CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

020351/S-044
020808/S-025

Trade Name:	Visipaque Injection Visipaque Pharmacy Bulk Package, 320 mgI/mL
Generic or Proper Name:	Iodixanol
Sponsor:	GE HealthCare Inc.
Approval Date:	April 5, 2017
Indication:	Prior Approval Supplement proposes the addition of a new indication for the coronary computed tomography angiography (CCTA) to assist diagnostic evaluation of patients with suspected coronary artery disease.

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20351/S-0044
NDA 20808/S-0025

SUPPLEMENT APPROVAL

GE HealthCare Inc.
Attention: Nic Scalfarotto, D.V.M.
Head Regulatory Affairs, US/Canada
100 Results Way
Marlborough, MA 01752

Dear Dr. Scalfarotto:

Please refer to your Supplemental New Drug Application (sNDA) dated October 5, 2016, received October 5, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Visipaque™ (Iodixanol) Injection and Visipaque™ Pharmacy Bulk Package, 320 mgI/mL.

This Prior Approval supplemental new drug application proposes the addition of a new indication for coronary computed tomography angiography (CCTA) to assist diagnostic evaluation of patients with suspected coronary artery disease.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at

http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 11years because studies are impossible or highly impractical due to the very low prevalence of coronary artery stenosis in pediatric patients in this age group. Visipaque is adequately labeled for use in CCTA in pediatric patients 12 to 18 years of age.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Frank Lutterodt, Regulatory Project Manager, at (301) 796-4251.

Sincerely,

{See appended electronic signature page}

Libero Marzella, M.D., Ph.D.
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LIBERO L MARZELLA
04/05/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VISIPAQUE safely and effectively. See full prescribing information for VISIPAQUE.

VISIPAQUE (iodixanol) injection, for intra-arterial or intra-venous use
Initial U.S. Approval: 1996

WARNING: NOT FOR INTRATHECAL USE
See full prescribing information for complete boxed warning
Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema. (4, 5.1)

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2)	4/2017
Dose and Administration (2.3)	4/2017
Warnings and Precautions (**5.10**)	4/2017

----------INDICATIONS AND USAGE----------
VISIPAQUE injection is a radiographic contrast agent indicated for the following:

Intra-arterial Procedures (1.1)
Adults and pediatric patients 12 years of age and over
- Intra-arterial digital subtraction angiography (270 and 320 mg Iodine/mL).
- Angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography (320 mg Iodine/mL).

Pediatric patients less than 12 years of age
- Angiocardiography, cerebral arteriography, and visceral arteriography (320 mg Iodine/mL).

Intravenous Procedures (1.2)
Adults and pediatric patients 12 years of age and over
- Computed tomography (CT) imaging head and body and excretory urography (270 and 320 mg Iodine/mL).
- CT imaging peripheral venography (270 mg Iodine/mL).
- Coronary computed tomography angiography (CCTA) to assist diagnostic evaluation of patients with suspected coronary artery disease (320 mg Iodine/mL).

Pediatric patients less than 12 years of age
- CT imaging of the head and body and excretory urography (270 mg Iodine/mL).

----------DOSAGE AND ADMINISTRATION----------
- Individualize the combination of volume and concentration of VISIPAQUE Injection considering age, body weight, size of the vessel, rate of blood flow within the vessel, and other applicable factors. (2.1, 2.2, 2.3, 2.4)
- For the adult patients, the maximum recommended total dose of iodine is 80 grams. (2.1)
- Patients should be adequately hydrated prior to and following the intravascular administration of iodinated contrast agents. (2.1, 5.3)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: In concentrations of 270 and 320 mg of organically bound iodine per mL (550 mg and 642 ml of Iodixanol per mL). (3)

----------CONTRAINDICATIONS----------
- Not indicated for intrathecal use. (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypersensitivity Reactions: life-threatening or fatal reactions can occur. Always have emergency equipment and trained personnel available. (5.2)
- Contrast Induced Acute Kidney Injury: Acute injury including renal failure can occur. Minimize dose and maintain adequate hydration to minimize risk. (5.3)
- Cardiovascular reactions: hemodynamic disturbances including shock and cardiac arrest may occur during or after administration. (5.4)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence greater than 0.5%) in adult patients after VISIPAQUE injection: Discomfort, warmth, pain; Cardiovascular: angina. Gastrointestinal: diarrhea, nausea, vomiting. Nervous System: agitation, anxiety, insomnia, nervousness, dizziness, headache, migraine, unusual skin sensations, sensory disturbance, fainting, sensation of spinning. Skin: itchy rash, severe itching, hives. Special Senses: Smell, taste, and vision alteration. (6.1) Pediatric patients experienced similar adverse reactions. (6.3)

To report SUSPECTED ADVERSE REACTIONS, contact GE Healthcare at 1-800-654-0118 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: A lactating woman may pump and discard breast milk for 10 hours after VISIPAQUE administration. (8.2)
- Geriatrics: Exercise caution in dose selection for elderly patients (8.5).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 4/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

FULL PRESCRIBING INFORMATION

WARNING: NOT FOR INTRATHECAL USE

Inadvertent intrathecal administration may cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema. (4, 5.1)

1 INDICATIONS AND USAGE

VISIPAQUE is indicated in for:

1.1 Intra-arterial Procedures

Adult and pediatric patients 12 years of age and older

- (270 and 320 mg Iodine/mL) intra-arterial digital subtraction angiography (IA-DSA).
- (320 mg Iodine/mL) angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography.

Pediatric patients less than 12 years of age

- (320 mg Iodine/mL) angiocardiography, cerebral arteriography, and visceral arteriography.

1.2 Intravenous Procedures

Adult and pediatric patients 12 years of age and older

- (270 mg Iodine/mL) CT imaging of the head and body, excretory urography, and peripheral venography.
- (320 mg Iodine/mL) CT imaging of the head and body, excretory urography, and coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease.

Pediatric patients less than 12 years of age

- (270 mg Iodine/mL) CT imaging of the head and body and excretory urography.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

- VISIPAQUE is for intravascular use only [see Boxed Warning, Contraindications (4), Warnings and Precautions (5.1)]
- Use sterile technique for all handling and administration of VISIPAQUE.
- Do not use if tamper-evident ring is broken or missing.
- Warm VISIPAQUE and administer at body or room temperature.
- Inspect VISIPAQUE for particulate matter or discoloration before administration, whenever solution and container permit. Do not administer if VISIPAQUE contains particulate matter or is discolored.
- Do not mix VISIPAQUE with, or inject in intravenous lines containing, other drugs or total nutritional admixtures.
- Use the lowest dose necessary to obtain adequate visualization.
- Individualize the volume, strength, and rate of administration of VISIPAQUE. Consider factors such as age, body weight, vessel size, blood flow rate within the vessel, anticipated pathology, degree and extent of opacification required, structures or area to be examined, disease processes affecting the patient, and equipment and technique to be employed.

- The maximum recommended total dose of iodine for adults is 80 grams.
- Avoid extravasation when injecting VISIPAQUE; especially in patients with severe arterial or venous disease [see Warnings and Precautions (5.6)].
- Hydrate patients before and after VISIPAQUE administration [see Warnings and Precautions (5.3)].

2.2 Intra-Arterial Dosage and Administration

- **Intra-arterial digital subtraction angiography** (IA-DSA) (270 and 320 mg Iodine/mL)
- **Angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography** (320 mg Iodine/mL)

Use Injection rates approximately equal to the flow rate in the vessel being injected. The usual single injection volumes or total dose per patient (mL/kg) for adults and adolescents over 12 years of age are listed in Table 1:

TABLE 1

ADULTS and PEDIATRIC PATIENTS 12 YEARS OF AGE AND OLDER VISIPAQUE SINGLE DOSE RECOMMENDATIONS FOR INJECTION INTO SELECTED ARTERIES				
	ARTERIOGRAPHY	IA-DSA*		
Intra-Arterial Injection Sites	320 mg Iodine/mL	270 mg Iodine/mL	320 mg Iodine/mL	Maximum Total Dose
Carotid Arteries Vertebral Arteries	10 - 14 mL 10 - 12 mL		5 - 8 mL 5 - 8 mL	Usually Not to Exceed 175 mL
Right Coronary Artery Left Coronary Artery Left Ventricle	3 - 8 mL 3 - 10 mL 20 - 45 mL			Usually Not to Exceed 200 mL
Renal Arteries Aortography Major Branches of Aorta Aortofemoral Runoffs Peripheral Arteries	8 - 18 mL 30 - 70 mL 10 - 70 mL 20 - 90 mL 15 - 30 mL	10 - 25 mL 20 - 50 mL 5 - 30 mL -- --	-- 10 - 50 mL 2 - 10 mL 6 - 15 mL 3 - 15 mL	Usually Not to Exceed 250 mL

*IA-DSA = Intra-Arterial Digital Subtraction Angiography

2.3 Intravenous Dosage and Administration

- **Computed Tomography of the Head or Body** (270 mg Iodine/mL and 320 mg Iodine/mL)
- **Excretory Urography** (270 mg Iodine/mL and 320 mg Iodine/mL)
- **Peripheral Venography** (270 mg Iodine/mL)
- **Coronary Computed Tomography Angiography (CCTA)** (320 mg Iodine/mL)

Recommended dosage of VISIPAQUE is dependent on: the administration procedure, patient weight, and CT device factors, as detailed in Table 2.Calibrate the intravenous injection rate so that image acquisition coincides with peak arterial concentration. The time between VISIPAQUE injection and peak arterial concentration varies between patients. Selected dosing for different indications in adults and pediatric patients over 12 years of age are shown in Table 2.

TABLE 2

ADULTS and PEDIATRIC PATIENTS 12 YEARS OF AGE AND OLDER VISIPAQUE DOSING RECOMMENDATIONS FOR INTRAVENOUS CONTRAST ADMINISTRATION				
Study Type	Comment	270 mg	320 mg	Maximum Total Volume

		Iodine/mL	Iodine/mL	
CT of Head or Body	Bolus Infusion	75 - 150 mL 100 - 150 mL	75 - 150 mL 100 - 150 mL	150 mL
Excretory Urography	Normal Renal Function	1 mL/kg	1 mL/kg	100 mL
Venography	Per lower extremity	50 - 150 mL		250 mL
CCTA[1]	Bolus injection with test bolus[2] or bolus tracking		50 - 150 mL[3] (4 - 7 mL per second)	150 mL

[1]For pediatric patients aged 12-17, recommended dose is 1-2 mL/kg.
[2]The main VISIPAQUE volume may be preceded by a test bolus consisting of 20 mL VISIPAQUE, immediately followed by a 20 mL saline flush, both injected at rate of 4-7 mL/sec.
[3]Injection of VISIPAQUE with saline can be either biphasic (without dilution phase) or triphasic (with dilution phase). Alternatively, a dose of 1 mL/kg may be used to calculate total VISIPAQUE dose (excluding any test bolus). For CCTA acquired at < 120 kVp, the dose of VISIPAQUE may be reduced by up to 15% in patients < 85 kg and BMI < 30 kg/m^2. For CCTA acquired on a scanner with more than 64 detector rows, the dose of VISIPAQUE may be reduced in proportion to the scan duration.

2.4 Dosage in Pediatric Patients Less Than 12 Years of Age

Intra-arterial Dosage and Administration

Angiocardiography, cerebral arteriography, and visceral arteriography (320 mg Iodine/mL)**:**

The recommended dosage is 1 to 2 mL/kg. The maximum dose should not exceed 4 mL/kg.

Intravenous Dosage and Administration

Computerized Tomography and Excretory Urography (270 mg Iodine/mL)**:**

The recommended dosage is 1 to 2 mL/kg. The maximum dose should not exceed 2 mL/kg.

3 DOSAGE FORMS AND STRENGTHS

Injection: Non-ionic, isotonic, water-soluble, sterile, pyrogen-free, colorless to pale yellow solution in the following strengths:

- 270 mg of organically bound iodine per mL (550 mg Iodixanol per mL).
- 320 mg of organically bound iodine per mL (642 ml of Iodixanol per mL).

