Accessed September 3, 2024.

Andreini D, Pontone G, Bartorelli AL, Agostoni P, Mushtaq S, Antonioli L, et al. Comparison of the diagnostic performance of 64-slice computed tomography coronary angiography in diabetic and non-diabetic patients with suspected coronary artery disease. Cardiovascular Diabetology. 2010;9:80-89.

Andreini D, Pontone G, Mushtaq S, Conte E, Perchinunno M, Guglielmo M, et al. Atrial Fibrillation: Diagnostic accuracy of coronary CT angiography performed with a whole-heart 230-µm spatial resolution CT scanner. Radiology. 2017;284:676-84.

Bretlau T, Hansen RH, Thomsen HS. CT urography and hematuria: a retrospective analysis of 771 patients undergoing CT urography over a 1-year period. Acta Radiol. 2015;56:890-96.

Brodoefel H, Tsiflikas I, Burgstahler C, Reimann A, Thomas C, Schroeder S, et al. Cardiac dual-source computed tomography: effect of body mass index on image quality and diagnostic accuracy. Invest Radiol. 2008;43:712-18.

Centers for Disease Control and Prevention. Heart Disease Prevalence. https://www.cdc.gov/nchs/hus/topics/heart-disease-prevalence.htm. Reviewed August 2024. Accessed September 3, 2024.

Gottschalk A, Stein PD, Goodman LR, and Sostman HD. Overview of prospective investigation of pulmonary embolism diagnosis II. Seminars in Nuclear Medicine. 2002;32(3):173-182.

Gruschwitz P, Petritsch B, Schmid A, Schmidt MAM, Grunz J-P, Kuhl PJ, et al. Noise-optimized virtual monoenergetic reconstructions of dual-energy CT angiographies improve assessability of the lower leg arterial segments in peripheral arterial occlusive disease. Radiography. 2023;29:19-27.

Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of

Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021;144(22):e36-e454.

Henry Holzgrefe, Georg Ferber, Pascal Champeroux, Michael Gill, Masaki Honda, Andrea Greiter-Wilke, Theodore Baird, Olivier Meyer, Muriel Saulnier. Preclinical QT safety assessment: Cross-species comparisons and human translation from an industry consortium. Journal of Pharmacological and Toxicological Methods, 2014, 69, 61-101.

Iezzi R, Cotroneo AR, Filippone A, Giancristofaro D, Storto ML. Four-detector row computed tomographic angiography in the evaluation of infrarenal aorta and peripheral arterial occlusive disease: influence of contrast medium concentration. JCAT J Comput Assist Tomogr. 2008;32:690-96.

Kahn C, Leichter I, Lederman R, Sosna J, Duvdevani M, Yeshua T. Quantitative assessment of renal obstruction in multi-phase CTU using automatic 3D segmentation of the renal parenchyma and renal pelvis: A proof of concept. Eur J Radiol Open. 2022;25:100458.

Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Inter Suppl. 2012;2:1-138.

Kim HJ, Yoon DY, Kim ES, Yun EJ, Jeon HJ, Lee JY, et al. 256-row multislice CT angiography in the postoperative evaluation of cerebral aneurysms treated with titanium clips: using three-dimensional rotational angiography as the standard of reference. Eur Radiology. 2020;30:2152-60.

Martingano P, Cavallaro MF, Bertolotto M, Stacul F, Ukmar M, Cova MA. Magnetic resonance urography vs computed tomography urography in the evaluation of patients with haematuria. Radiol Med. 2013;118:1184-98.

Millon D, Derelle AL, Omoumi P, Tisserand M, Schmitt E, Foscolo S, et al. Nontraumatic subarachnoid hemorrhage management: evaluation with reduced iodine volume at CT angiography. Radiology. 2012;264:203-09.

Napoli A, Anzidei M, Zaccagna F, Cavallo Marincola B, Zini C, Brachetti G, et al. Peripheral arterial occlusive disease: diagnostic performance and effect on therapeutic management of 64-section CT angiography. Radiology. 2011:976-86.

Pontone G, Bertella E, Mushtaq S, Loguercio M, Cortinovis S, Baggiano A, et al. Coronary artery disease: diagnostic accuracy of CT coronary angiography--a comparison of high and standard spatial resolution scanning. Radiology. 2014;271:688-94.

Portnoy O, Guranda L, Apter S, Eiss D, Amitai MM, Konen E. Optimization of 64-MDCT urography: effect of dual-phase imaging with furosemide on collecting system opacification and

radiation dose. AJR Am J Roentgenol. 2011;197:W882-W886.

Schaefer PJ, Pfarr J, Trentmann J, Wulff AM, Langer C, Siggelkow M, et al. Comparison of noninvasive imaging modalities for stenosis grading in mesenteric arteries. Fortschr Röntgenstr. 2013;185:628-34.

Somashekar DK, Davenport MS, Cohan RH, Dillman JR, Ellis JH. Effect of intravenous low-osmolality iodinated contrast media on patients with myasthenia gravis. Radiology. 2013;267:727-34.

(b) (4)

Stein PD, Fowler SE, Goodman LR, Gottschalk A, Hales CA, Hull RD, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med. 2006;354:2317-27.

Stueckle CA, Haegele KF, Jendreck M, Zipser MC, Kirchner J, Kickuth R, et al. Multislice computed tomography angiography of the abdominal arteries: Comparison between computed tomography angiography and digital subtraction angiography findings in 52 cases. Australas Radiol. 2004;48:142-47.

Toshiyuki Matsunaga, Takeshi Mitsui, Takuma Harada, Masanori Inokuma, Hiroyuki Murano, and Yasunori Shibutani. QT Corrected for Heart Rate and Relation Between QT and RR Intervals in Beagle Dogs. J Pharm Tox Meth. 1998, 38, 201-209

(b) (4)

16.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): IOM-104A (Original studies: 48,848-001A, 48,848-001B, 48,848-002A, and 48,848-002B)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 18		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

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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

Sponsor of covered study: _____</td></tr>
<tr><td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td><td>Yes ☐</td><td>No ☐ (Request details from Applicant)</td></tr>
<tr><td>Is a description of the steps taken to minimize potential bias provided:</td><td>Yes ☐</td><td>No ☐ (Request information from Applicant)</td></tr>
<tr><td colspan="3">Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0</td></tr>
<tr><td>Is an attachment provided with the reason:</td><td>Yes ☐</td><td>No ☐ (Request explanation from Applicant)</td></tr>
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Covered Clinical Study (Name and/or Number): IOM-104C (Original studies: 48,848-004A and 48,848-004B)

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<tr><td colspan="3">Total number of investigators identified: 10</td></tr>
<tr><td colspan="3">Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0</td></tr>
<tr><td colspan="3">Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0</td></tr>
<tr><td colspan="3">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: _____</td></tr>
</table>

Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): IOM-104D (Original studies: 48,848-005A and 48,848-005B)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 10		
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 Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to	Yes ☐	No ☐ (Request information

minimize potential bias provided:		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)

Covered Clinical Study (Name and/or Number): IOM-104E (Original studies: 48,848-007A, 48,848-007B, 48,848-008A, and 48,848-008B)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 11		
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 Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Napoli et al. 2011, Albrecht et al. 2007, Andreini et al. 2010, Pontone et al. 2014, Portnoy et al. 2011, and Martingano et al. 2013

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 54		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1 (Albrecht et al. 2007)		
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 Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

16.3. OCP Appendices (Technical documents supporting OCP recommendations)

16.3.1. Summary of Bioanalytical Method Validation and Performance

Were relevant metabolite concentrations measured in the clinical pharmacology studies?

Yes, plasma and urine concentrations of the active parent, iomeprol, were measured in the clinical pharmacology studies. Iomeprol does not undergo significant metabolism.

For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total concentrations of iomeprol were measured in the clinical trials. This was appropriate as iomeprol does not bind to plasma proteins.

What bioanalytical methods are used to assess concentrations?

High-performance liquid chromatography (HPLC) and X-ray fluorescence (XRF) spectroscopy methods were used in eight clinical pharmacology studies (Studies 87020, 7/86, B16880/042, B16880/054, 48848-010, 48848-011, J081-001, and B16880/037). This review focused on the XRF method used in Studies 87020 and 7/86 (Table 74) and HPLC methods used in B16880/042, B16880/054, 48848-010, and 48848-011 (Table 75). The PK data from these studies were used to characterize PK of iomeprol.

As the above studies were conducted between 1986 and 1998, bioanalytical methods used in these studies do not meet the 2022 ICH M10 Guidance for Industry (e.g., without QC for the XRF method and HPLC method RF5568). The XRF method was used in the early studies and RF5568 method was further modified in method B16880/054. These methods were validated as per the industry standard at the time of their development. In addition, the dose normalized PK profiles of iomeprol were comparable across the studies demonstrating that the bioanalytical methods were consistent with each other in characterizing PK profiles of iomeprol. Thus, the bioanalytical methods were appropriate for characterizing PK profiles of iomeprol.

The analytical method in Study J081-001 in healthy Japanese volunteers is not reported. The PK data from Study J081-001 were not used to characterize PK of Iomeprol in this submission. Of note, the reported PK parameters in Study J081-001 were similar with those in Study 87029 in healthy Caucasian volunteers. The PK data from Study B16880/037 were from intrathecal injection.

Table 74. Spectrometry and X-Ray Fluorescence (XRF) Method Summary

Method Report	RF1805	
Site	Bracco	
Analytes	Iodine in Plasma	Iodine in Urine
Validated assay range	1 to 1000 µgI/mL	1 to 3000 µgI/mL
Calibration range	1 to 1000 µgI/mL	1 to 1000 µgI/mL
Number of standard calibrators	7	8
Regression model & weighting	Linear interpolation to least squares, both in decimal (for the range 1 to 10	Linear interpolation to least squares, both in decimal (for the range 1 to 30 µgI/mL)

	µgI/mL) and in (natural) log scale (for the range 10 to 1000 µgI/mL)	and in (natural) log scale (for the range 30 to 3000 µgI/mL)
Studies Supported	87020; 7/86	

Source: Table A and B of Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods - Addendum

Table 75. HPLC Methods Summary

Method Report	RF5568		B16880/054			PCLI9701V	PCLI9702V
Site	Bracco		(b) (4)				
Analytes	Iomeprol in plasma	Iomeprol in urine	Iomeprol in plasma	Iomeprol in dialysis fluid	Iomeprol in urine	Iomeprol in plasma	Iomeprol in urine
Validated assay range (µg/mL)	3 - 2000	6 - 2000	3 - 2000	3 -2000	6 -2000	3 -3000	10 - 2500
Calibration range (µg/mL)	3 - 2000	6 - 2000	3 - 2000	3 -2000	6 -2000	3 -3000	10 - 2500
Number of standard calibrators	9	9	NA	NA	NA	11	10
Regression model & weighting	Least-squares linear regression	Least-squares linear regression	NA	NA	NA	1/x linear regression	1/x linear regression
Accuracy of QCs performance during accuracy & precision	NA	NA	3 QCs - 10 µg/mL: 7.81% - 1005 µg/mL: 1.06% - 1688 µg/mL: 0.858%	3 QCs - 19.9 µg/mL: -7.29% - 997 µg/mL: 2.26% - 1674 µg/mL: 2.07%	3 QCs - 10.1 µg/mL: 6.33% - 1009 µg/mL: 3.82% - 1696 µg/mL: 3.90%	3 QCs - 3 µg/mL: 95.1 to 111% - 150 µg/mL: 97.8 to 102% - 3000 µg/mL: 102 to 104%	3 QCs - 10 µg/mL: 92.3 to 101% - 250 µg/mL: 100 to 102% - 2500 µg/mL: 98.4 to 101%
Inter-batch % CV of QCs performance during accuracy & precision	NA	NA	- 10 µg/mL: 5.34% - 1005 µg/mL: 7.46% - 1688 µg/mL: 8.12%	- 19.9 µg/mL: 8.79% - 997 µg/mL: 6.69% - 1674 µg/mL: 4.39%	- 10.1 µg/mL: 2.89% - 1009 µg/mL: 2.93% - 1696 µg/mL: 2.20%	- 3 µg/mL: 8.07% - 150 µg/mL: 2.04% - 3000 µg/mL: 1.12%	- 10 µg/mL: 4.61% - 250 µg/mL: 1.27% - 2500 µg/mL: 1.41%
Studies Supported	B16880/042		B16880/054			48848-010; 48848-011	

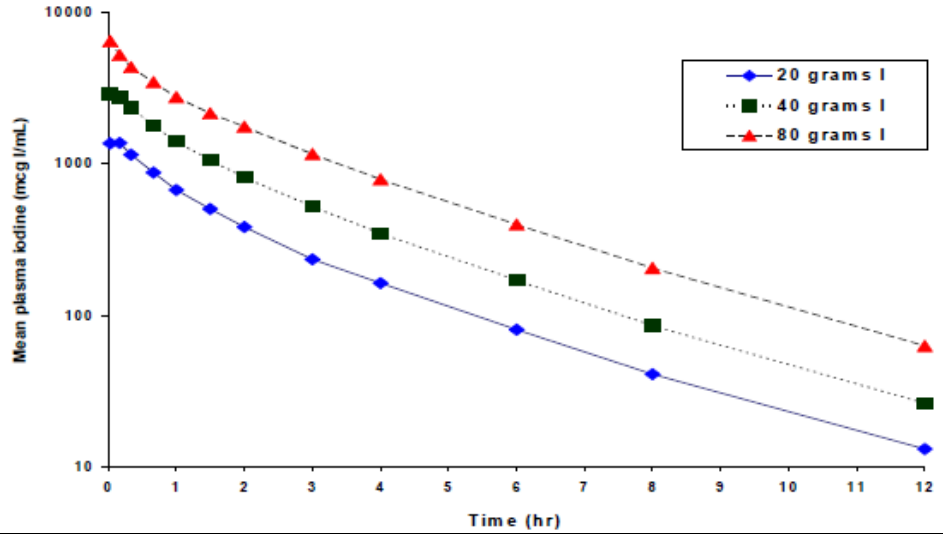
Source: Table E, F, I, J, K and L of Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods – Addendum.
Abbreviations: NA = not available, QCs = quality controls.

16.3.2. **Clinical PK**

Iomeprol PK properties following a single dose Iomervu IV administration were assessed in six clinical studies. These studies were conducted in adult healthy participants (Study 87020 (N=18)), in participants with renal impairment (Study B16880/042 (N=20)), in adult patients on hemodialysis (Study B16880/054 (N=8)), in adult patients referred for a CT scan (Study 7/86 (N=8); Study 48,848-011 (N = 17, patients 65 years and older)), and in pediatric patients referred for a CT scan in Study 48-848-010 (N=19, age 3-17 years).

Iomeprol PK following single intravenous administration was characterized in Study 87020 in healthy volunteers aged 20 to 45 years. Mean plasma concentration-time data of iodine after a single dose at three dose levels are shown in Figure 2. Iodine plasma concentrations were used to calculate the iomeprol pharmacokinetic parameters. The summary statistics of PK parameters of iomeprol after a single dose are presented in Table 76. The mean CL_{tot} value of 0.10 L/hr/kg (~ 117 mL/min for a patient with body weight of 70 kg) suggested that glomerular filtration is the primary elimination mechanism for the study agent. Approximately 90% of iodine dose was recovered in the urine during a 24-hour interval. PK parameters were independent of dose from 20 to 80 gram iodine total dose while the dose normalized by body weight ranged from 250 mgI/kg to 1250 mgI/kg.

Figure 2. Mean Plasma Iodine Concentration-Time Profiles Following Iomervu Administration to Healthy Volunteers



Dose levels: 20 grams I (Iomervu 400 mgI/mL 50 mL), 40 grams I (Iomervu 400 mgI/mL 100 mL), 80 grams I (Iomervu 400 mgI/mL 200 mL).
Cmax of Iodine: 1.52 ± 0.25 mg I/mL (20 grams I); 3.03 ± 0.40 mg I/mL (40 grams I); 6.6 ± 1.4 mgI/mL (80 grams I).

Source: Figure 2 in 2.7.2 Summary of Clinical Pharmacology Studies and Table B in 5.5.3.1 Report of Cmax and AUC calculation for Study 87020.

Table 76. Pharmacokinetic Parameters of Iomeprol in Healthy Volunteers in Study 87020

Parameter	20 gI (n=6)	40 gI (n=6)	80 gI (n=6)	All Doses (n=18)
$t_{½\alpha}$ (hr)	0.45 ± 0.18[a]	0.50 ± 0.29	0.18 ± 0.09	0.37 ± 0.24
$t_{½\beta}$ (hr)	1.94 ± 0.35	1.86 ± 0.39	1.68 ± 0.24	1.83 ± 0.33
V_c (L/kg)	0.16 ± 0.02	0.17 ± 0.03	0.16 ± 0.03	0.16 ± 0.03
V_β (L/kg)	0.30 ± 0.07	0.28 ± 0.05	0.26 ± 0.02	0.28 ± 0.05
CL_{tot} (L/hr/kg)	0.10 ± 0.01	0.10 ± 0.01	0.10 ± 0.02	0.10 ± 0.01
$Ae_{ur,0\text{-}2}$ (% of dose)	44.3 ± 4.8	56.1 ± 7.6	50.0 ± 9.3	---
$Ae_{ur,0\text{-}24}$ (% of dose)	86.7 ± 5.3	89.3 ± 3.8	91.0 ± 12.2	---
$Ae_{ur,0\text{-}96}$ (% of dose)	87.1 ± 5.2	89.6 ± 3.9	91.5 ± 12.9	89.4 ± 8.1

Source: Table data derived from CSR for Study 87020, Tables 5 and 9.
[a] Values are mean ± standard deviation.
gI = grams of iodine; $t_{½\alpha}$ = half-life of the alpha phase (2-compartment model); $t_{½\beta}$ = half-life of the beta phase (2-compartment model; V_c = apparent volume of the central compartment; V_β = volume of distribution associated with the beta phase (2-compartment model); CL_{tot} = total (plasma) clearance; $Ae_{ur,x\text{-}y}$ = amount of compound excreted in urine from time x to time y.

Cmax of Iomeprol: 3.1 ± 0.50 mg/L (20 gI); 6.2 ± 0.82 mg /mL (40 gI); 13.5 ± 2.8 mg /mL (80 gI).
AUC_{inf} of Iomeprol: 5.3 ± 1.1 mg·h/L (20 gI); 11.0 ± 1.5 mg·h/mL (40 gI); 23.3 ± 3.9 mg·h/mL (80 gI).

Source: Table E in 2.7.2 Summary of Clinical Pharmacology Studies and Table B in 5.5.3.1 Report of Cmax and AUC calculation for Study 87020.

Please refer to Section 6.2.2 regarding iomeprol PK in patients with renal impairment.

16.3.3. Pharmacometrics Review

19.4.3.1 APPLICANT'S POPULATION PHARMACOKINETICS ANALYSIS

Objectives: To describe concentration-time data arising from clinical studies of Iomervu; To identify and characterize patient factors which influence the PK and PK variability of Iomervu; To estimate the magnitude of unexplained variability in PK in this patient population; and to use the model for simulating concentration-time profiles of iomeprol in pediatric patients.

Data: Plasma and urine data from Studies 87020, 7/86, B16880/042, 48,848-010, and 48,848-011 were pooled to create the NONMEM database. In all studies, Iomervu was administered as a single dose with dense PK sampling. A summary of the studies is shown in Table 77.

Table 77. Doses and Concentrations of Iomeprol Used in Human PK Studies

Study	Population (study size)	Conc. & Route	Volume	Dose Levels
87020, Healthy volunteer	Caucasian male (N=18 Iomervu, N=6 placebo). All subjects who received Iomervu: *Age:* 33.6 (20–45) yr	400 mgI/mL Intravenous	50, 100, or 200 mL	20 gI, 40 gI, or 80 gI
7/86, Patients undergoing urography	(N=10) *Age:* 42.0 (20-60) yr	300 mgI/mL IV bolus (n=4) IV infusion, 14.3 mL/min (n=6)	20, 50, or 100 mL	6 gI, 15 gI, or 30 gI
B16880/042, Renal Impairment Study	Normal (n=6), CL_{inulin}: 120 (80-154) mL/min *Age:* 37.2 (22-58) yr Mild (n=6), CL_{inulin}: 72 (55-85) mL/min *Age:* 55.0 (36-74) yr Moderate (n=6), CL_{inulin}: 38 (29-49) mL/min *Age:* 70.3 (58-79) yr Severe (n=4), CL_{inulin}: 20 (16-23) mL/min *Age:* 53.8 (34-73) yr	400 mgI/mL Intravenous	50 mL	20 gI
48,848-010 Pediatric patients referred for body computed tomography	Children (n=10), *Age:* 8.3 (3-12) yr Adolescents (n=10), *Age:* 15.4 (13-17) yr	400 mgI/mL Intravenous	32 to 124 mL	609 mg/kg to 2108 mg/kg of iomeprol; total doses of 26.144 to 101.308 g of iomeprol, corresponding to 12.8 to 49.6 gI
48,848-011, Elderly patients referred for body computed tomography	N=20, *Age:* 70.9 (65-78) yr	400 mgI/mL Intravenous	95 to 179 mL	918 mg/kg to 2212 mg/kg of iomeprol; total doses of 77.615 to 146.243 g of iomeprol, corresponding to 38 to 71.6 gI

For Study 48,848-011, patient (b) (6) had first examination with 8 mL but was terminated due to IV infiltration, CT exam was not performed; Second examination was performed one month afterward with 100 mL In the Clinical Study Report, these two volumes were averaged as 54 mL in the exposure summary table. For the PK analysis, data from the second exam was utilized. mgI/mL - milligrams of iodine per milliliter; gI - grams of iodine, mL – milliliter, min – minute, kg – kilograms, mg –milligrams, N, n – number, CL – clearance, yr – year, IV – intravenous, g – gram, CT exam - computerized tomography scan, PK – pharmacokinetics
Source: Table 1 of Applicant's PPK Report

There were 90 subjects included in the dataset. A summary of the continuous covariates is in Table 78, and the categorical covariates are in Table 79.

Table 78. Summary of Continuous Covariates

Covariate	Mean	SD	Q1	Median	Q3	Range
Age (years)	42.99	23.60	20.25	43.00	67.75	3 - 79
Height (cm)	167.08	16.31	160.66	171.00	178.00	94.5 - 192
Weight (kg)	70.24	17.86	62.70	72.25	80.45	15.5 - 109.32
BMI (kg/m^2)	24.81	4.99	21.49	24.32	28.08	14.0 - 41.7
BSA (m^2)	1.78	0.30	1.68	1.82	1.99	0.622 - 2.206
Creatinine (µmol/L)	96.36	92.49	53.04	70.72	88.40	26.52 - 530.4
CrCL (ml/min)	08.21	55.87	72.03	107.69	139.77	13.5 - 305.23

SD: standard deviation; Q1: 25 percentile; Q3: 75 percentile; CrCL: creatinine clearance.
Source: Table 3 of Applicant's PPK Report

Table 79. Summary of Categorical Covariates

Covariate	Category	N	%
Study	48,848-010	20	22.2
	48,848-011	20	22.2
	B16880/042	22	24.4
	7/86	10	11.1
	87020	18	20
Age Group	<18 years	20	22.2
	>=18 years	70	77.8
Sex	Male	67	74.4
	Female	23	25.6
Race	White	52	57.8
	Black or African American	3	3.3
	Hispanic	6	6.7
	Filipino	1	1.1
	Unknown	28	31.1
Health Status	Healthy	18	20.0
	Patients	72	80.0

Source: Table 4 of Applicant's PPK Report

Methods: PPK modeling for iomeprol was conducted using the first-order conditional estimation with SADDLE_HESS=1 SADDLE_RESET=1 method in nonlinear mixed-effects modeling (NONMEM; Version 7.4.4). Compartment models with between-subject variability (BSV) and covariates effects were evaluated. R v3.0.2 was used for associated analysis.
Based on the final model, Cmax and AUC were simulated to evaluate doses that achieved similar exposure for pediatric patients versus adults.

Results:

The final model is a 3-compartment linear model with elimination of iomeprol from the central compartment (ADVAN11 TRANS4). The final model included the effects of creatinine clearance (CrCL) and healthy volunteer subjects on clearance (CL). Allometric scaling was included on all the parameters except CL since the CrCL effect includes a body size component. The final iomeprol model parameter estimates are shown below. The precision of the parameters was acceptable at 15.6% standard error (SE) or less. The ETA (η, interindividual variability) shrinkage was low at 22.1% standard deviation (SD) or less. Residual variability was low at 10.8% coefficient of variability (CV). All the parameters except for CL included allometric scaling where the intercompartmental clearance (Q2 and Q3) parameter values were multiplied by (body weight/72.25)$^{0.75}$ and the volume of distribution (V1, V2, and V3) parameter values were

multiplied by (body weight/72.25)[1]. The condition number for the final model was 5.38, indicating a well-conditioned model. The final PK model parameters are shown in Table 80.