Available in the following formats: Single-dose vial, single-dose glass bottle, Single dose polymer bottle (*PLUS*PAK)

4 CONTRAINDICATIONS

VISIPAQUE is contraindicated for Intrathecal use [see Warnings and Precautions (5.1)]:

5 WARNINGS AND PRECAUTIONS

5.1 Risks Associated with Inadvertent Intrathecal Administration

VISIPAQUE is for intravascular use only and is contraindicated for intrathecal use [see Contraindications (4) *and* Dosage and Administration (2.1)]. Inadvertent Intrathecal administration can cause death, convulsions/seizures, cerebral hemorrhage, coma, paralysis, arachnoiditis, acute renal failure, cardiac arrest, rhabdomyolysis, hyperthermia, and brain edema.

5.2 Hypersensitivity Reactions

VISIPAQUE can cause life-threatening or fatal hypersensitivity reactions including anaphylaxis. Manifestations include respiratory arrest, laryngospasm, bronchospasm, angioedema, and shock. Most severe reactions develop shortly after the start of the injection (within 3 minutes), but reactions can occur up to hours later. There is an increased risk in patients with a history of a previous reaction to contrast agent, and known allergies (i.e., bronchial asthma, drug, or food allergies) or other hypersensitivities. Premedication with antihistamines or corticosteroids does not prevent serious life-threatening

reactions, but may reduce both their incidence and severity.

Obtain a history of allergy, hypersensitivity, or hypersensitivity reactions to iodinated contrast agents and always have emergency resuscitation equipment and trained personnel available prior to VISIPAQUE administration. Monitor all patients for hypersensitivity reactions.

5.3 Contrast Induced Acute Kidney Injury

Acute kidney injury, including renal failure, may occur after VISIPAQUE administration. Risk factors include: pre-existing renal impairment, dehydration, diabetes mellitus, congestive heart failure, advanced vascular disease, elderly age, concomitant use of nephrotoxic or diuretic medications, multiple myeloma / paraproteinaceous diseases, repetitive and/or large doses of an iodinated contrast agent.

Use the lowest necessary dose of VISIPAQUE in patients with renal impairment. Adequately hydrate patients prior to and following VISIPAQUE administration. Do not use laxatives, diuretics, or preparatory dehydration prior to VISIPAQUE administration.

5.4 Cardiovascular Adverse Reactions

Life-threatening or fatal cardiovascular reactions including hypotension, shock, cardiac arrest have occurred with the use of VISIPAQUE. Most deaths occur during injection or five to ten minutes later, with cardiovascular disease as the main aggravating factor. Cardiac decompensation, serious arrhythmias, and myocardial ischemia or infarction can occur during coronary arteriography and ventriculography.

Based upon clinical literature reported deaths from the administration of iodinated contrast agents range from 6.6 per million (0.00066%) to 1 in 10,000 (0.01%). Use the lowest necessary dose of VISIPAQUE in patients with congestive heart failure and always have emergency resuscitation equipment and trained personnel available. Monitor all patients for severe cardiovascular reactions

5.5 Thromboembolic Events

Angiocardiography

Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke can occur during angiocardiography procedures with both ionic and nonionic contrast media. During these procedures, increased thrombosis and activation of the complement system occurs. Risk factors for thromboembolic events include: length of procedure, catheter and syringe material, underlying disease state, and concomitant medications.

To minimize thromboembolic events, use meticulous angiographic techniques, and minimize the length of the procedure. Avoid blood remaining in contact with syringes containing iodinated contrast agents, which increases the risk of clotting. Avoid angiocardiography in patients with homocystinuria because of the risk of inducing thrombosis and embolism.

5.6 Extravasation and Injection Site Reactions

Extravasation of VISIPAQUE Injection may cause tissue necrosis and/or compartment syndrome, particularly in patients with severe arterial or venous disease. Ensure intravascular placement of catheters prior to injection. Monitor patients for extravasation and advise patients to seek medical care for progression of symptoms.

5.7 Thyroid Storm in Patients with Hyperthyroidism

Thyroid storm has occurred after the intravascular use of iodinated contrast agents in patients with hyperthyroidism, or with an autonomously functioning thyroid nodule. Evaluate the risk in such patients before use of VISIPAQUE.

5.8 Hypertensive Crisis in Patients with Pheochromocytoma

Hypertensive crisis has occurred after the use of iodinated contrast agents in patient with pheochromocytoma. Monitor patients when administering VISIPAQUE if pheochromocytoma or catecholamine-secreting paragangliomas are suspected. Inject the minimum amount of contrast necessary, assess the blood pressure throughout the procedure, and have measures for treatment of a hypertensive crisis readily available.

5.9 Sickle Cell Crisis in Patients with Sickle Cell Disease.

Iodinated contrast agents when administered intravascularly may promote sickling in individuals who are homozygous for sickle cell disease. Hydrate patients prior to and following VISIPAQUE administration and use VISIPAQUE only if the necessary imaging information cannot be obtained with alternative imaging modalities.

5.10 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCAR) may develop from 1 hour to several weeks after intravascular contrast agent administration. These reactions include Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS). Reaction severity may increase and time to onset may decrease with repeat administration of contrast agents; prophylactic medications may not prevent or mitigate severe cutaneous adverse reactions. Avoid administering VISIPAQUE to patients with a history of a severe cutaneous adverse reaction to VISIPAQUE.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Risks Associated with Inadvertent Intrathecal Administration [see Warnings and Precautions (5.1)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.2)]
- Contrast Induced Kidney Injury [see Warnings and Precautions (5.3)]
- Cardiovascular Adverse Reactions [see Warnings and Precautions (5.4)]
- Thromboembolic Events [see Warnings and Precautions (5.5)]
- Severe Cutaneous Reactions [see Warnings and Precautions (5.10)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

VISIPAQUE is often associated with sensations of discomfort, warmth or pain. In a subgroup of 1259 patients; 30% who received VISIPAQUE or a comparator had application site discomfort, pain, warmth or cold. VISIPAQUE had a trend toward fewer patient reports of moderate or severe pain or warmth. Pain was reported in 2% of patients receiving VISIPAQUE and 10% of patients receiving a comparator. Heat was reported in 29% of patients receiving VISIPAQUE and 51% of patients receiving a comparator.

Table 3 shows the incidence of events reported in blinded, controlled clinical studies of VISIPAQUE in a total of 1244 adult patients. Adverse events (AEs) are listed by body system and in decreasing order of occurrence greater than 0.5% of patients. One or more adverse events were reported in 20% of patients during the study period (24 to 72 hours). In a 757 patient subgroup, the number of women reporting adverse events was 83/299 (28%) and the number of men was 77/458 (16%). A total of 3% of women and 0.8% of men reported chest pain.

TABLE 3

ADVERSE EVENTS REPORTED IN CONTROLLED CLINICAL TRIALS IN GREATER THAN 0.5% OF 1244 ADULT PATIENTS RECEIVING VISIPAQUE OR OTHER IODINATED CONTRAST AGENTS			
NUMBER OF PATIENTS EXPOSED		VISIPAQUE **N (%) = 1244**	**Pooled Comparators N (%) = 861**
Number of Patients with Any Adverse Event		248 (19.9)	194 (22.5)
Body As a Whole	Patients with Any Event	41 (3.3)	22 (2.6)
	Edema (any location)	7 (0.6)	0 (0)
Cardiovascular	Patients with Any Event	37 (3.0)	39 (4.5)
	Angina Pectoris/Chest Pain	28 (2.2)	22 (2.6)
Gastrointestinal	Patients with Any Event	51 (4.1)	46 (5.3)
	Diarrhea	7 (0.6)	6 (0.7)

	Nausea	35 (2.8)	32 (3.7)
	Vomiting	10 (0.8)	11 (1.3)
Nervous System	Patients with Any Event	101 (8.1)	60 (7.0)
	Agitation, Anxiety, Insomnia, Nervousness	10 (0.8)	0 (0)
	Dizziness	8 (0.7)	8 (0.9)
	Headache/Migraine	31 (2.5)	15 (1.7)
	Paresthesia	12 (1.0)	1 (0.1)
	Sensory Disturbance	10 (0.8)	9 (1.0)
	Syncope	8 (0.6)	1 (0.1)
	Vertigo	30 (2.4)	20 (2.3)
Skin (not including application site)	Patients with Any Event	42 (4.6	18 (2.1)
	Nonurticarial Rash or Erythema	26 (2.1)	4 (0.5)
	Pruritus	20 (1.6)	3 (0.3)
	Urticaria	6 (0.5)	10 (1.2)
Special Senses	Patients with Any Event	57 (4.6	38 (4.4)
	Parosmia	6 (0.5)	4 (0.5)
	Taste Perversion	43 (3.5)	32 (3.7)
	Scotoma	14 (1.1)	2 (0.2)

The following selected adverse events were reported in ≤0.5% of the 1244 patients.

Body as a Whole—General Disorders: back pain, fatigue, malaise.

Cardiovascular Disorders: arrhythmias, cardiac failure, conduction abnormalities, hypotension, myocardial infarction.

Gastrointestinal System Disorders: dyspepsia.

Hypersensitivity Disorders: pharyngeal edema.

Nervous System: cerebral vascular disorder, convulsions, hypoesthesia, stupor, confusion.

Peripheral Vascular Disorders: flushing, peripheral ischemia.

Renal System Disorders: abnormal renal function, acute renal failure, hematuria.

Respiratory System Disorders: asthma, bronchitis, dyspnea, pulmonary edema, rhinitis.

Skin and Appendage Disorders: hematoma, increased sweating.

Special Senses, Other Disorders: tinnitus.

Vision Disorders: abnormal vision.

6.2 Post-marketing Experience

The following additional adverse reactions have been identified during post approval use of VISIPAQUE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to exposure.

Cardiovascular Disorders: Cardiac arrest, palpitations, spasms of coronary arteries, hypertension, and flushing.

Endocrine Disorders: Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been uncommonly reported following iodinated contrast media administration to adult and pediatric patients, including infants. Some patients were treated for hypothyroidism. Hypoglycemia, hyperthyroidism.

Eye Disorders: Transient visual impairment including cortical blindness, diplopia, and blurred vision.

Gastrointestinal Disorders: Abdominal pain, pancreatitis, salivary gland enlargement.

General Disorders and Administration Site Conditions: Chills, pyrexia, pain and discomfort, administration site reactions including extravasation.

Immune System Disorders: Hypersensitivity reactions, anaphylactic shock including, life-threatening or fatal anaphylaxis.

Nervous System Disorders: Tremor (transient), coma, disturbance in consciousness, transient contrast-induced encephalopathy caused by extravasation of contrast media (including amnesia, hallucination, paralysis, paresis, transient speech disorder, aphasia, dysarthria).

Psychiatric Disorders: Anxiety, agitation.

Respiratory, Thoracic, and Mediastinal Disorders: Cough, sneezing, throat irritation or tightness, laryngeal edema, pharyngeal edema, bronchospasm.

Skin and subcutaneous tissue disorders: Reactions range from mild (e.g. rash, erythema, pruritus, urticaria, and skin discoloration)to severe: [e.g. Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS)].

6.3 Pediatric Adverse Reactions

The overall character, quality, and severity of adverse reactions in pediatric patients is similar to that reported in adult patients from post marketing surveillance and other information.

Additional safety data was obtained in studies of VISIPAQUE in 459 pediatric patients. A total of 26 patients ranged in age from birth to <29 days, 148 ranged from 29 days to 2 years, 263 from 2 to <12 years, and 22 from 12 to 18 years. A total of 252 (55%) of the patients were male. The racial distribution was: Caucasian-81%, Black-14%, Oriental-2%, and other or unknown-4%. The proportion of patients undergoing an intra-arterial procedure by age was: 92 % (<29 days), 55% (29 days – 6 months), and 29 % (>6 months). In these studies, adverse events were numerically higher in pediatric patients less than one year of age compared to older pediatric patients.

In pediatric patients who received intravenous injections of VISIPAQUE for computerized tomography or excretory urography, a concentration of 270 mg Iodine/mL was used in 144 patients, and a concentration of 320 mg Iodine/mL in 154 patients. All patients received one intravenous injection of 1-2 mL/kg.

In pediatric patients who received intra-arterial and intracardiac studies, a concentration of 320 mg Iodine/mL was used in 161 patients. Twenty-two patients were < 29 days of age; 78 were 29 days to 2 years of age; and 61 were over 2 years. Most of these pediatric patients received initial volumes of 1-2 mL/kg and most patients received a maximum of 3 injections.

7 DRUG INTERACTIONS

7.1 Drug-Drug Interactions

- **Metformin**

In patients with renal impairment, metformin can cause lactic acidosis. Iodinated contrast agents appear to increase the risk of metformin induced lactic acidosis, possibly as a result of worsening renal function. Stop metformin at the time of, or prior to, VISIPAQUE 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. Re-evaluate eGFR 48 hours after the imaging procedure, and reinstitute metformin only after renal function is stable.

- **Radioactive Iodine**

Administration of iodinated contrast agents may interfere with thyroid uptake of radioactive iodine (I-131 and I-123) and decrease therapeutic and diagnostic efficacy in patients with carcinoma of the thyroid. The decrease in efficacy lasts for 6-8 weeks.

- **Beta-adrenergic Blocking Agents**

The use of beta-adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions, and reduces the responsiveness of treatment of hypersensitivity reactions with epinephrine. Because of the risk of hypersensitivity reactions, use caution when administering VISIPAQUE to patients taking beta-blockers.

- **Oral Cholecystographic Contrast Agents**

Renal toxicity has been reported in patients with liver dysfunction who were given an oral cholecystographic agent followed by intravascular iodinated contrast agents. Postpone the administration of VISIPAQUE in patients who have recently received an oral cholecystographic contrast agent.

7.2 Drug Laboratory Test Interactions

- **Effect on Thyroid tests**

The results of protein bound iodine and radioactive iodine uptake studies, which depend on iodine estimation, will not accurately reflect thyroid function for at least 16 days following administration of iodinated contrast agents. However, thyroid function tests which do not depend on iodine estimations (e.g., T3 resin uptake and total or free thyroxine T4 assays) are not affected.

- **Effect on Urine Tests**

As reported with other contrast agents, VISIPAQUE may produce a false-positive result for protein in the urine using urine dip tests However, the Coomassie blue method has been shown to give accurate results for the measurement of urine protein in the presence of VISIPAQUE. In addition, care should be used in interpreting the results of urine specific gravity measurements in the presence of high levels of VISIPAQUE and other contrast agents in the urine. Refractometry or urine osmolality may be substituted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with iodixanol use in pregnant women to inform any drug-associated risks. In animal reproduction studies, no developmental toxicity occurred with intravenous iodixanol administration to rats and rabbits at doses up to 0.24 (rat) or 0.48 (rabbit) times the maximum recommended human intravenous dose (*see Data*).

All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Reproduction studies were performed in rats and rabbits with intravenous administration of iodixanol at doses up to 2 g Iodine/kg, daily, from implantation of the embryo (gestation day 7 in rat; 6 in rabbit) through closure of the hard palate (gestation day 17 in rats; 18 in rabbits). No maternal toxicity occurred, and no adverse effects occurred on fetal survival, embryo-fetal development, or the ability of dams to rear a litter.

8.2 Lactation

Risk Summary

There are no data on the presence of iodixanol in human milk, the effects on the breastfed infant or the effects on milk production. Iodinated contrast agents are poorly excreted into human milk and are poorly absorbed by the gastrointestinal tract of a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VISIPAQUE and any potential adverse effects on the breastfed infant from VISIPAQUE or from the underlying maternal condition.

Clinical Considerations

Interruption of breastfeeding after exposure to iodinated contrast agents is not necessary because the potential exposure of the breastfed infant to iodine is small. However, a lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 10 hours (approximately 5 elimination half-lives) after VISIPAQUE administration in order to minimize drug exposure to a breast fed infant.

8.4 Pediatric Use

The safety and efficacy of VISIPAQUE have been established in pediatric patients down to birth for angiocardiography, cerebral arteriography, visceral arteriography, CT imaging of the head and body, and excretory urography. The safety and efficacy of VISIPAQUE have also been established in pediatric patients 12 years and older for intra-arterial digital subtraction angiography, peripheral arteriography, CT imaging peripheral venography and CCTA. Use of VISIPAQUE is supported by evidence from adequate and well controlled studies of VISIPAQUE in adults and additional safety data

obtained in 459 pediatric patients. In general, the types of adverse reactions reported are similar to those of adults. A higher number of adverse events in patients less than 1 year of age compared to older patients were observed in a study of VISIPAQUE *[see Adverse Events (6.3)]*. The elimination of VISIPAQUE is slower in this age group *[see Clinical Pharmacology (12.3)]*.

Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been uncommonly reported following iodinated contrast media administration to pediatric patients, including infants. Some patients were treated for hypothyroidism *[See Adverse Reactions (6.2)]*.

Pediatric patients at higher risk of experiencing an adverse reaction during and after administration of any contrast agent may include those with asthma, hypersensitivity to other medication and/or allergens, cyanotic and acyanotic heart disease, congestive heart failure, or a serum creatinine greater than 1.5 mg/dL. Pediatric patients with immature renal function or dehydration may be at increased risk for adverse events due to slower elimination of iodinated contrast agents *[see Clinical Pharmacology (12.3)].*

8.5 Geriatric Use

In clinical studies of VISIPAQUE, 254/757 (34%) of patients were 65 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. In general, dose selection for an elderly patient should be cautious usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

The adverse effects of overdosage of any contrast agent may be life-threatening and affect mainly the pulmonary and cardiovascular systems. Treatment of an overdosage is directed toward the support of all vital functions and prompt institution of symptomatic therapy. VISIPAQUE Injection does not bind to plasma or serum protein and can be dialyzed.

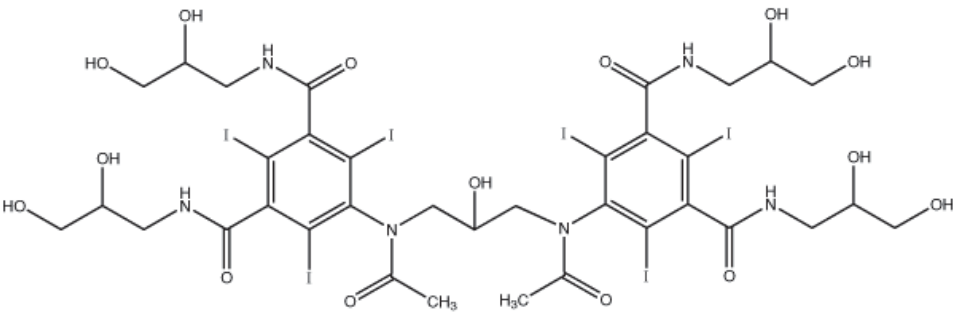
11 DESCRIPTION

11.1 Chemical Characteristics

VISIPAQUE (iodixanol) injection is a dimeric, iso-osmolar, nonionic, water-soluble, radiographic contrast medium for intravascular (intravenous and intra-arterial) use. It is provided as a ready-to-use sterile, pyrogen-free, and preservative free, colorless to pale yellow solution.

The chemical formula is 5,5´-[(2-hydroxy-1,3-propanediyl) bis(acetylimino)] bis[N,N´-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3- benzenedicarboxamide] with a molecular weight of 1550.20 (iodine content 49.1%)

VISIPAQUE ($C_{35}H_{44}I_6N_6O_{15}$) has the following structural formula:



VISIPAQUE is available in two strengths:

- VISIPAQUE 270 mg Iodine/mL (550 mg Iodixanol/mL), 0.074 mg calcium chloride dehydrate, 1.87 mg sodium chloride, 1.2 mg tromethamine, and 0.1 mg edetate calcium disodium.
- VISIPAQUE 320 mg Iodine/mL (652 mg iodixanol / mL), 0.044 mg calcium chloride dehydrate, 1.11 mg sodium chloride, 1.2 mg tromethamine and 0.1 mg edetate calcium disodium.

Sodium chloride and calcium chloride have been added, resulting in an isotonic solution for injection providing for both concentrations a sodium/calcium ratio equivalent to blood.

The pH is adjusted to 7.4 with hydrochloric acid and/or sodium hydroxide to achieve a range between pH 6.8 and 7.7 at 22°C.

11.2 Physical Characteristics

The two concentrations of VISIPAQUE Injection (270 mg Iodine/mL and 320 mg Iodine/mL) have the following physical properties:

TABLE 4

Physical Properties of VISIPAQUE			
Parameter		Concentration (mg Iodine/mL)	
		320	**270**
Osmolality (mOsmol/kg water)		290	290
Viscosity (cP)	@ 20°C	26.6	12.7
	@ 37°C	11.8	6.3
Density (g/mL)	@ 20°C	1.369	1.314
	@ 37°C	1.356	1.303

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Intravascular injection of iodixanol opacifies vessels in the path of flow of the contrast agent, permitting visualization of internal structures.

In imaging of the body, iodinated contrast agents diffuse from the vascular into the extravascular space. In a normal brain with an intact blood-brain barrier, contrast does not diffuse into the extravascular space. In patients with a disrupted blood-brain barrier, contrast agent accumulates in the interstitial space in the region of disruption.

12.2 Pharmacodynamics

Following administration of VISIPAQUE, the degree of enhancement is directly related to the iodine content in an administered dose. Peak iodine plasma levels occur immediately following rapid injection. The time to maximum contrast enhancement can vary, depending on the organ, from the time that peak blood iodine concentrations are reached to one hour after intravenous bolus administration. When a delay between peak blood iodine concentrations and peak contrast is present, it suggests that radiographic contrast enhancement is at least in part dependent on the accumulation of iodine-containing medium within the lesion and outside the blood pool.

For angiography, contrast enhancement is greatest immediately (15 seconds to 120 seconds) after rapid injection. Iodinated contrast agents may be visualized in the renal parenchyma within 30-60 seconds following rapid intravenous injection. Opacification of the calyces and pelves in patients with normal renal function becomes apparent within 1-3 minutes, with optimum contrast occurring within 5-15 minutes.

12.3 Pharmacokinetics

Distribution

In an *in vitro* human plasma study, iodixanol did not bind to protein. The volume of distribution in adults was 0.26 L/kg body weight, consistent with distribution to extracellular space.

Elimination

In 40 healthy, young male volunteers receiving a single intravenous administration of VISIPAQUE in doses of 0.3 to 1.2 gram Iodine/kg body weight, the elimination half-life was 2.1 hr. (± 0.1). Renal clearance was 110 ± 14 mL/min, equivalent to glomerular filtration (108 mL/min). These values were independent of the dose administered.

Metabolism

Iodixanol does not undergo metabolism.

Excretion

In adults, approximately 97% of the injected dose of iodixanol is excreted unchanged in urine within 24 hours, with less than 2% excreted in feces within five days post-injection.

Specific Populations

Pediatric: Forty pediatric patients ≤12 years old, with renal function that is normal for their age, received multiple intra-arterial administrations of VISIPAQUE in doses of 0.32 to 3.2 gram Iodine/kg body weight. The elimination half-lives for these patients are shown in Table 5.

Dose adjustments to account for differences in elimination half-life in pediatric patients less than 6 months of age have not been studied.

TABLE 5

MEAN ELIMINATION HALF-LIFE* IN PEDIATRIC PATIENTS		
Age Range	Number of Patients	Elimination half-life
		(hr. ± SD)
Newborn - < 2 months	8	4.1 ± 1.4
2 - 6 months	8	2.8 ± 0.6
6 - 12 months	9	2.4 ± 0.4
1 - 2 years	5	2.3 ± 0.6
2 - 12 years	10	2.3 ± 0.5
Adults	40	2.1 ± 0.1

Renal Impairment: In patients with significantly impaired renal function, the total clearance of iodixanol is reduced and the half-life is increased. In a study of 16 adult patients who were scheduled for renal transplant, the mean creatinine clearance was 13.6 ± 4.7 mL/min). In these patients, plasma half-life was 23 hours ($t_{1/2}$ for typical patients = 2.1 hours).

renal impairment have not been studied. In patients with normal blood brain barriers and severe renal impairment, iodinated contrast agents have been associated with blood-brain barrier disruption and accumulation of contrast in the brain.