Table 80. Parameter Estimates of the Final PPK Model

Parameter	Estimate	RSE (%)	IIV (%)	ETA Shrinkage SD%	EBV Shrinkage SD%
CL (L/hr)	1.14	5.5	26%	9.8	10.9
V1 (L)	2.36	1.6	34%	4.6	5.1
Q2 (L/hr)	1.79	3.8	39%	21.0	21.5
V2 (L)	1.92	1.6	19%	22.1	22.8
Q3 (L/hr)	0.547	15.6	59%	6.7	7.1
V3 (L)	7.67	2.2	-	-	-
Residual Variability	10.8%CV	3.0	-	-	-
CrCL on Clearance	0.86	5.8	-	-	-
HV on Clearance	1.36	7.3	-	-	-

SE – standard error, CV – coefficient of variation, L- liters, hr – hour, SD – standard deviation, CL – clearance, V1 – central volume, Q2 – first inter-compartmental clearance, V2 – first peripheral volume, Q3 – second inter-compartmental clearance, V3 – second peripheral volume, CrCL – creatinine clearance, HV – healthy volunteer, EBV - empirical Bayes variance, IIV – interindividual variability, ETA – η, interindividual variability.

Source: Table 14 of Applicant's PPK Report.

Mean and standard deviation (SD) of plasma iomeprol CL of individual subjects empirical bayes estimates (EBE) are summarized in Table 81 by age category or renal impairment. CL increases with increasing age. CL in renally impaired adults is approximately 44% of the non-renally impaired adults.

Table 81. Summary of Iomeprol Clearance (CL) by Age Group

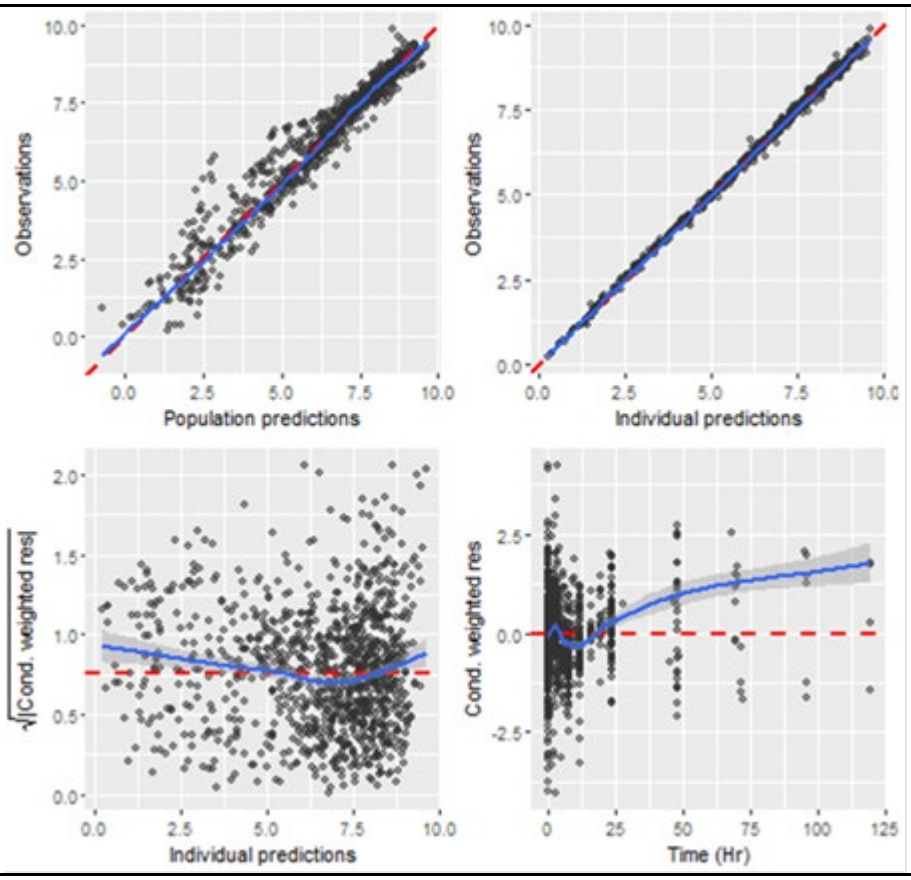
Age Group (yr)	Renal Function	Plasma CL (L/h)		Plasma CL (L/h/kg)	
		mean	sd	mean	sd
2 to <6*	Normal	1.67	NA	0.107	NA
6 to <12	Normal	3.43	0.78	0.102	0.040
12 to <18	Normal	4.42	1.92	0.068	0.017
Adult	Non-renally Impaired	4.05	1.69	0.054	0.023
Adult	Renal Impaired	1.81	1.22	0.025	0.020

*Only 1 subject (age 3 years) in this age group; L – liter, h – hour, kg – kilogram, NA – not applicable/available, sd – standard deviation

Source: Table 16 of Applicant's PPK Report.

Goodness-of-Fit plots are provided in Figure 3.

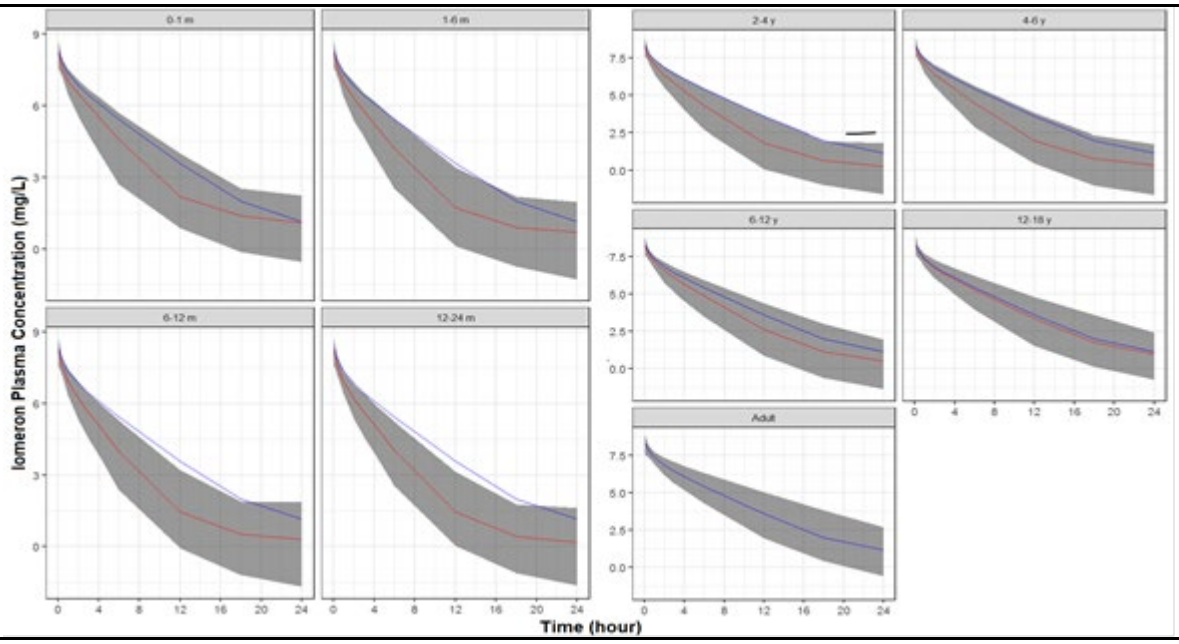
Figure 3. Goodness of Fit Plots for the Final PPK Model



Source: Figure 7 of Applicant's PPK Report

The simulations were conducted for iomeprol doses of 609 mg/kg by age group as shown in Figure 4 for male and Figure 5 for female.

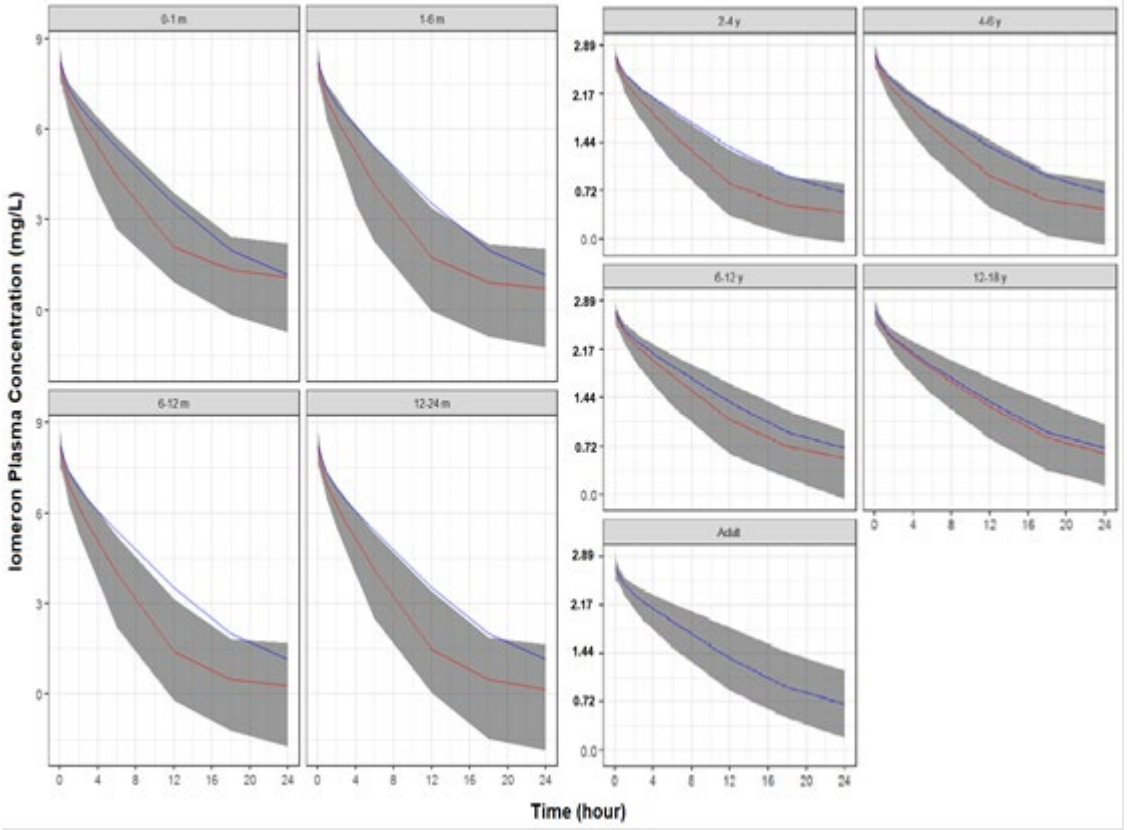
Figure 4. Simulated Concentration Versus Time Profiles of 609 mg/kg Iomeprol Dose in Male Pediatric Subjects Compared to Adults (Blue Line)



Note: These plots show the 95% prediction interval in gray with the median value as a red line. The blue line is an overlay of the median value for adults.

Source: Figures 27 and 28 of Applicant's PPK Report.

Figure 5. Simulated Concentration Versus Time Profiles of 609 mg/kg Iomeprol Dose in Female Pediatric Subjects Compared to Adults (Blue Line)

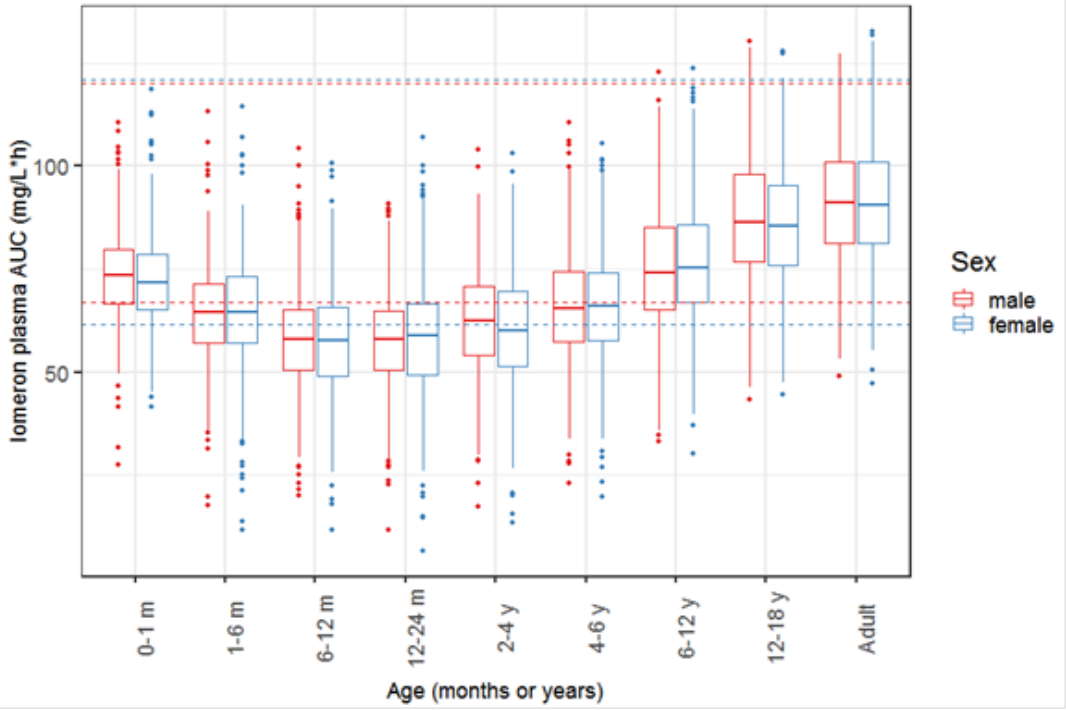


Note: These plots show the 95% prediction interval in gray with the median value as a red line. The blue line is an overlay of the median value for adults.