VISIPAQUE has been shown to be dialyzable. In an *in vitro* hemodialysis study, after 4 hours of dialysis with a cellulose membrane, approximately 36% of iodixanol was removed from the plasma. After 4 hours of dialysis with polysulfone membranes, approximately 49% of iodixanol was removed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed with iodixanol to evaluate carcinogenic potential. Iodixanol was not genotoxic in a series of studies including the Ames test, the CHO/HGPRT assay, a chromosome aberration assay in CHO cells, and a mouse micronucleus assay.

Iodixanol did not impair the fertility of male or female rats when administered at doses up to 0.24 times the maximum recommended human dose.

14 CLINICAL STUDIES

VISIPAQUE was studied in 1244 adult patients. Approximately one-half (590) of the VISIPAQUE patients were 60 years of age or older; the mean age was 56 years (range 18-90). A total of patients, 806 (65%) were male. The racial distribution was: Caucasian-85%, Black-12%, Oriental <1%, and other or unknown-3%.

A total of 1235 patients were evaluable for efficacy. Efficacy assessment was based on quality of the radiographic

diagnostic visualization (i.e., either: excellent, good, poor, or none) and on the ability to make a diagnosis (i.e., either: confirmed a previous diagnosis, found normal, or diagnosed new findings).

14.1 Intra-arterial Administration Studies

Angiocardiography, cerebral arteriography, peripheral arteriography, and visceral arteriography were studied with either one or both concentrations of VISIPAQUE Injection (270 mg Iodine/mL or 320 mg Iodine/mL). In these intra-arterial studies, diagnostic visualization ratings were good or excellent in all the patients and a radiologic diagnosis was made in all of the patients. In additional intra-arterial studies, overall quality of diagnostic visualization was rated optimal in the majority of patients and a radiologic diagnosis was made in all (100%) of the patients. The number of patients studied in each indication is provided below.

Angiocardiography was evaluated in two randomized, double-blind clinical studies in 101 adult patients given VISIPAQUE 320 mg Iodine/mL. Seven additional angiocardiography studies were performed in 217 adult patients given VISIPAQUE 320 mg Iodine/mL. Visualization ratings were good or excellent in all the patients given VISIPAQUE; a radiologic diagnosis was made in the majority of the patients. Confirmation of the radiologic findings by other diagnostic methods was not obtained.

Cerebral arteriography was evaluated in two randomized, double-blind clinical trials in 51 adult patients given VISIPAQUE 320 mg Iodine/mL. Two additional cerebral arteriography studies were performed in 15 adult patients given VISIPAQUE Injection 270 mg Iodine/mL, 40 patients given VISIPAQUE 320 mg Iodine/mL. Visualization ratings were good or excellent in all the patients a radiologic diagnosis was made in the majority of the patients. Confirmation of the radiologic findings by other diagnostic methods was not obtained.

Peripheral arteriography was evaluated in two randomized, double-blind clinical trials in 49 adult patients given VISIPAQUE 320 mg Iodine/mL. Four additional peripheral arteriography studies were performed in 41 adult patients given VISIPAQUE 270 mg Iodine/mL, 85 patients given VISIPAQUE 320 mg Iodine/mL Visualization ratings were good or excellent in 100% of the patients given VISIPAQUE; a radiologic diagnosis was made in the majority of the patients. Confirmation of the radiologic findings by other diagnostic methods was not obtained.

Visceral arteriography was evaluated in two randomized, double-blind clinical trials in 55 adult patients given VISIPAQUE 320 mg Iodine/mL. Visualization ratings were good or excellent in all of the patients; a radiologic diagnosis was made in the majority of the patients. Confirmation of the radiologic findings by other diagnostic methods was not obtained.

Similar studies with digital subtraction angiography (DSA) were completed with comparable findings noted in cerebral arteriography, peripheral arteriography, and visceral arteriography. Studies have not been conducted to determine the lowest effective concentration of VISIPAQUE.

14.2 Intravenous Administration Studies

Excretory urography, computed tomography (CT) of the head, CT of the body, peripheral venography, and coronary computed tomography angiography (CCTA) were studied with either one or both VISIPAQUE Injection concentrations (270 mg Iodine/mL or 320 mg Iodine/mL). In the non-CCTA intravenous studies, diagnostic visualization ratings were good or excellent in 96-100% of the patients and a radiologic diagnosis was made in all of the patients given VISIPAQUE. In the CCTA studies results were computed in terms of sensitivity and specificity compared to a standard of reference. The number of patients studied in each indication is provided below.

Excretory urography was evaluated in one uncontrolled, unblinded clinical trial in 40 patients, 20 given VISIPAQUE 270 mg Iodine/mL and 20 given VISIPAQUE 320 mg Iodine/mL, and in two randomized, double-blind clinical trials in 50 adult patients given VISIPAQUE 270 mg Iodine/mL, 50 patients given VISIPAQUE 320 mg Iodine/mL. Visualization ratings were good or excellent in all of the patients given VISIPAQUE; a radiologic diagnosis was made in the majority of the patients. Confirmation of the radiologic findings by other diagnostic methods was not obtained.

CT of the head was evaluated in two randomized, double-blind clinical trials in 49 adult patients given VISIPAQUE 270 mg Iodine/mL, in 50 patients given VISIPAQUE 320 mg Iodine/mL. CT of the body was evaluated in three randomized, double-blind clinical trials in 104 adult patients given VISIPAQUE 270 mg Iodine/mL, and 109 patients given VISIPAQUE 320 mg Iodine/mL. In both CT of the head and body, visualization ratings were good or excellent in all of the patients given VISIPAQUE; a radiologic diagnosis was made in the majority of the patients. Confirmation of the radiologic findings by other diagnostic methods was not obtained.

Peripheral venography was evaluated in two randomized, double-blind clinical studies in 46 adult patients given VISIPAQUE 270 mg Iodine/mL. Visualization ratings were good or excellent in all of the patients given VISIPAQUE; a radiologic diagnosis was made in the majority of the patients. The results were similar to those of the active control. Confirmation of the radiologic findings by other diagnostic methods was not obtained.

VISIPAQUE 320 mg Iodine/mL for CCTA was evaluated in two prospective, multicenter clinical studies in a total of 1106 adult patients. The patient population consisted of stable outpatients with chest pain or other symptoms suggestive of coronary artery disease, and no known history of coronary disease. All the CCTAs were done using 64 detector row CT scanners. Most of the patients received beta-blocker medication for heart rate control and nitroglycerin for vasodilation. Patients with irregular cardiac rhythm or heart rate above 100 beats per minute were excluded. The mean patient age was 57 years in the first study and 59 years in the second study. Both studies had more men than women (59% male in the first study and 51% male in the second study), and more Caucasian patients (88% in the first study and 78% in the second study) than Black, Asian, or other patients. The BMI range was 17-50 with a mean of 31 in the first study and a BMI range of 15-71 with a mean of 30 in the second study.

In the first study, 230 patients (906 vessels) were evaluable for efficacy using the reference standard of invasive coronary angiography. Seventy-five vessels (8%, in 49 patients) were evaluated as positive for ≥ 50% stenosis. The CCTA images were randomized and read by three blinded, independent readers; the coronary angiography images were interpreted by an independent, blinded reader. Assuming independence between vessels, the vessel-level sensitivity (95% CI) for assessing ≥ 50% stenosis was 76% (63, 86) for reader 1, 89% (79, 95) for reader 2 and 77% (65, 86) for reader 3. The vessel-level specificity (95% CI) was 85% (81, 89) for reader 1, 84% (81, 87) for reader 2, and 89% (86, 91) for reader 3. The vessel-level sensitivity and specificity for assessing ≥ 70% stenosis were similar.

In a second study, 857 patients were evaluable for efficacy. Patients were followed up for 12 months after CCTA and the reference standard was a composite of pre-specified clinical outcomes (death, major adverse cardiac event, or coronary revascularization). Seventy-six patients (9%) experienced one or more of the pre-specified outcomes over 12 months of follow-up. The sensitivity (95% CI) and specificity (95% CI) of a positive CCTA finding (≥ 50% stenosis at the patient level) to predict one or more of the pre-specified clinical outcomes was 95% (87, 99) and 87% (84, 89), respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How supplied

VISIPAQUE injection is a ready-to-use sterile, pyrogen-free, preservative free, colorless to pale yellow solution available in two (2) strengths. It is supplied in the following configurations:

VISIPAQUE (iodixanol) Injection 270 mg Iodine/mL:

50 mL single-dose vial, boxes of 10	(NDC 0407-2222-01)
50 mL single-dose glass bottle, boxes of 10	(NDC 0407-2222-06)
50 mL in single-dose +*PLUS*PAK™ (polymer bottle), boxes of 10	(NDC 0407-2222-16)
100 mL single-dose glass bottle, boxes of 10	(NDC 0407-2222-02)
100 mL in single-dose +*PLUS*PAK™ (polymer bottle), boxes of 10	(NDC 0407-2222-17)
150 mL single-dose glass bottle, boxes of 10	(NDC 0407-2222-03)
150 mL in single-dose +*PLUS*PAK™ (polymer bottle), boxes of 10	(NDC 0407-2222-19)
200 mL in single-dose +*PLUS*PAK™ (polymer bottle), boxes of 10	(NDC 0407-2222-21)

VISIPAQUE (iodixanol) Injection 320 mg Iodine/mL:

50 mL single-dose vial, boxes of 10	(NDC 0407-2223-01)
50 mL single-dose glass bottle, boxes of 10	(NDC 0407-2223-06)
50 mL in single-dose +*PLUS*PAK™ (polymer bottle), boxes of 10	(NDC 0407-2223-16)
100 mL single-dose glass bottle, boxes of 10	(NDC 0407-2223-02)
100 mL in single-dose +*PLUS*PAK™ (polymer bottle), boxes of 10	(NDC 0407-2223-17)
150 mL single-dose glass bottle, boxes of 10	(NDC 0407-2223-03)
150 mL in single-dose +*PLUS*PAK™ (polymer bottle), boxes of 10	(NDC 0407-2223-19)
200 mL single-dose glass bottle, boxes of 10	(NDC 0407-2223-04)

200 mL in single-dose +*PLUS*PAK™ (polymer bottle), boxes of 10 (NDC 0407-2223-21)

16.2 Storage

Protect VISIPAQUE from direct exposure to sunlight.

Store VISIPAQUE at controlled room temperature, 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature].

VISIPAQUE may be stored in a contrast media warmer for up to one month at 37°C (98.6°F).

Do not freeze. Discard any product that is inadvertently frozen, as freezing may compromise the closure integrity of the immediate container.

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions
Advise the patient concerning the risk of hypersensitivity reactions that can occur both during and after VISIPAQUE administration. Advise the patient to report any signs or symptoms of hypersensitivity reactions during the procedure and to seek immediate medical attention for any signs or symptoms experienced after discharge *[see Warnings and Precautions (5.2)].*
Advise patients to inform their physician if they develop a rash after receiving VISIPAQUE *[see Warnings and Precautions (5.10)].*

Contrast Induced Acute Kidney Injury
Advise the patient concerning appropriate hydration to decrease the risk of contrast induced acute kidney injury *[see Warnings and Precautions (5.3)].*

Extravasation
If extravasation occurs during injection, advise patients to seek medical care for progression of symptoms *[see Warnings and Precautions (5.6)].*

Distributed by GE Healthcare Inc., Marlborough, MA 01752 U.S.A.

Manufactured by GE Healthcare Ireland, Cork, Ireland

Product of Norwegian origin.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020351/S-044
020808/S-025

SUMMARY REVIEW

Summary Review for Regulatory Action

Responsible Organization	Division of Medical Imaging Products (DMIP)
Date	04/3/2017
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA	20351 and 20808
Supplement	44
Applicant Name	GE Healthcare
Date of Submission	10/06/2016
PDUFA Goal Date	04/05/2017
Proprietary Name **Established (USAN) Name**	Visipaque iodixanol
Dosage Form **Strength**	injection 320 mg iodine/ml
Indication	Adults and pediatric patients 12 and over: coronary computed tomography angiography (CCTA) to assist diagnostic evaluation of patients with suspected coronary artery disease (320 mg Iodine/mL)
Regulatory Action	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of Discipline Reviewers**
OND/DMIP Clinical	Karen Bleich MD
OND/DMIP CTDL	Anthony Fotenos MD
OCP Clinical Pharmacology	Christy John PhD
OBP/DBI Statistical	Satish Misra PhD
OND/DMIP Labeling	Michele Fedowitz MD
PMHS Pediatrics	Erica Radden MD
OPDP Labeling	Zarna Patel PharmD
OLDP/DPMI CMC	David Place PhD

CTDL – Cross Discipline Team Leader
DBI – Division of Biostatistics I
DPMI – Division of Postmarketing Activities I
OBP – Office of Biostatistics
OCP – Office of Clinical Pharmacology
OLDP – Office of Lifecycle Drug Products
OND – Office of New Drugs
OPDP – Office of Prescription Drug Promotion
PMHS – Pediatric and Maternal Health Staff

Introduction

On October 6, 2016 GE Healthcare (Applicant) submitted a 505(b)(1) efficacy supplement to their New Drug Application (NDA 20351) for Visipaque (iodixanol) injection and Visipaque Pharmacy Bulk Pack (NDA 20808).

This application provides the following new indication for the Visipaque 320 mg iodine/ml formulation: "for use in adults and pediatric patients 12 and over, for coronary computed tomography angiography (CCTA) to assist diagnostic evaluation of patients with suspected coronary artery disease." This application also provides for revised prescribing information that conforms to the physician labeling rule (PLR), adds a class warning for iodinated contrast about the risk of severe cutaneous reactions, and updates the dosage and safety information for Visipaque use in pediatric patients.

Iodixanol is a dimeric, isoosmolar, nonionic, water-soluble, iodinated X-ray contrast agent for intravascular administration. Iodixanol opacifies vessels in the path of flow of the contrast agent, permitting radiographic visualization of the internal structures until significant dilution and elimination occurs.

This review summarizes my assessment of the approvability of this application based on the submission and on the assessments by the FDA reviewers listed above.

Regulatory History

Visipaque (iodixanol) injection (NDA 20351) is classified pharmacologically as a radiographic contrast agent. Visipaque was approved in the US on March 22, 1996 and is indicated for administration by the intra-arterial and intravenous route for use in a variety of radiologic procedures in adult and pediatric patients. The pharmacy bulk package (NDA 20808) was approved on August 29, 1997.

I reference the regulatory history of the present efficacy supplement in the investigational new drug application (IND 34585) and the summaries by the clinical reviewer Dr. Bleich and by the cross discipline team leader Dr. Fotenos. The Agency agreed on the plan for the present submission following the change in the proposed indication for CCTA in alignment with the current clinical use of the procedure.

CCTA was earlier envisaged as an alternative to invasive coronary angiography (ICA) for the diagnosis of coronary artery disease (CAD). Consequently, the demonstration of the performance of CCTA against ICA within a justifiable non-inferiority margin was considered necessary. The present proposed indication for CCTA is to assist in the evaluation of patients with suspected CAD. This indication is consistent with the current use of CCTA as an alternative to functional stress testing and as a gatekeeper to the cardiac catheterization laboratory.

In patients with low to intermediate likelihood of CAD, noninvasive evaluation of coronary anatomy and myocardial function/perfusion are performed before ICA. This practice of non-invasive testing before ICA also reflects the more selective use of coronary intervention based on the findings of clinical outcomes studies. For the proposed indication, it was not required that Visipaque CCTA achieve a specific performance threshold relative to the reference standard of ICA or relative to another diagnostic test.

The review was designated as priority under the Prescription Drug User Act (PDUFA).A priority designation was given because Visipaque CCTA represents a meaningful improvement as a non-invasive procedure for the visualization of coronary anatomy in patients with a serious condition (suspected coronary artery disease). No radiographic contrast agent is approved for this use. FDA takes action on a priority application within 6 months of filing.

Coronary Artery Disease

I reference the FDA clinical review by Dr. Bleich for a summary of the impact of CAD on the public health, and a discussion of the available options for anatomic and functional imaging of the coronary arteries.

Coronary artery disease is the principal cause of morbidity and mortality in men and women in the US and accounts for major health expenditures. Seven iodinated contrast agents, formulated in various iodine concentrations, are approved in the US for use for intraarterial and intravenous procedures including CT. None of the contrast agents is labeled for use for CCTA. CCTA is widely used in clinical practice.

1. Chemistry Manufacturing and Controls

No new data on pharmaceutical and microbiological product quality are provided in this submission and none are needed. No changes to the CMC labeling are needed. I concur with the CMC review chemist, Dr. Place, that the environmental toxicity assessment for iodixanol is sufficient.

2. Nonclinical Pharmacology and Toxicology

No new preclinical data are provided in the submission and none are needed.

3. Clinical Pharmacology and Biopharmaceutics

I concur with the recommendation by the FDA clinical pharmacology reviewer, Dr. John, that this supplemental NDA be approved.

No dose finding data was acquired in the efficacy studies. The recommended dosing is based on clinical studies conducted by applicant, on the scientific literature and on practice guidelines. Dr. John evaluated the evidence for weight-based and fixed-volume dosing and found both to be suitable for achieving suitable peak opacification levels and contrast-to-noise ratios for visualization of the coronary artery lumen. Both dosing methods are therefore recommended options in the labeling. No pharmacokinetic or drug interaction data are provided in the submission and none were deemed to be necessary.

Dr. Bleich's review describes the site-specific factors to be considered to achieve optimal visualization of the coronaries at the time of CT scanning. These factors include scanner technology, tube voltage, reconstruction algorithms, scan time delay, ECG gating, patient heart rate and blood volume, contrast infusion rate and dilution phase.

The dosage and administration section of the labeling considers the factors that influence dosing, including patient's body weight (surrogate for blood volume), and CT scanner factors including kVp and number of detector rows. The recommended total volume of Visipaque ranges from 50 to 150 ml at infusion rates of 4 to 7 ml per second. Alternatively, a dose of 1 mL/kg may be used to calculate total Visipaque dose (not to exceed 150 ml). The injection of Visipaque with saline can be either biphasic (without a dilution phase) or triphasic (with a dilution phase). The main Visipaque injection may be preceded by a test bolus of 20 mL to calculate the scan time delay. For pediatric patients aged 12-17, the recommended dose of Visipaque is 1-2 mL/kg.

4. Clinical Microbiology

This section is not applicable to this NDA.

5. Clinical/Statistical Efficacy

I concur with the recommendation by the FDA clinical reviewers (Drs. Bleich and Fotenos) and by the statistical reviewer (Dr. Misra) that the efficacy supplement be approved. The Agency relied on two studies GE-189-002, and GE-012-096 for the finding of efficacy of Visipaque CCTA. Dr. Misra verified the primary efficacy analyses.

The first study, GE-189-002, was designed to evaluate the diagnostic performance of CCTA with Visipaque Injection (320 mgI/mL) for detecting the presence or absence of significant (≥ 50% stenosis threshold) coronary artery obstruction in patients suspected of having CAD. The standard of reference ICA images were interpreted by a single independent blinded reader. Each CCTA examination was independently read by three readers who evaluated each coronary segment individually.

The CCTA results were analyzed at the vessel level by-reader, instead of by a majority read. The Imputation for unevaluable segments was incorrect (either false positive or false negative). Vessels < 2 mm were excluded from analysis. **Table 1** shows the sensitivity and specificity of Visipaque CCTA for detection of CAD relative to ICA. The performance of Visipaque is judged to be satisfactory.

Table 1. Visipaque CCTA vessel-level sensitivity and specificity for detection of > 50% stenosis

	Sensitivity n=75	Specificity n=831
Reader 1	76% (63, 86)	85% (81, 89)
Reader 2	89% (79, 95)	84% (81, 87)
Reader 3	77% (65, 86)	89% (86, 91)

The numbers in parentheses are 95% confidence intervals

The second study, GE-012-096, was a multi-center registry designed to prospectively assess the value of Visipaque CCTA findings in predicting the occurrence of downstream adverse cardiac events in stable patients with chest pain who were referred for CCTA for their medical care. The prognostic value was assessed in terms of the sensitivity, specificity of CCTA as compared to subsequent ICA findings or clinical outcomes during each follow-up period. The study design does not allow an assessment of the added value of CCTA to other clinical prognostic measures.

The standard of reference was either the subject's ICA findings (if performed) or binary subject outcomes during the follow-up period. A clinical outcome consisted of the presence of one or more of the following events: MACE: cardiac death, non-fatal myocardial infarction, or unstable angina requiring hospitalization; all-cause mortality; coronary revascularization.

The performance of Visipaque CCTA for the prediction of cardiac events at 12 months of follow up was 95% sensitivity and 87% specificity (see **Table 2**).

Table 2. Performance of Visipaque CCTA for prediction of cardiac events

Follow-up period	Sensitivity	Specificity
1 month	96% (87,100) 49/51	85% (82, 87) 681/806
6 month	96% (88, 99) 68/71	87% (84, 89) 677/782
12 month	95% (87, 99) 72/76	87% (84, 89) 667/767

The numbers in parentheses are 95% confidence intervals

The event rates for patients with a baseline positive CCTA compared to those with a negative CCTA were as follows at 12 months of follow-up: MACE 5.7% vs 0.1%; revascularization 40% vs 0.6%; any cardiac event 41% vs 0.6%. It is notable that the rate of coronary revascularization drives the study's composite endpoint; it is unclear to what extent revascularization can be considered an independent downstream adverse event.

The Applicant provided the published results from three additional CCTA studies performed using Visipaque 320 mgI/mL. No primary data was provided or needed. I agree with the assessment of the clinical reviewers that the additional information supports the generalizability of Visipaque CCTA.

6. Safety

I concur with the assessment of the FDA clinical reviewers that no new serious and unexpected adverse reactions or other new risks have been identified for the use of Visipaque in the patient population (N =1106) studied. The majority of study subjects (70%) received beta-adrenergic blocking agents for the CCTA. The risks posed by the hypersensitivity reactions to iodinated contrast are greater in patients receiving beta blockers. The labeling adds information about the risk of this interaction between the two drugs.

The literature and pharmacovigilance data indicate a higher frequency of adverse event reports for cardiac than non-cardiac examinations. The procedural risk associated with invasive intra-arterial coronary angiography and the concomitant morbidities in the patients undergoing these procedures account for these observations. Dr. Bleich notes that the technological improvements in CT hardware and software have resulted in

effective radiation doses that are generally similar or lower than doses associated with non-interventional ICA or radionuclide myocardial perfusion imaging.

Consistent with the requirement for class-wide labeling, a warning was added about the risk of severe cutaneous adverse reactions identified in the postmarketing experience for iodinated contrast agents. These reactions are delayed in onset and are caused by hypersensitivity.

7. Advisory Committee Meeting

No advisory committee meeting was needed for this submission.

8. Pediatrics

The application requires a pediatric assessment under the Pediatric Research Equity Act (PREA). The Applicant requested a full waiver of the requirement to conduct pediatric studies of CCTA because atherosclerotic coronary artery stenosis is an adult disease. However, the Pediatric Review Committee (PeRC) recommended a review of the clinical experience of CCTA for assessment of coronary artery stenosis.

I concur with the assessment by the FDA reviewers (Drs. Bleich, and Radden) that Visipaque CCTA is effective for use in pediatric patients older than 12 years of age. The assessment is based on partial extrapolation of efficacy from adults and on reports on the use of iodinated contrast in CCTA for visualization of coronary artery stenosis in adolescents with Kawasaki's disease. Dr. Bleich determined that the reports provide the necessary information on dosing for iodinated contrast. The safety of Visipaque for CT in pediatric patients has already been established.

I concur with Dr. Fedowitz's assessment that for certain pediatric indications for use in pediatric patients between ages 1 and 12 , the lower limit of age can be extended from 1 year of age to birth based on evidence from the scientific literature, from studies conducted by the Applicant and from pharmacovigilance data.