Source: Figures 30 and 77 (with scale adjusted proportionally) of Applicant's PPK Report.

Figure 6 through Figure 9 are box plots of AUC, Cmax, C20 (concentrations at 20 minutes post-dose), and C30 (concentrations at 30 minutes post-dose) by age group and sex. Overall, the simulated AUC, Cmax, C20, and C30 values generally overlap the 95th percentiles of the adult subjects.

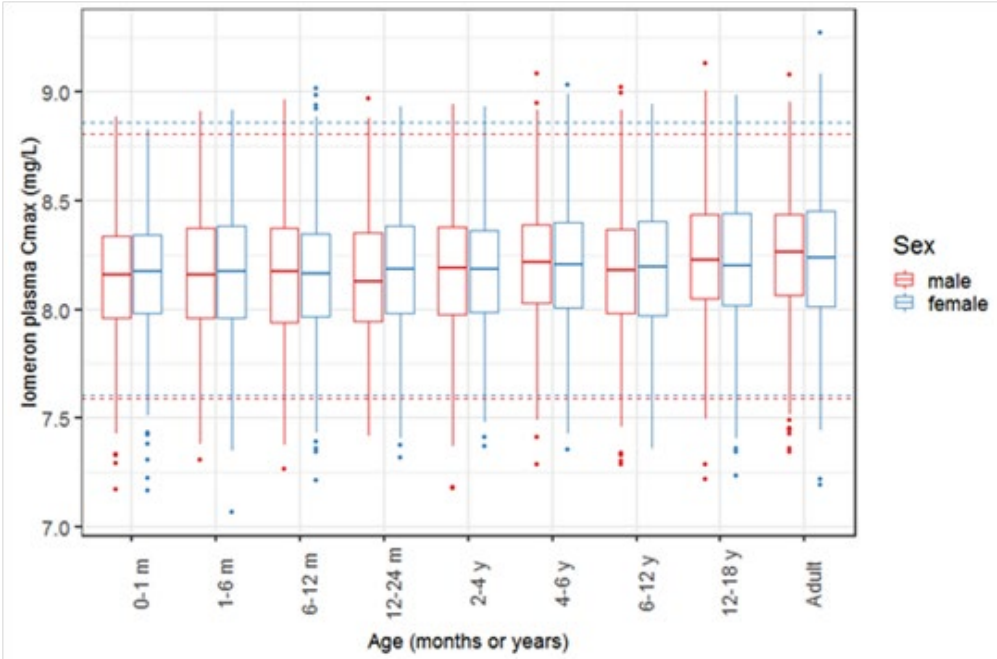
Figure 6. Comparison of AUC (0-24h) by Age Group for Male and Female Subjects Based on 609 mg/kg Dose Simulations



Note: The red lines and boxes correspond to male subjects in these plots, and the blue lines and boxes correspond to female subjects. The horizontal lines show the 95 percentiles of the adult male or female subjects.

Source: Figure 31 of Applicant's PPK Report.

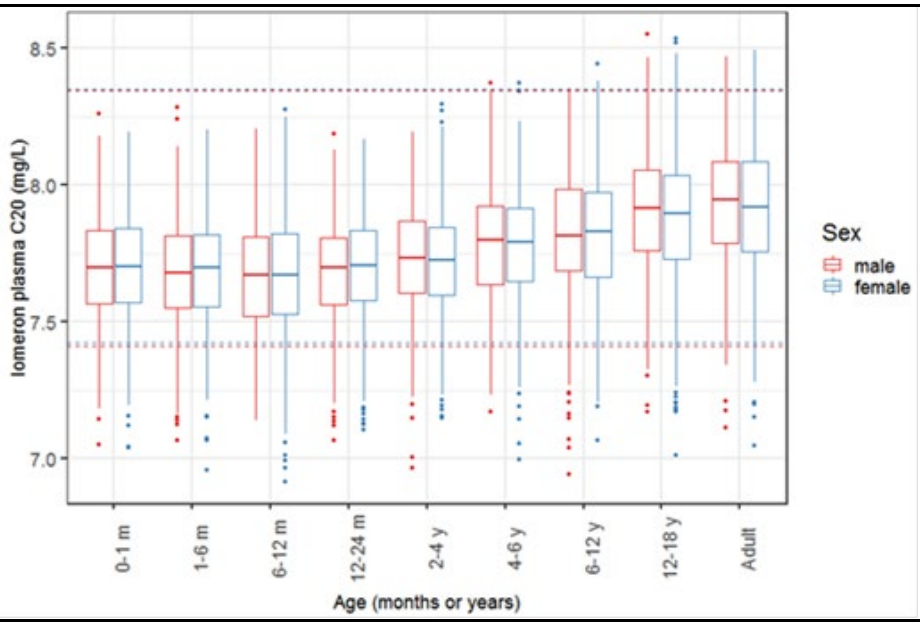
Figure 7. Comparison of Cmax by Age Group for Male and Female Subjects Based on 609 mg/kg Dose Simulations



Note: The red lines and boxes correspond to male subjects in these plots, and the blue lines and boxes correspond to female subjects. The horizontal lines show the 95 percentiles of the adult male or female subjects.

Source: Figure 32 of Applicant's PPK Report.

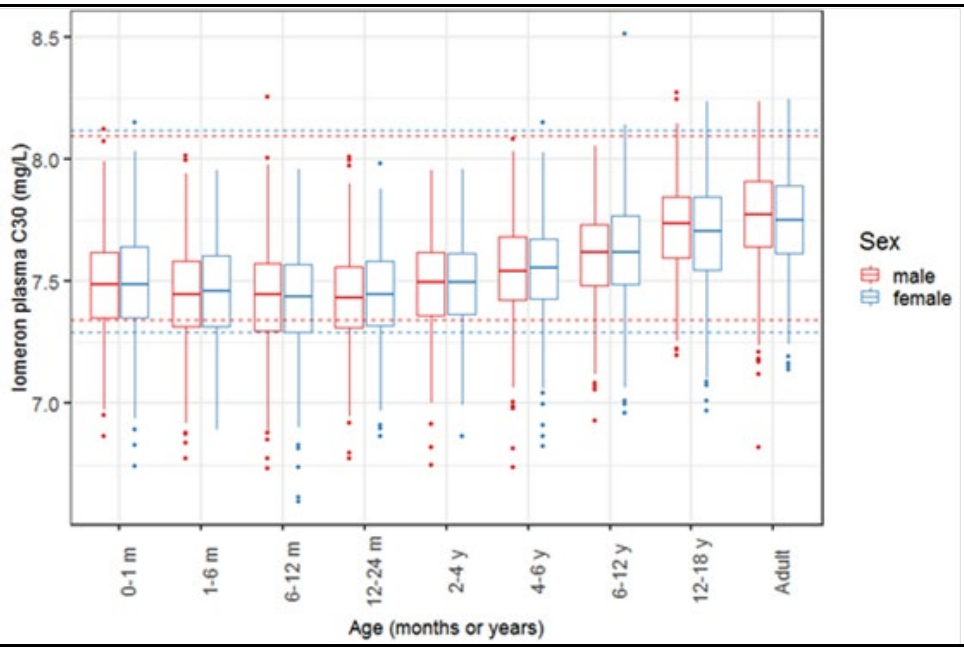
Figure 8. Comparison of Iomeprol Concentration at 20 Minutes After the Start of Infusion (C20) by Age Group for Male and Female Subjects Based on 609 mg/kg Dose Simulations



Note: The red lines and boxes correspond to male subjects in these plots, and the blue lines and boxes correspond to female subjects. The horizontal lines show the 95 percentiles of the adult male or female subjects.

Source: Figure 33 of Applicant's PPK Report.

Figure 9. Comparison of Iomeprol Concentration at 30 Minutes After the Start of Infusion (C30) by Age Group for Male and Female Subjects Based on 609 mg/kg Dose Simulations

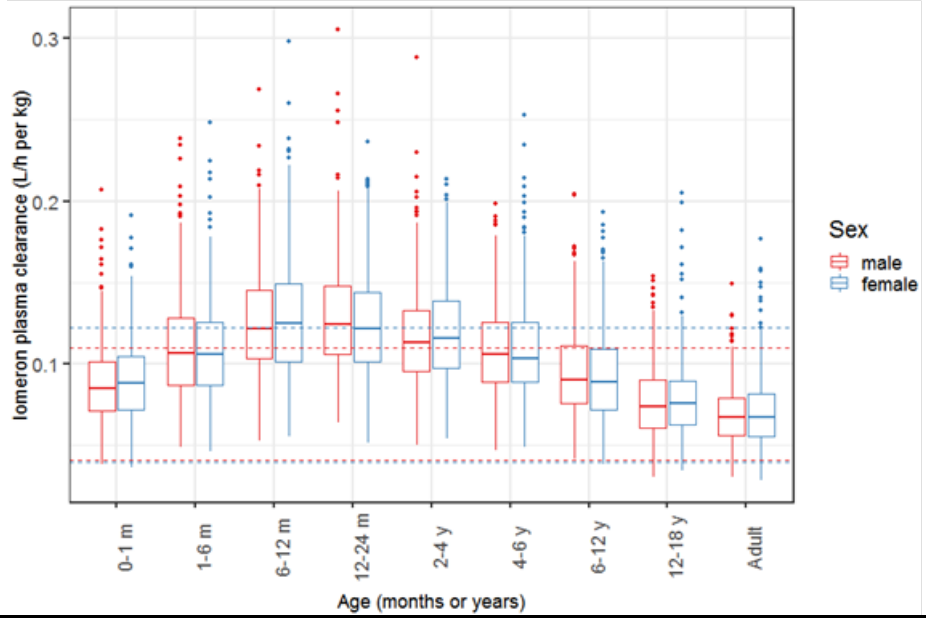


Note: The red lines and boxes correspond to male subjects in these plots, and the blue lines and boxes correspond to female subjects. The horizontal lines show the 95 percentiles of the adult male or female subjects.

Source: Figure 34 of Applicant's PPK Report.

Figure 10 and Figure 11 are similar plots to the above, with these plots comparing the iomeprol CL and the volume of distribution at steady-state (Vss) by age group and sex. Overall, CL and Vss values generally overlap the 95th percentiles of the adult subjects.

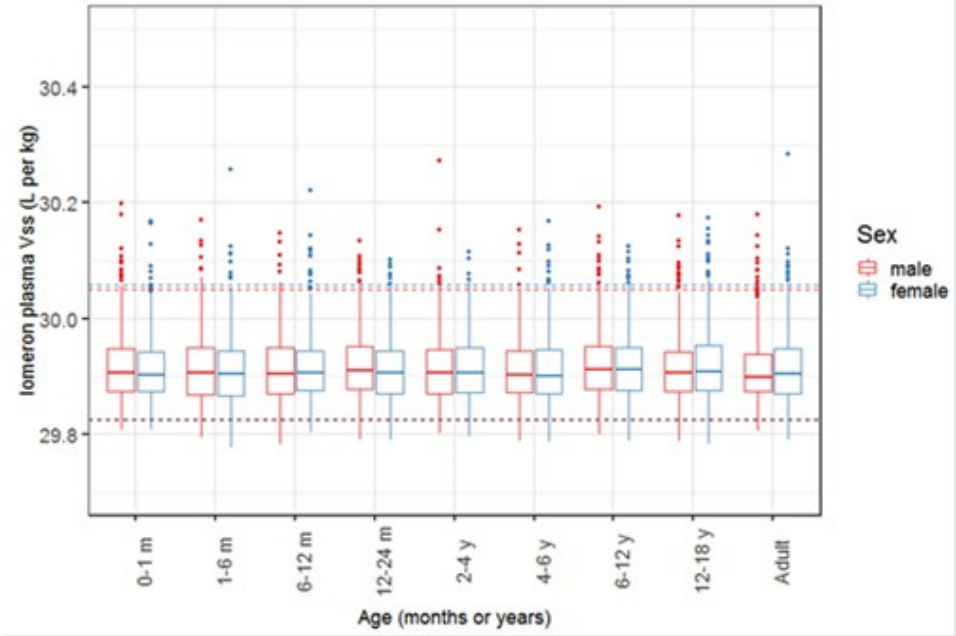
Figure 10. Comparison of Clearance by Age Group for Male and Female Subjects



Note: The red lines and boxes correspond to male subjects in these plots, and the blue lines and boxes correspond to female subjects. The horizontal lines show the 95 percentiles of the adult male or female subjects.

Source: Figure 35 of Applicant's PPK Report.

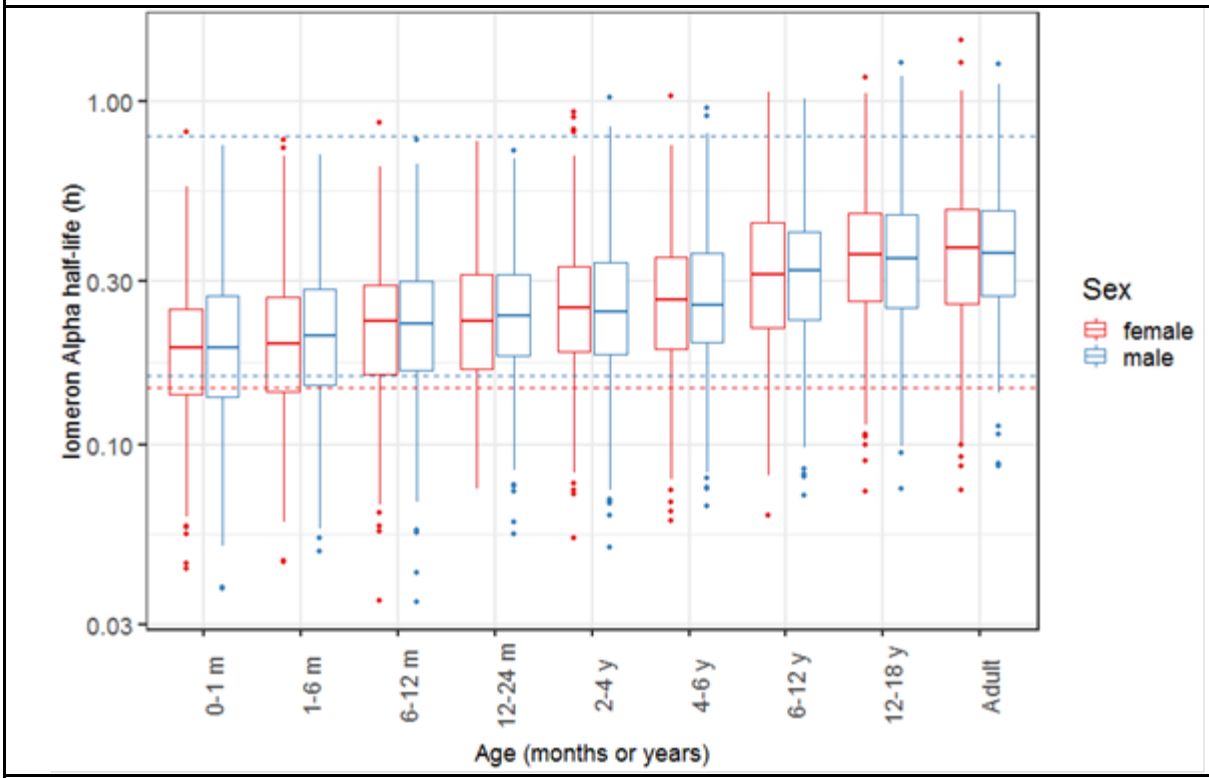
Figure 11. Comparison of Volume of Distribution at Steady State by Age Group for Male and Female Subjects



Note: The red lines and boxes correspond to male subjects in these plots, and the blue lines and boxes correspond to female subjects. The horizontal lines show the 95 percentiles of the adult male or female subjects.
Source: Figure 36 of Applicant's PPK Report.

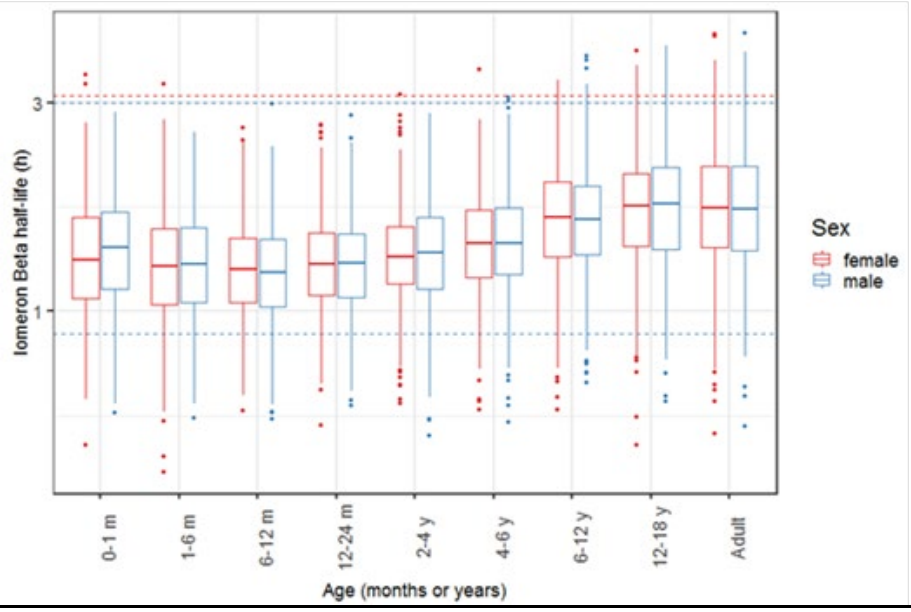
Figure 12 through Figure 15 are similar plots to the above, comparing the half-lives of iomeprol by age group and sex. The alpha and beta half-lives generally overlap the 95th percentiles of the adult subjects. The gamma and effective half-lives are longer in the youngest subjects (under 4 years of age). This can be attributed to the relatively larger V3 in the youngest subjects resulting in longer effective half-lives.

Figure 12. Comparison of Alpha Half-Life by Age Group for Male and Female Subjects Based on 609 mg/kg Dose Simulations



Note: The red lines and boxes correspond to male subjects in these plots, and the blue lines and boxes correspond to female subjects. The horizontal lines show the 95 percentiles of the adult male or female subjects.
Source: Figure 37 of Applicant's PPK Report.

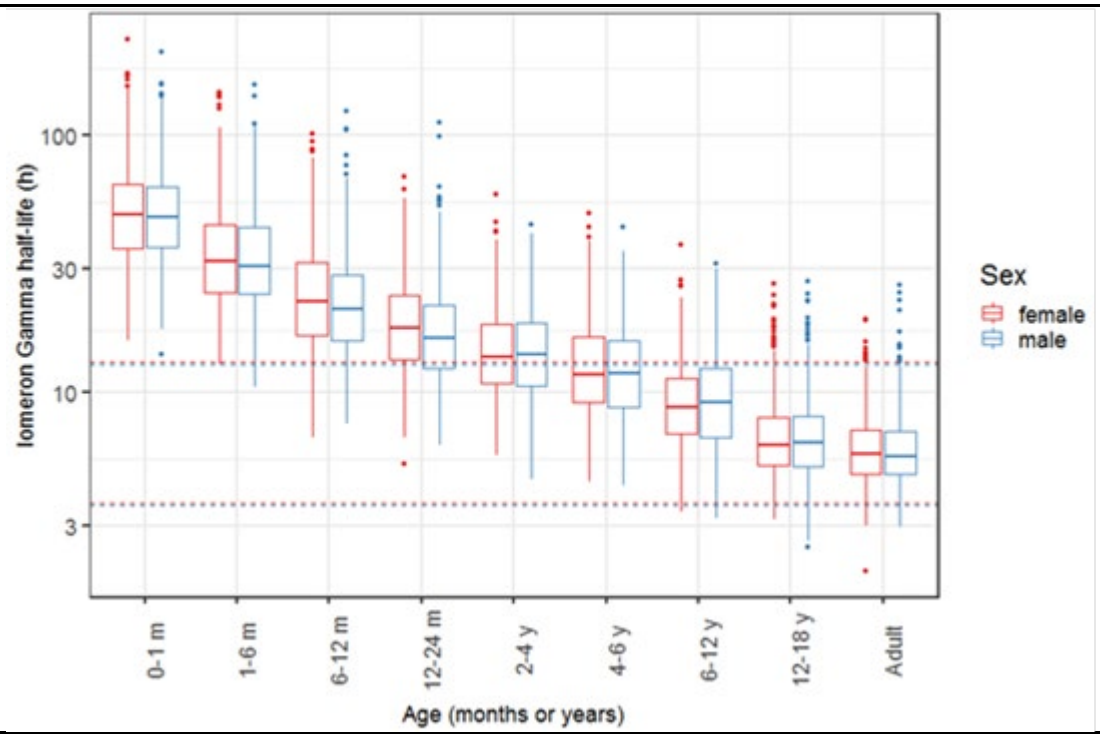
Figure 13. Comparison of Beta Half-Life by Age Group for Male and Female Subjects Based on 609 mg/kg Dose Simulations



Note: The red lines and boxes correspond to male subjects in these plots, and the blue lines and boxes correspond to female subjects. The horizontal lines show the 95 percentiles of the adult male or female subjects.

Source: Figure 38 of Applicant's PPK Report.

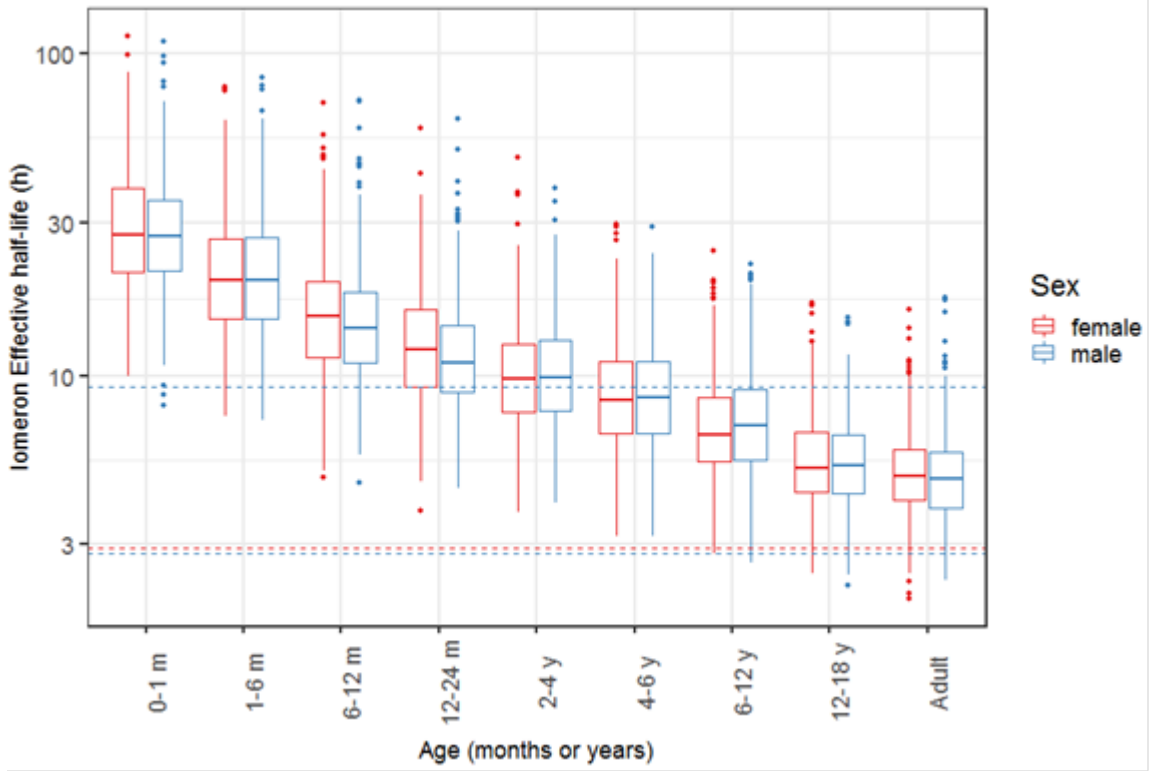
Figure 14. Comparison of Gamma Half-Life by Age Group for Male and Female Subjects Based on 609 mg/kg Dose Simulations



Note: The red lines and boxes correspond to male subjects in these plots, and the blue lines and boxes correspond to female subjects. The horizontal lines show the 95 percentiles of the adult male or female subjects.