9. Other Relevant Regulatory Issues

I concur with the assessments by the FDA primary reviewers (Dr. Fedowitz, and Patel), that the prescribing information as amended meets the format and content requirements (21 CFR 201.56-57) and raises no issues from the promotional perspective. I reference the appended labeling for the final agreed upon labeling

by the Agency and the Applicant. Immediate container labels and cartons are unchanged.

I agree with the FDA review team that no postmarketing requirements or commitments, and no risk mitigation and evaluation strategies are needed. No audit of study data by the Office of Scientific Investigations was necessary.

10. Decision/Risk Benefit Assessment

I concur with the FDA reviewers' unanimous recommendation to approve the application for Visipaque for use in CCTA examinations of adults and pediatric patients 12 and over to assist in the diagnostic evaluation of suspected coronary artery disease.

The performance of Visipaque CCTA is sufficiently reliable in the evaluation of patients with low-to-intermediate probability of coronary artery stenosis, and thus can decrease the need for ICA.

The safety profile of Visipaque is well established. No new safety signals of Visipaque in this indicated patient population have been identified. Radiation exposure from CCTA is comparable or lower than the exposure associated with ICA or radionuclide myocardial perfusion imaging. The risk benefit of Visipaque CCTA is favorable.

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/s/

LIBERO L MARZELLA
04/03/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020351/S-044
020808/S-025

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 20351-S044 & 20808- S025
Visipaque(Iodixanol) Injection

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Erica Radden
Mona Khurana
Libero Marzella
Donald Klein
David Place
Frank Lutterodt
Hina Mehta
Michele Fedowitz
Christy John
Anthony Fotenos
Jyoti Zalkikar
Satish Misra
Idalia Rychlik

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020351/S-044
020808/S-025

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Application Type	Supplemental New Drug Application
Application Number(s)	NDA 020351 s44
Priority or Standard	Priority
Submit Date(s)	October 6th, 2016
Received Date(s)	October 18th, 2016
PDUFA Goal Date	April 5th, 2017
Division/Office	Division of Medical Imaging Products/Office of Drug Evaluation IV
Reviewer Name(s)	Anthony Fotenos, MD, PhD
Review Completion Date	March 22nd, 2017
Established Name	Iodixanol
(Proposed) Trade Name	Visipaque Injection
Applicant	GE Healthcare
Formulation(s)	320mgI/mL
Dosing Regimen	70-80 mL main bolus volume (does not include optional test bolus volume of 20 mL) at a flow rate of (b) (4) mL/s, followed by 20 mL saline flush
Applicant Proposed Indication(s)/Population(s)	For use in coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease.
Recommendation on Regulatory Action	Approval
Recommended Indications	For use in coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease.

1. Introduction

This is a cross-discipline team leader (CDTL) review focused on GE Healthcare's efficacy supplement to NDA 20351 (associated NDA 20808 and IND 34585) in support of an expanded indication for the use of Visipaque (320 mgI/mL) "for coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease" (CAD). This review is based on reading the primary reviews written by Karen Bleich (clinical), Michele Fedowitz (labeling), Satish Misra (biometrics), John Christy (Clinical Pharmacology), Zarna Patel (Drug Promotion), selective reading and data analysis of the submission, and study of published literature. My aim is briefly to summarize highlights from the primary reviews, provide some cross-disciplinary context and commentary regarding the submission, and document my opinion of benefit-risk.

2. Background

This efficacy supplement is being reviewed in FDA's Office of New Drugs (OND) under a PDUFA priority review timeline because CCTA addresses diagnostic needs for a serious condition and, if approved, would provide an improvement in effectiveness for the class of iodinated contrast drugs, none of which are currently approved for CCTA. The supplement meets the filing requirements under Section 505(b)(1) of the FD&C Act because the two pivotal investigations relied upon by the applicant were conducted by and for the sponsor. However, relative to clinical practice in 2017, there is little new about CCTA, which requires the use of intravenous iodinated contrast to create a visible difference in attenuation between the coronary arteries and surrounding myocardium during CT imaging of the heart. I provide the following larger contextual timeline to whet the interest of the reader curious about the history and contemporary patterns of general CCTA and associated procedure use (see also Figure 1); note this falls outside the scope of evidence relied upon by the review team:

- 1998: Achenbach and colleagues publish early CCTA images [Achenbach 1998].

- 2008: The Council for Certification in Cardiovascular Imaging establishes of the Certification Board of Cardiovascular Computed Tomography (CBCCT) "to develop and administer a practice-related examination in the field of CCTA and to award certification to those physicians who successfully complete the CBCCT examination process" (http://www.cccvi.org/).

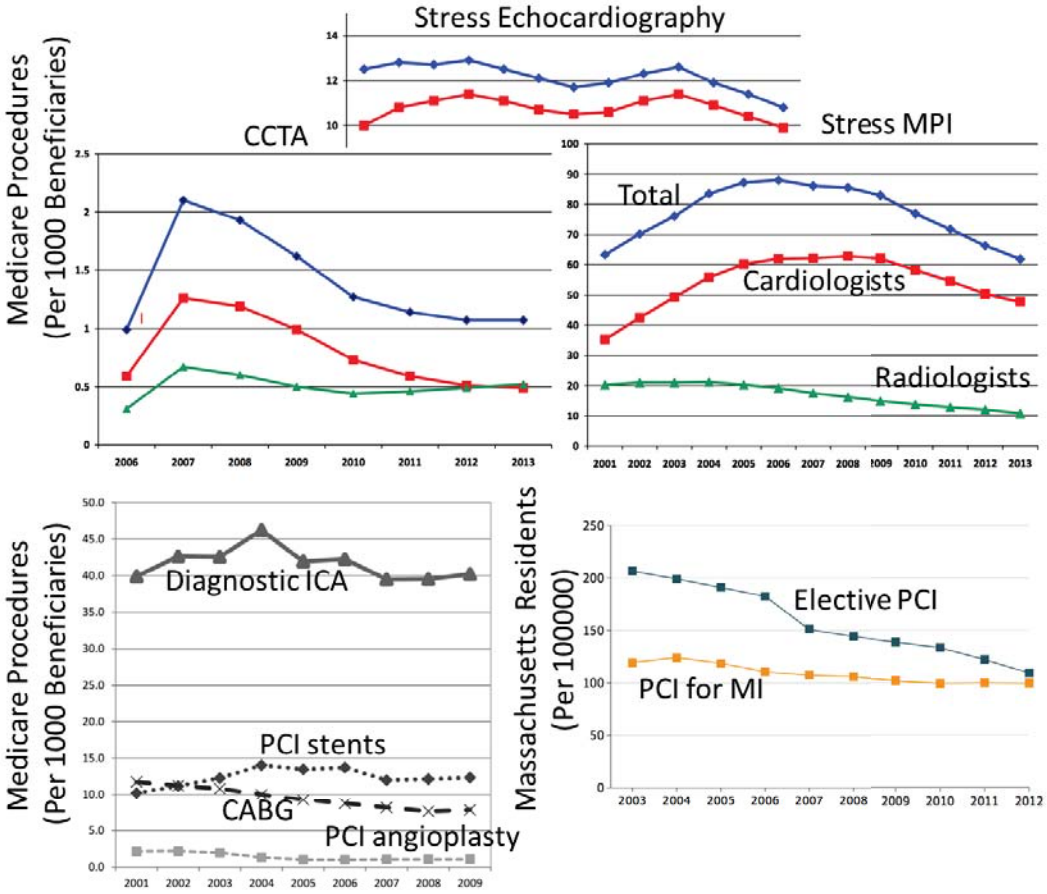
- 2008: In considering whether to alter the prevailing pattern of third-party payer reimbursement at the local level, based on the concern that providers "are using CCTA as an additional test added to exercise testing and nuclear imaging rather than thoughtfully considering the appropriate mix of these tests," the Centers for Medicare and Medicaid Services (CMS) publishes a

Decision Memo for CCTA stating, "While public comments and specialty society opinion following the CMS proposed decision to use Coverage with Evidence Development [CED] did not dispel the uncertainty of the test's clinical utility, they did strongly favor maintaining the local coverage policies for CTA. In light of this, CMS has decided to make no change in the current National Coverage Determination" [CMS 2008].

- 2016: The United Kingdom's National Institute for Health and Care Excellence (NICE) upgrades CCTA to first-line investigation for all stable patients without known significant CAD who present with typical or atypical angina or non-anginal/ECG-abnormal chest pain. Functional imaging or invasive angiography are recommended only secondarily in patients whose CCTA is equivocal or positive [NICE 2016].

- 2017: A group of clinical trialists writes on their efforts to advance beyond diagnostic performance endpoints for trials of CCTA and, by extension, at the vanguard of the larger field of diagnostic evidence generation, "Several themes emerge from reviewing recent randomized controlled trials (RCTs) in stable ischemic heart disease imaging...The preponderance of negative trials reveals weaknesses in trial design, eligibility criteria, or other factors...Future RCTs should incorporate more innovative trials designs to focus on reducing novel clinical outcomes while achieving cost minimization. Possible RCTs may also consider randomization by varied diagnostic/therapeutic or care planning management approaches and their impact on clinical outcomes" [Shaw 2017].

Figure 1 Published data on the utilization of CCTA and related procedures
CAD-related procedures, including CCTA, are common in the United States. Upper: *The number of non-invasive diagnostic imaging procedures between 2001 and 2013 for stress echocardiography, CCTA (2001-2013), and stress MPI billed to Medicare in total (blue) and broken down by physician specialization (cardiologist=red, radiologist=green) appeared to peak around 2007.* Bottom left: *Though practice guidelines recommend non-invasive imaging as a gatekeeper for ICA, there does not appear to be an obvious correlation between the number of non-invasive diagnostic procedures and the gap between diagnostic and invasive procedures ("ICA diagnostic yield") between 2001 and 2009.* Bottom right: *In a Massachusetts population, PCIs done in the absence of MI were considered elective and trended down between 2003 and 2012 to the point where the breakdown is most recently approximately balanced. Assuming total volume ~ 2*Medicare, the following are reasonable ballpark volume estimates for 2009: total non-invasive diagnostic imaging procedures ~5 million (≈4 million MPIs, 600 thousand stress echocardiograms, 90 thousand CCTAs); total invasive diagnostic catheterizations ~2 million; total revascularizations ~1 million (700 thousand stents [60% elective], 400 hundred thousand CABGs [70% elective], 50 thousand angioplasties). For comparison, the annual population incidence of acute MI was estimated to be 600 thousand in 2008 (25% STEMI; Benjamin 2017). Adapted from [Levin 2016, Riley 2011, and Yeh 2015]. CAD = coronary artery disease; CCTA = coronary CT angiography; CABG = coronary artery bypass graft; ICA = interventional coronary angiography; MI = myocardial infarction; MPI = myocardial perfusion imaging; PCI= percutaneous coronary intervention.*



Dr. Bleich's tabulation of regulatory milestones leading up to the current submission describes an evolution in thinking by the review team between 2009 and 2015 regarding the filability of the sponsor's pivotal diagnostic performance study (Table 1).

Table 1: Dr. Bleich's tabulation of regulatory milestones

Date	Application	Description
8/27/2009	IND 034585	Meeting minutes (3/22/2009) from face-to-face meeting regarding sponsor's submitted clinical trial results. FDA concluded "given the inadequacy of the reviewed study data to form the basis for an approvable NDA submission, FDA recommends that additional pivotal studies are needed to support the use of Visipaque as an imaging agent in CCTA for diagnosis and exclusion of CAD."
6/16/2015	IND 034585	Sponsor submitted correspondence requesting a meeting to discuss Phase 3 study design and clinical program to support a coronary CTA indication for Visipaque
11/10/2015	IND 034585	Face-to-face meeting for re-positioning of sponsor's request based on newly available information and guidelines. The sponsor-proposed Phase 3 study was deemed unnecessary by FDA. FDA suggested a future pre sNDA meeting for presentation of the relevant studies and publications.
5/13/2016	IND 034585	Pre-sNDA meeting requested by sponsor to discuss the studies
		and publications for an sNDA filing for CCTA.
6/13/2016	IND 034585	Meeting package was submitted by the sponsor.
7/11/2016	IND 034585	Written responses were provided by DMIP
7/13/2016	IND 034585	Face-to-face meeting in which FDA agreed that the currently proposed indication "to assist in the diagnostic evaluation of patients with suspected CAD" appeared sufficiently supported for sNDA filing review.
10/6/2016	NDA 020351	Receipt of sNDA 44

Why did the review team's thinking evolve?

- Reason #1: the primary gatekeeper role of CCTA in a two-gatekeeper testing sequence has crystalized over time (primary-non-invasive testing: prior to invasive coronary angiography [ICA]; secondary ICA testing: prior to invasive revascularization). As a primary gatekeeper, CCTA is more similar in purpose to stress-rest myocardial perfusion imaging (MPI) than to ICA, despite the "coronary angiography" in two of the three procedure terms. This reframing of the role of CCTA from ICA-replacement to ICA-gatekeeper is reflected in revision of the proposed Visipaque CCTA indication from the one proposed in 2009 (" compared

to now ("assist in the diagnostic evaluation of patients with suspected coronary artery disease").

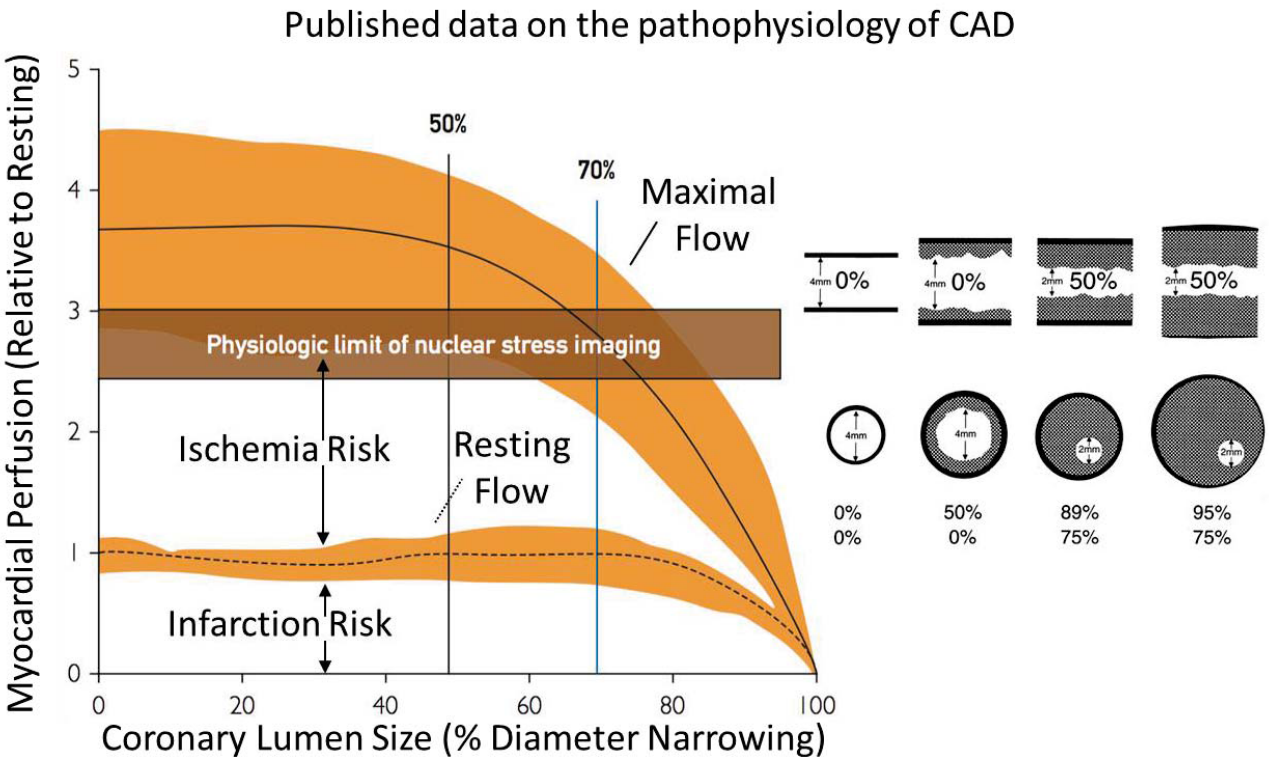
- Reason #2: Given the shared gatekeeping roles of CCTA and MPI, it is pertinent that the Division of Medical Imaging Products (DMIP) has not required superiority against pre-specified better-than-chance sensitivity and specificity thresholds for approval of the following imaging drugs (ICA consistently used as the standard of reference): Cardiolite (NDA 19785, 1995), Myoview (NDA 20372, 2001), Thallium-201 (NDA 18150, 2004), Ammonia-13 (NDA 22119, 2006), and CardioGen (NDA 19414, 2009).

- Reason #3: Multiple controlled trials have randomized patients with stable ischemic heart disease to CCTA vs. stress MPI or ECG testing. A recent published review of these found CCTA to be consistently non-inferior or better for CAD-related events over a period between 1 to 2.1 years of follow-up [Shaw 2017]. In addition, under particularly well controlled therapeutic trial conditions, baseline CAD severity quantified by ICA has been found more prognostic for death and MI compared to CAD severity quantified by MPI over 2.5 to 7 years of follow-up [Mancini 2014].

- Reason #4: Previous reviewers have argued for minimum sensitivity performance thresholds as high as 95% based on the rationale that "false negatives based on CCTA images could have dire clinical consequences" (IND 34585, 8/25/2009). Current evidence on the magnitude of benefit from invasive revascularization suggests that the probability of dire consequences from delayed intervention may be smaller than previously appreciated, particularly in patients excluded by ECG/troponins for ST-elevation myocardial infarction (STEMI; see Figures 2 and 3).

Figure 2: Published data on the pathophysiology of CAD

Inadequate delivery of oxygen secondary to poor or absent blood flow to the myocardium is the common pathophysiological mechanism of CAD. Upper left: *The relation between myocardial perfusion and coronary lumen size is non-linear (solid and dashed lines) and variable (orange areas). Functional testing, including qualitative stress-rest myocardial perfusion imaging, aims to characterize relative regional decreases in the white space between the orange areas marked "Ischemia Risk" and depends on the finding that the decline in maximal flow occurs to the left of the onset of decline in resting flow. Upper right: Anatomical testing, including coronary angiography, typically aims to evaluate vessel lumen size quantified as percent diameter narrowing. Note the potential differences between percent luminal diameter narrowing (upper numbers), cross-sectional atheroma involvement (middle numbers), and luminal area narrowing (bottom numbers) in the illustrated example of coronary atherosclerosis, reflecting both geometrical principles and pathological processes of "negative" (lumen-independent) and "positive" (lumen dependent) remodeling.* Lower left: *CAD manifests clinically in the form of angina, a more deterministic causal link. In populations with high-calorie, low-exercise lifestyles, atherogenesis is detectable on gross pathology in childhood. Angina reflects atherosclerotic progression to the point where a patient seeks medical care, typically for activity-related chest pain in middle age or older adulthood. The micrographs show cross sections through a normal coronary artery (left) and an obstructive plaque (right; the medial lesion between 3 and 6 o'clock represents calcification).* Lower right: *CAD also manifests clinically in the form of acute coronary syndromes (ACS), a more stochastic causal link, associated with increased risk of death from arrhythmia and/or pump failure. The illustrated waveform comes from an unplanned live observation of plaque disruption during an ultrasound experiment in a mouse model of atherosclerosis [Daeichin 2016]. Note the change in the normal pattern of arterial pulsatility (upper row) over a period of a few seconds (bottom row), leading to downstream cessation of blood flow (not shown). Long-running debate continues regarding the use of percent diameter narrowing to predict rupture [Niccoli 2013] and supports the need for further research to identify and time culprit lesions in ACS prospectively. Note that both stable and acute heart disease may also occur in the absence of CAD, which is why the more general term ischemic heart disease is sometimes preferred. Adapted from [Daeichin 2016, Daniels 2012, Fishbein 2006, Rumberger 2017, and http://library.med.utah.edu/WebPath]. CAD = coronary artery disease.*


Published data on the pathophysiology of CAD
Myocardial Perfusion (Relative to Resting)
Coronary Lumen Size (% Diameter Narrowing)
50%
70%
Maximal Flow
Physiologic limit of nuclear stress imaging
Ischemia Risk
Resting Flow
Infarction Risk
0% 0%
50% 0%
89% 75%
95% 75%

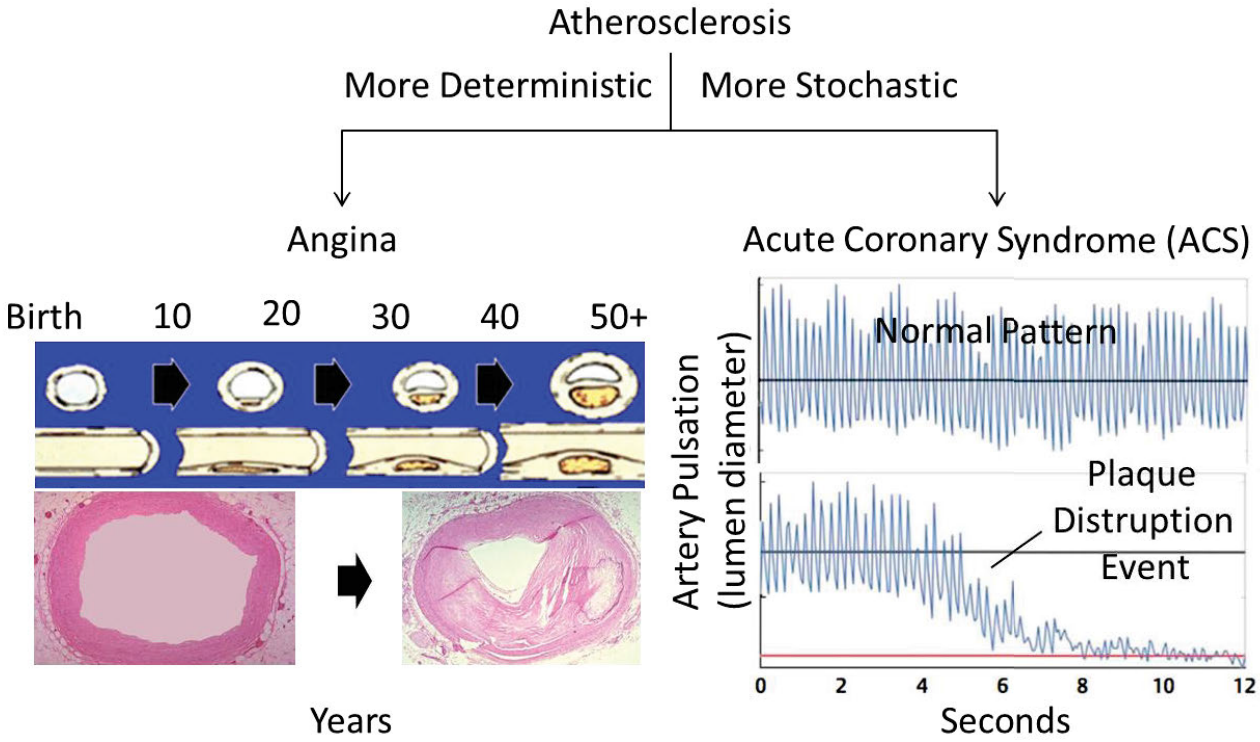
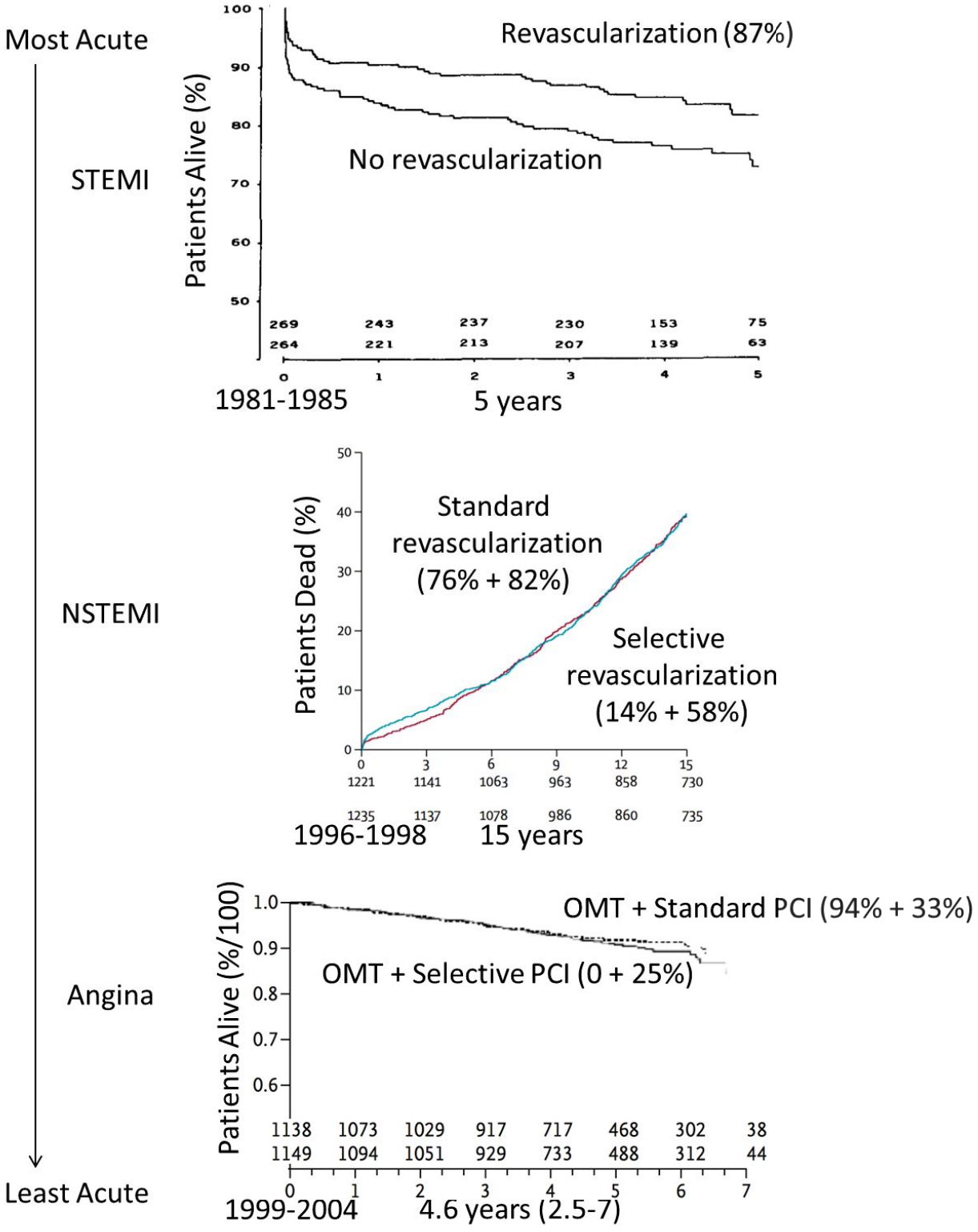