Source: Figure 39 of Applicant's PPK Report.

Figure 15. Comparison of Effective Half-Life by Age Group for Male and Female Subjects Based on Iomeprol 609 mg/kg Dose Simulations



Note: The red lines and boxes correspond to male subjects in these plots, and the blue lines and boxes correspond to female subjects. The horizontal lines show the 95 percentiles of the adult male or female subjects.
Source: Figure 40 of Applicant's PPK Report.

Reviewer's Comments on Applicant's Analysis: *The Applicant's modeling analyses are acceptable in general. However, the reported estimate values for the final model are natural log transformed, i.e., the estimates for CL, V1, Q2, V2, Q3 and V3 should be 3.13, 10.6, 5.99, 6.82, 1.73, and 2143, respectively.*

The covariate effect of healthy condition (Study 87020 = 1 versus other studies =0) on CL could be confounded with CRCL effect on CL. Therefore, it is difficult to interpret its clinical application.

19.4.3.2. FDA REVIEWER'S ANALYSIS

Objectives: To run the PPK analysis without data from Study 87020, and to simulate C20 and C30 by CRCL category afterwards.
Method: Applicant's NONMEM dataset (with data from Study 87020 removed) and control stream for the final model were used. NONMEM v75 and R v4.1.0 were applied for analyses.

Results: By excluding data from Study 87020, FDA analysis results are similar to Applicant's analysis results with shrinkage for Q2 reduced from 21% to 8.7%, and interindividual variability

(IIV) for Q2 reduced from 39% to 16% as shown in Table 82. The relative standard error (RSE) (%) values are also similar to Applicant's analysis which are not reported in Table 83.

Table 82. Parameter Estimates of the Final Population Pharmacokinetics Model

Parameter	Applicant (All Data)			FDA (Exclude Data from Study 87020)		
	Estimate (RSE%) η	IIV (%)	ETA Shrinkage SD%	Estimate (RSE%)	IIV (%)	ETA Shrinkage SD%
LN of CL (L/hr)	3.13 (34.3%)	26%	9.8	3.02 (12.8%)	30.6%	10.2
LN of V1 (L)	10.6 (9.8%)	34%	4.6	10.3 (4.8%)	35.4%	4.1
LN of Q2 (L/hr)	5.99 (17.9%)	39%	21.0	6.77 (8.0%)	16.3%	8.7
LN of V2 (L)	6.82 (15.1%)	19%	22.1	6.95 (4.2%)	19.7%	17.5
LN of Q3 (L/hr)	1.73 (64.3%)	59%	6.7	1.74 (21.3%)	63.5%	6.8
LN of V3 (L)	2143 (0.1%)	-	-	2220 (37.9%)	-	-
Residual Variability	10.8%CV (3.0%)	-	-	0.104 (6.3%)	-	-
CrCL on Clearance	0.86 (5.8%)	-	-	0.87 (6.4%)	-	-
HV on Clearance	1.36 (7.4%)	-	-	-	-	-

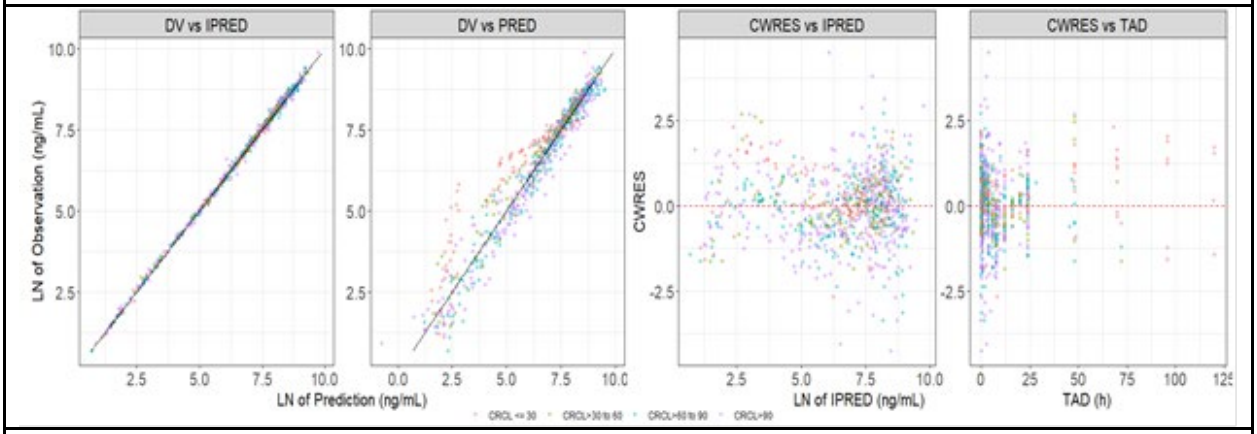
IIV-interindividual variability, ETA- interindividual variability η, LN- natural log, CL-clearance, L-liter, hr-hour, V1-central distribution volume, V2-first peripheral distribution volume, V3-second peripheral distribution volume, Q2-distribution clearance between V2 and V1, Q3-distribution clearance between V1 and V3, CrCL-creatinine clearance, HV-health volunteer. SD-standard deviation, RSE-relative standard error.

Note: RSE% of FDA estimates were based on 500 runs of bootstrap.

Source: FDA PPK Analysis and Table 14 of Applicant's PPK Report.

The goodness of fit (GOF) plots of FDA PPK analysis are provided in Figure 16.

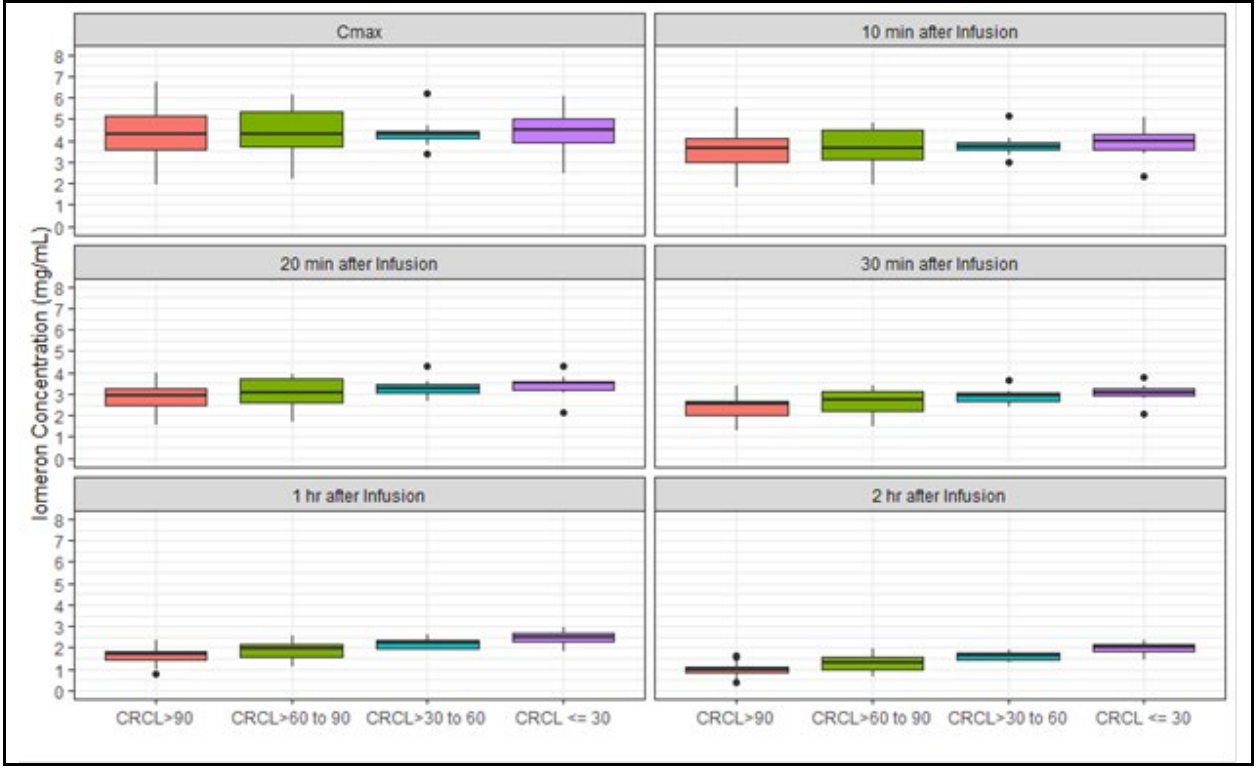
Figure 16. GOF of FDA PPK Analysis Excluding Data from Study 87020



Note: Different colors represent different creatinine clearance (CrCL) categories.
Source: FDA Reviewer's PPK Analysis.

Figure 17 shows simulated iomeprol concentrations by CRCL category for 609 mg/kg based on NONMEM dataset excluding data from Study 87020. The plot suggests more consistent iomeprol concentration among subjects between 20 and 30 min after the infusion, and CRCL effect appears not significant during this period.

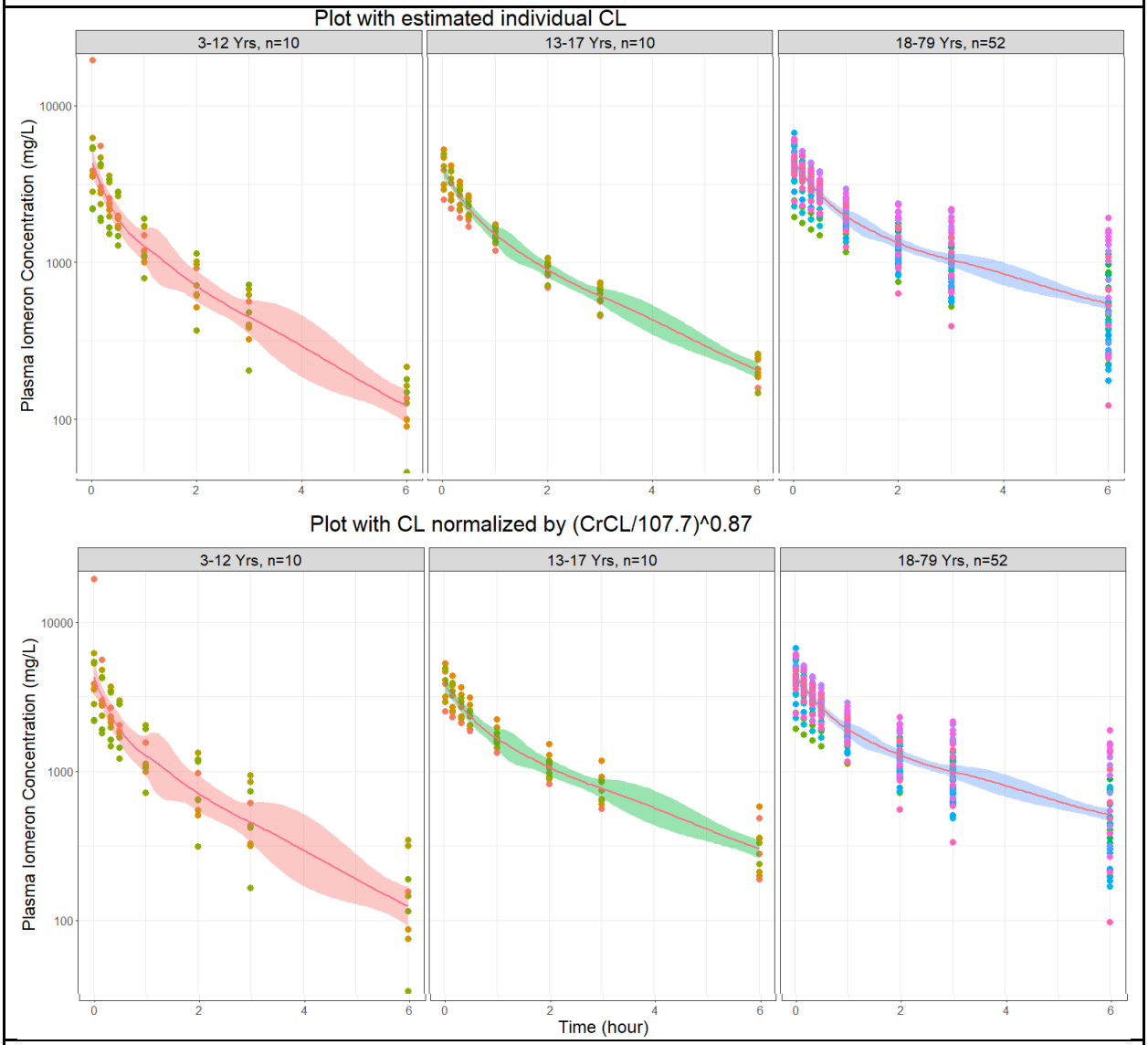
Figure 17. Simulated Iomeprol Concentration for 609 mg/kg Based on NONMEM Dataset Excluding Data from Study 87020



CrCL: creatinine clearance in mL/minute.
Source: FDA Reviewer's PPK Analysis.

Figure 18 shows simulated iomeprol concentrations by age subgroup for 609 mg/kg based on NONMEM dataset excluding data from Study 87020. The upper panel is simulated for individual patients with true CL values estimated from the PPK analysis where the CRCL is relatively higher in younger patients, and the first plot of the upper panel shows the most rapid elimination in patients 3-12 years old. The lower panel is simulated for individual patients with each CL value normalized to CRCL=107.7 mL/min/m^2 where the plots suggest more consistent iomeprol concentration among the three age groups, and younger patients again show the most rapid elimination of the drug.

Figure 18. Simulated Iomeprol Pharmacokinetics Profile for 609 mg/kg Based on Population Pharmacokinetics Dataset Excluding Data from Study 87020



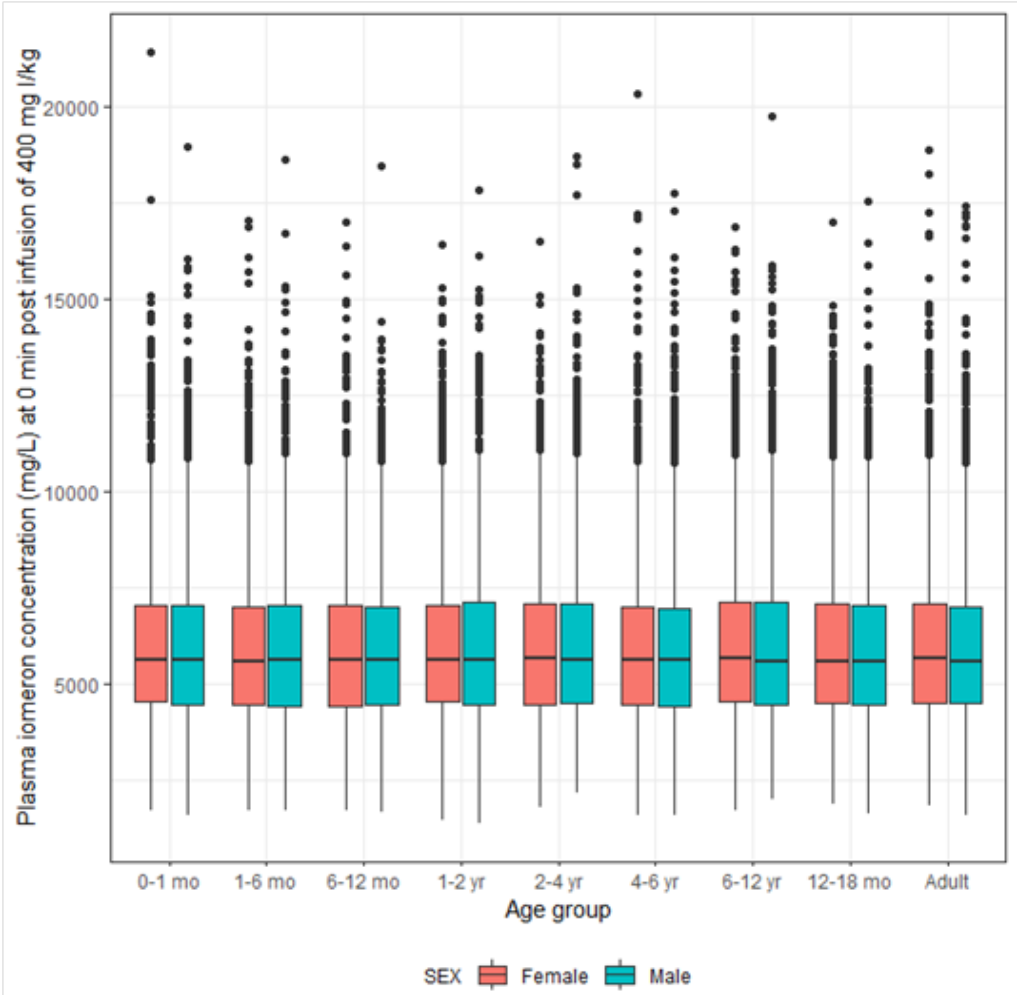
CL-clearance, CrCL-creatinine clearance, mg-milligram, L-liter, Yrs-years.
Source: FDA Reviewer's PPK Analysis

The elimination half-lives for different durations by age group are listed in Table 83 based on true CL values estimated from the PPK analysis. The table also shows that iomeprol is short-lived in younger patients.

Table 83. Derived Half Life Values for Different Time Period After Dose for Patients of Different Age Groups				
Age Group (n)	**Half Life Mean ± SD (hr) for Different Duration**			
	1min ~ 0.5 hr	**0.5 ~ 1hr**	**1 ~ 3hr**	**3 ~ 6hr**
3-12 Years (10)	**0.51 ± 0.17**	**0.84 ± 0.21**	**1.35 ± 0.17**	**1.60 ± 0.15**
13-17 Years (10)	**0.65 ± 0.13**	**0.92 ± 0.18**	**1.55 ± 0.15**	**1.91 ± 0.10**
18-79 Years (52)	**0.80 ± 0.27**	**1.16 ± 0.40**	**2.55 ± 1.28**	**4.39 ± 3.48**
Source: FDA reviewer's analysis.				

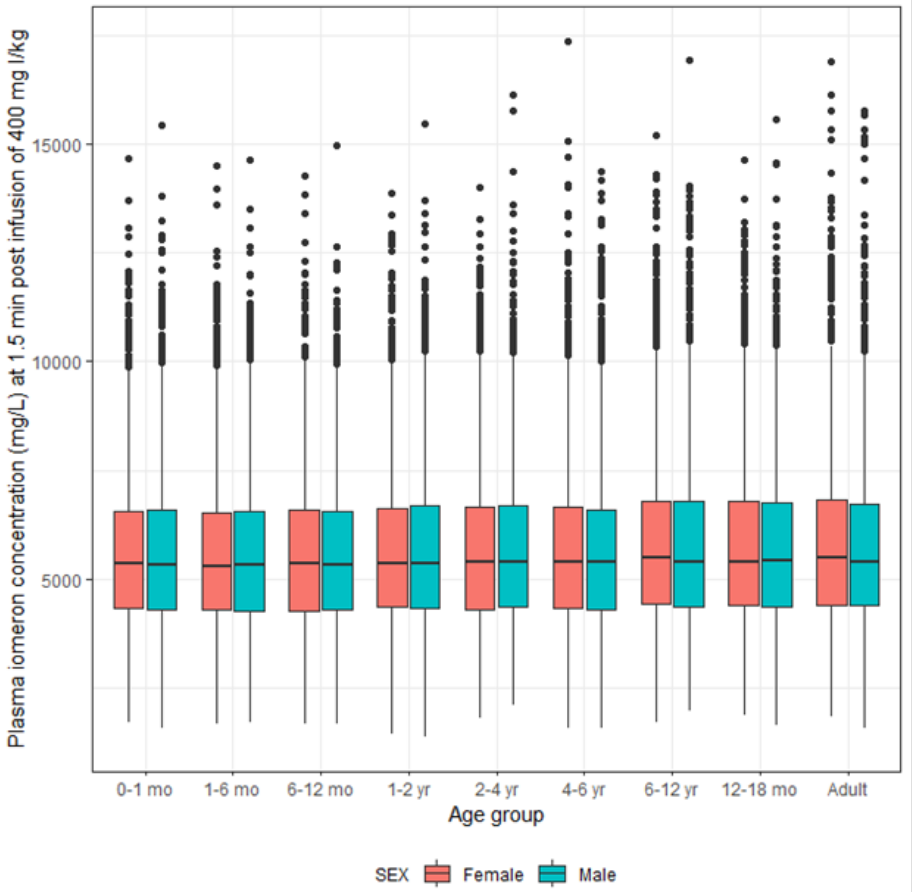
Based on the simulated plots in Figure 18 and the half-life values listed in Table 83, the exposure of iomeprol is similar in pediatric patients and adult patients at image time of 0-5 minutes after injection for the same per kg dose, as shown in Figure 19, Figure 20, Figure 21, Figure 22, Figure 23, and Figure 24 generated by FDA reviewer's simulations based on Tables 22-23 of the Applicant's original PPK report and FDA reviewer's PPK model.

Figure 19. Simulated Iomeprol Concentration at 0 Minute After IV Infusion of 400 mg I/kg to Patients of Different Age Groups



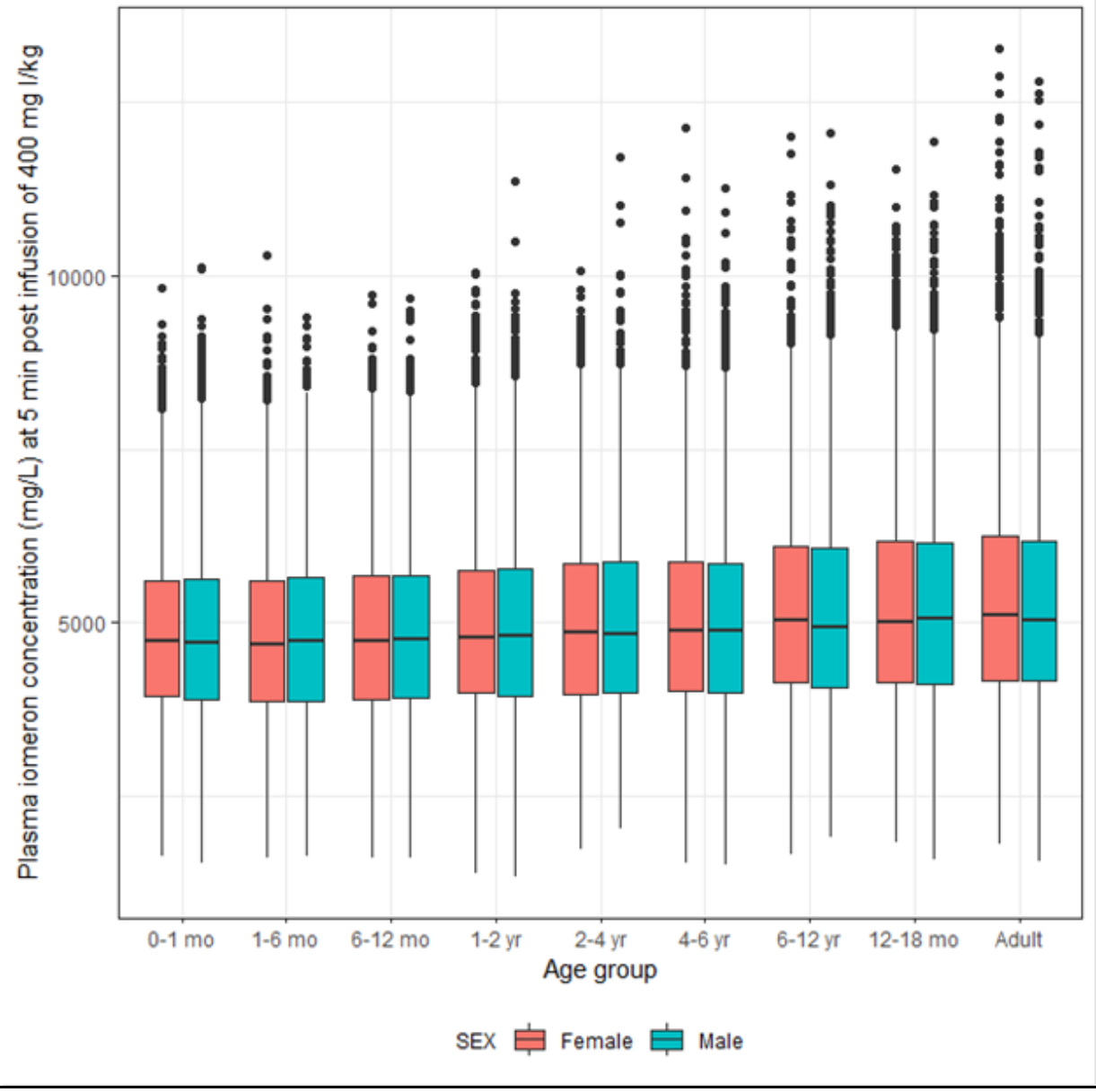
Source: FDA Reviewer's PPK Analysis.

Figure 20. Simulated Iomeprol Concentration at 1.5 Minutes After IV Infusion of 400 mg I/kg to Patients of Different Age Groups



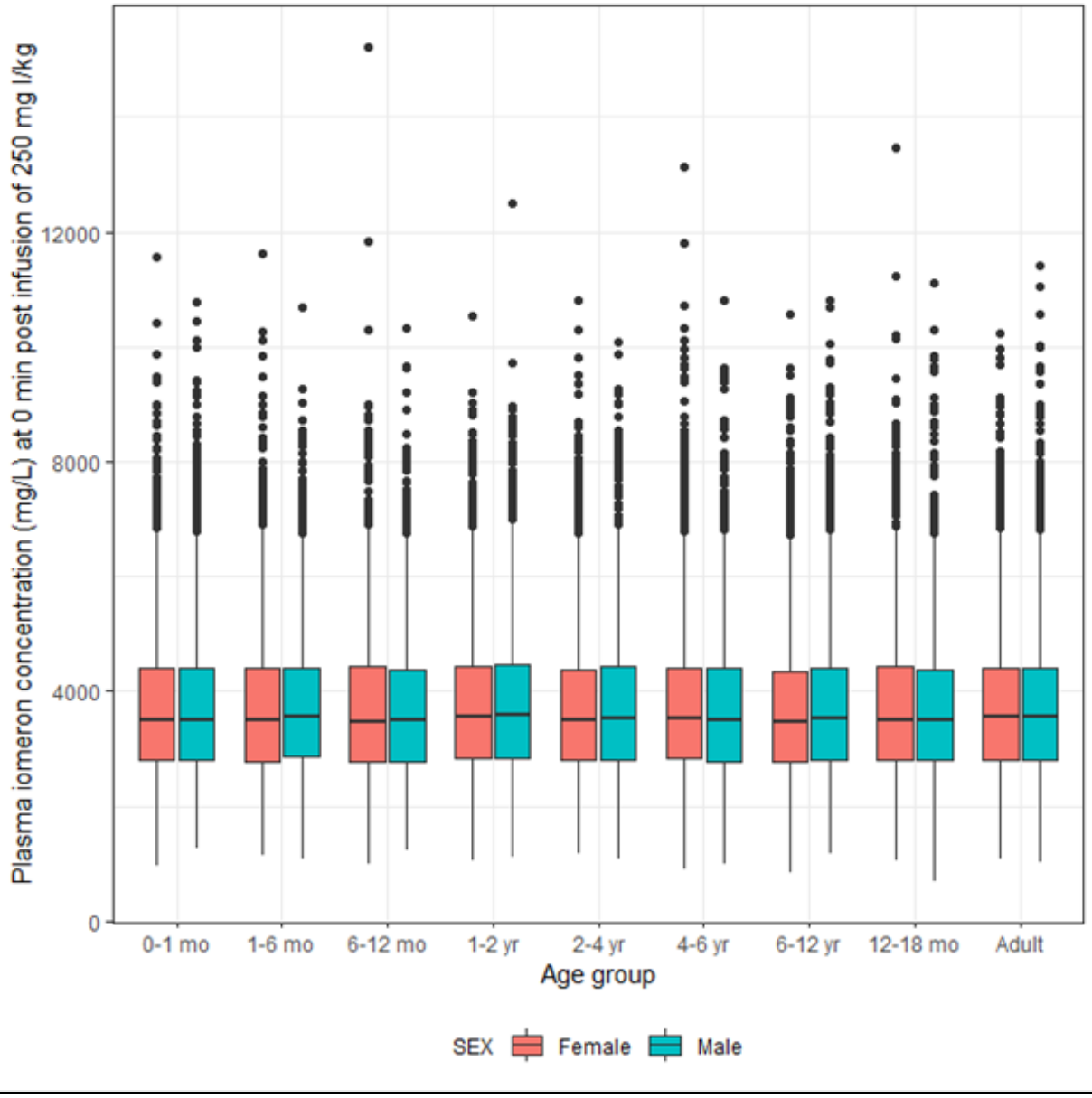
Source: FDA Reviewer's PPK Analysis.

Figure 21. Simulated Iomeprol Concentration at 5 Minutes After IV Infusion of 400 mg I/kg to Patients of Different Age Groups



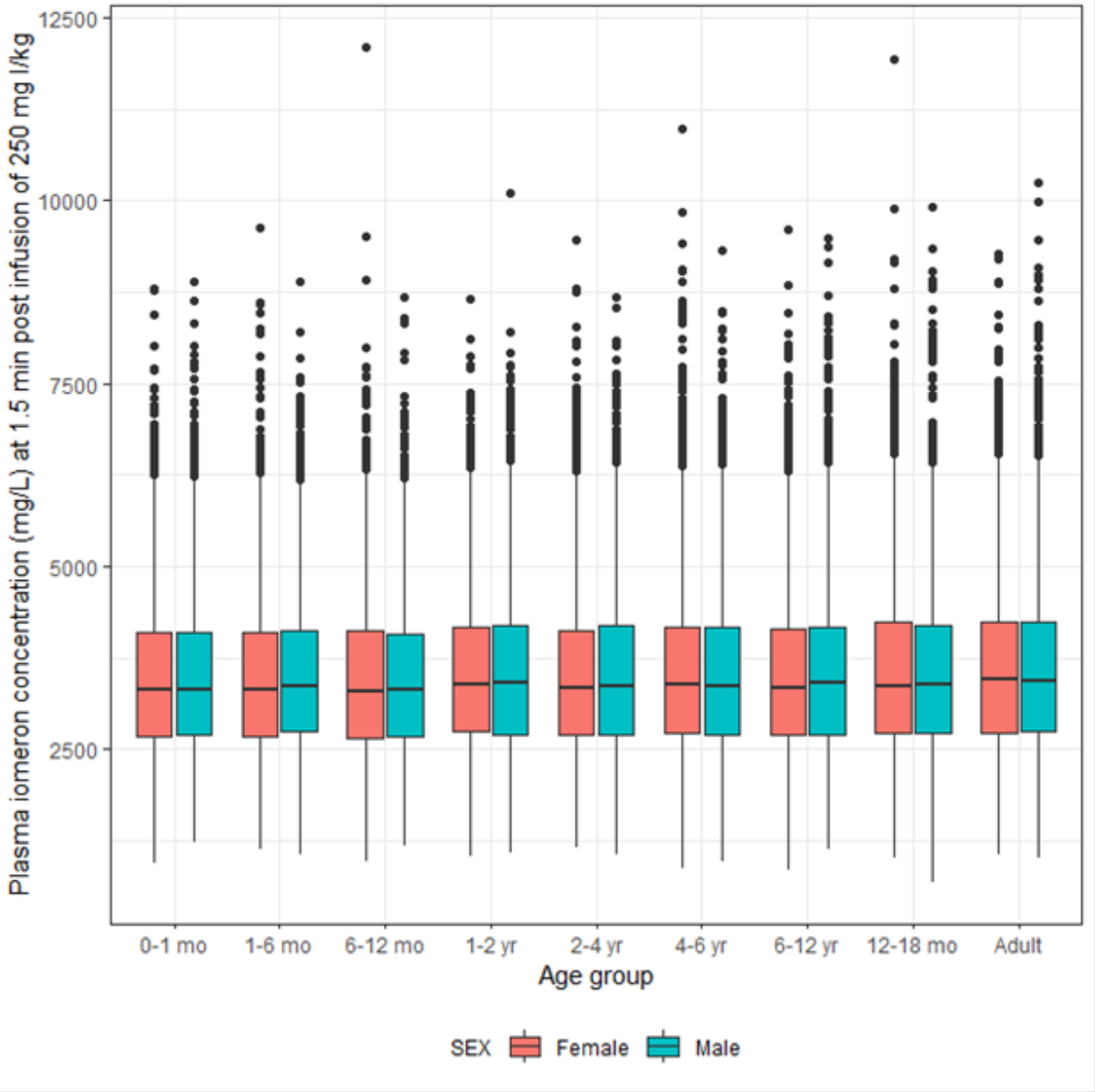
Source: FDA Reviewer's PPK Analysis.

Figure 22. Simulated Iomeprol Concentration at 0 Minute After IV Infusion of 250 mg I/kg to Patients of Different Age Groups



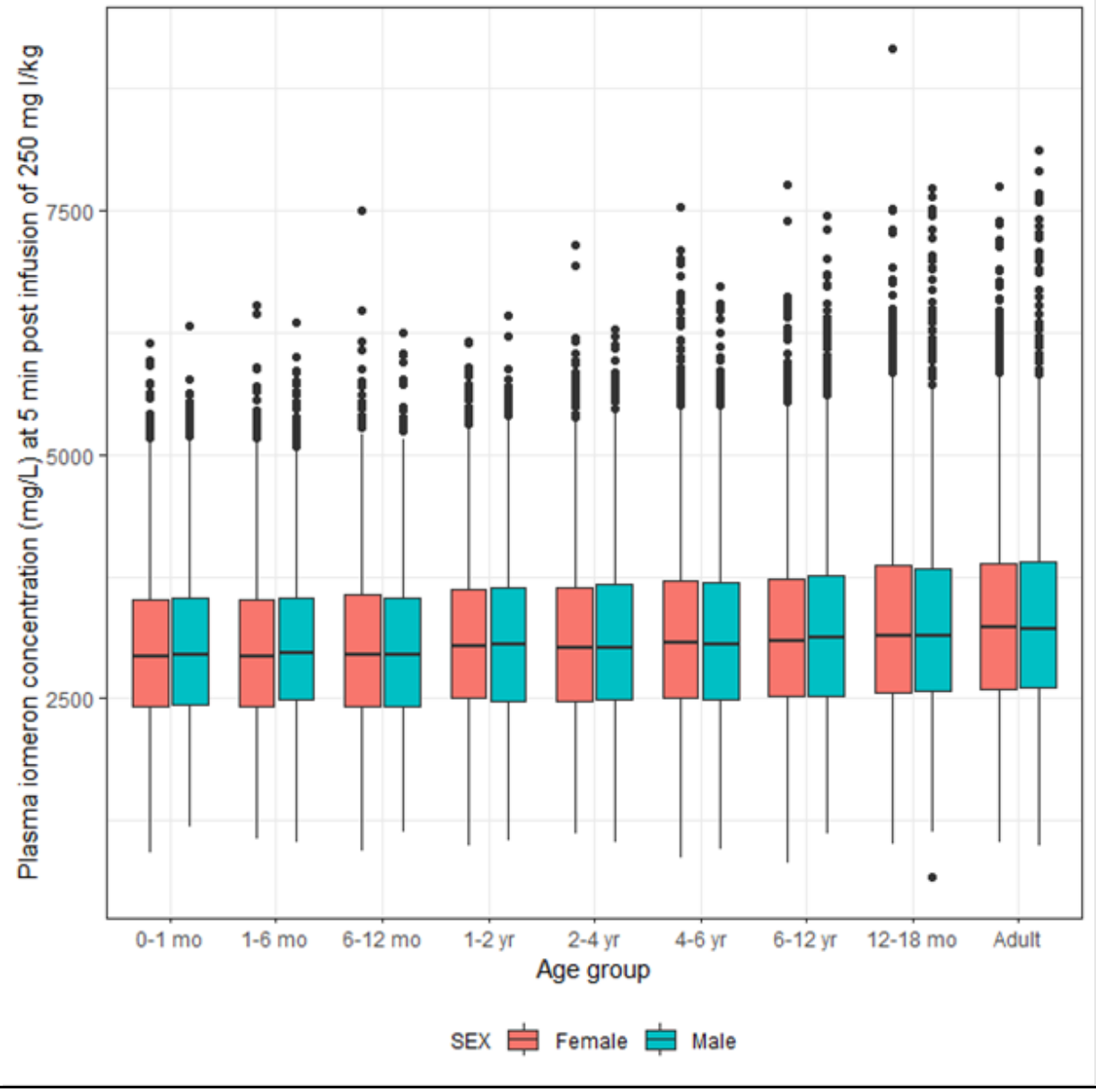
Source: FDA Reviewer's PPK Analysis.

Figure 23. Simulated Iomeprol Concentration at 1.5 Minutes After IV Infusion of 250 mg I/kg to Patients of Different Age Groups



Source: FDA Reviewer's PPK Analysis.

Figure 24. Simulated Iomeprol Concentration at 5 Minutes After IV Infusion of 250 mg I/kg to Patients of Different Age Groups



Source: FDA Reviewer's PPK Analysis.

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