Atherosclerosis
More Deterministic
More Stochastic
Angina
Acute Coronary Syndrome (ACS)
Birth
10
20
30
40
50+
Years
Normal Pattern
Plaque Disruption Event
Artery Pulsation (lumen diameter)
Seconds

Figure 3 Published data on the benefit of invasive revasculaization

The value of non-invasive diagnostic testing used as a gatekeeper for ICA and invasive revascularization depends in part on the benefit of the intervention. Current guidelines recommend invasive revascularization ideally within 2 hours of symptom onset in patients with STEMI, within 24 to 48 hours for most patients with NSTEMI, and as second-line therapy after optimal medical treatment for symptomatic relief in most patients with stable ischemic coronary artery disease. Efficacy evidence from representative trials underlying these guidelines strengthens in proportion to patient acuity and is briefly summarized. Upper: *In the Netherlands Interuniversity Trial [Simoons 1989], more patients with STEMI survived for 5 years after randomization to intracoronary thrombolysis within 4 hours of symptom onset compared to after no revascularization (assuming extremely non-uniform distribution of benefit, "number needed to treat" [NNT] to save one death over five years = 10; assuming uniform distribution of benefit, estimated gain in life expectancy for a 55-year-old patient = 1.5-5 years [Wright 1999]). Unspecified rates of post-randomization revascularization procedures in the control group may have attenuated reported efficacy.* Middle: *In the FRISC-II trial [Wallentin 2016], no survival advantage was demonstrated over 15 years for patients with NSTEMI (i.e., patients with significant ECG changes or positive cardiac enzymes) randomized to invasive angiography and revascularization (within 7 days and for ≥70% epicardial stenosis) compared to patients selectively revascularized for refractory symptoms or severe ischemia on exercise testing. Nevertheless, the 15-year rate of recurrent MI favored the standard revascularization group (38% vs 45%, NNT 14, mostly limited to the first 3 years post-randomization). The small numerical difference in mortality observed during the first 3 years (point benefit estimate ~24 days) was not statistically significant, a null finding also replicated in a recent meta-analysis [Elgendy 2016].* Bottom: *In the PROMISE trial [Boden 2007], no survival advantage was demonstrated over 2.5 to 7 years for patients with angina, objective evidence of myocardial ischemia, and ≥70% epicardial stenosis on invasive angiography randomized to OMT plus standard PCI compared to OMT plus selective PCI (recommended for patients with severe ischemia on MPI and progressive or intolerable angina after 6 to 8 weeks of maximum medical therapy). The same null result was found for myocardial infarction, stroke, and ACS hospitalization event rates, including pre-specified combinations. However, randomization to the more invasive treatment arm did lead to favorable patient-reported outcomes, particularly freedom from angina (for example, 53% vs. 42% at 3 months [compared to 21% vs. 23% at baseline]; NNT 9), an effect which persisted for up to 3 years. It is uncertain the extent to which unblinded patient bias may have contributed to this positive finding or the extent to which the 25% of patients who underwent delayed, selective PCI may have contributed to the general similarity between trial arms. Note that patients with left main stenosis ≥ 50% were excluded from the PROMISE trial and may represent a target population of particular potential CCTA benefit. No benefit in terms of overall or cardiac death or MI was similarly found in the FAME 2 trial (not shown; [De Bruyne 2012]). ICA = invasive coronary angiography; STEMI = ST elevation myocardial infarction; NSTEMI = non-ST elevation myocardial infarction; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.*

Published data on the benefit of invasive revascularization



Reason #5: The quality of supportive evidence in addition to the originally reviewed diagnostic performance study grew between 2009 and 2015 (see Table 2).

Table 2: Dr. Bleich's tabulation of sponsor's first pivotal study (GE-189-001) second pivotal study (GE-189-002) and selected supportive publications

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Main Evaluation	No. of patients enrolled	Study Population	No. of Centers
GE-Sponsored Studies							
GE-189-002 (VCT002)	Open-label, prospective, multi-center, non-randomized	Test bolus: 20 mL at 4-5 mL/s Main injection: 70-80 mL Visipaque at 3.5-5 mL/s	Diagnostic performance of CCTA using LightSpeed VCT scanner for detection of presence or absence of coronary artery obstruction in subjects with chest pain when compared against ICA as SOR	Blinded CCTA image evaluation using AHA 15 coronary segmental model	245	Outpatients with chest pain, scheduled for ICA	16
GE-189-002 reread (GE-012-101)	Open-label, prospective, multi-center, non-randomized, re-read	Re-read (n/a)	Same as above, with re-interpretation ICA and CCTA images from GE-189-002 according to new standards	Blinded CCTA image evaluation using SCCT 18 coronary segment model	232	Data from subjects previously dosed with Visipaque and imaged in GE-189-002	16
GE-012-096	Prospective, multi-center, registry	Not pre-specified, mean dose of 91.5 mL Visipaque, range of 30-180 mL	Prognostic value in terms of sensitivity, specificity, PPV, and NPV of CCTA compared to subsequent ICA findings or binary subject outcomes	CCTA compared to clinical outcomes or ICA up to 12 months	885	Outpatients with chest pain scheduled to undergo CCTA	17
Published Visipaque-only Studies							
ROMICAT	Prospective, single-center	80-100 mL Visipaque	Prognostic value of CCTA compared to occurrence of ACS during index	Blinded CCTA evaluation compared to	368	ED patients with chest pain, normal initial	1
			hospitalization, MACE during 6-month follow-up	ACS and MACE outcomes		troponin, and ECG.	
VCT001	Prospective, multi-center, non-randomized	50-150 mL Visipaque at 4-5 mL/s	Diagnostic performance of CCTA in terms of per patient and per vessel level analysis of stenosis ≥ 50% and ≥ 70% using QCA as SOR	Blinded image evaluation using AHA 15-segment coronary artery model	77	Outpatients with chest pain referred for ICA	3
PICTURE	Prospective, multi-center, non-randomized	Timing bolus: 10-20 mL at 4-5 mL/s. Main injection:80 mL Visipaque at 3.5-5 mL/s.	Diagnostic performance of CCTA and MPI SPECT in terms of sensitivity, specificity, NPV, and PPV of stenosis ≥50% and ≥70% using QCA as SOR	Blinded evaluation of CCTA and ICA images using the AHA 15-segment coronary artery model; and MPI	230	Outpatients with chest pain referred for nuclear MPI	12
Published Studies with Multiple Agents							
PROMISE	Prospective, randomized, multi-center	Multiple contrast agents/protocols	Comparison of CCTA to functional imaging for chest pain assessment	Clinical outcomes over 25 months	10,003	Symptomatic outpatients	68
SCOT-HEART	Prospective, randomized, multicenter	Multiple contrast agents/protocols	Comparison of CCTA with standard work-up, to standard work-up alone	Clinical outcomes over 1.7 years	4,142	Symptomatic outpatients	12

3. Clinical Pharmacology

Highlights of Dr. John's review include discussion of published data that suggest weight-based dosing of Visipaque may reduce beam-hardening artifacts compared to standard volume-based dosing and without a significant loss of coronary attenuation, typically targeted in the range around 350 HU [Nakura 2008]. Dr. John recommends addition of alternative 1 mL/kg instructions to the table entitled "Recommended Dosing for CCTA" in labeling. This table also includes optional with-dilution (also known as "split-bolus") instructions; an option aimed at improving right ventricular visualization via enlargement of the contrast bolus captured during the period of coronary imaging. These instructions closely reflect the dosing protocol used for the pivotal controlled GE-189-002 study. Pending supplement approval, Visipaque will be the first ICA to contain with-dilution instructions (a point of potential interest for conformant injector device labeling). The CCTA dosing table originally proposed by the sponsor compared to the table currently recommended by the review team is shown below (Table 3; note the two numbers in the right lower cells differ compared to the label in Dr. John's 3/15/2017 review due to correction of a typographic error identified, discussed, and corrected in the interim).

Table 3 sponsor's originally proposed and currently recommended labeling for CCTA dosing

Originally Proposed

(b)(4)

[redacted]

Recommended

- **Coronary Computed Tomography Angiography (CCTA)** (320 mg Iodine/mL)

Recommended dosage of VISIPAQUE is dependent on: the administration procedure, patient weight, and CT device factors, as detailed in Table 3.Calibrate the intravenous injection rate so that image acquisition coincides with peak arteria concentration. The time between VISIPAQUE injection and peak arterial concentration varies between patients.

ADULTS and PEDIATRIC PATIENTS[1] 12 YEARS OF AGE AND OLDER VISIPAQUE (320 mg Iodine/mL) DOSING RECOMMENDATIONS FOR CCTA						
Procedure	**Main VISIPAQUE Volume[2]**	**VISIPAQUE /saline Dilution Volume**	**Saline Flush**	**Injection Rate**	**Minimum VISIPAQUE Volume**	**Maximum VISIPAQUE Volume**
Without Dilution	70-80 mL[3,4]	[redacted]	40-50 mL	4-7 mL/sec	50 mL	150 mL
With Dilution	50-60 mL[4]	50 mL diluted VISIPAQUE (20 mL VISIPAQUE plus 30 mL saline)	20 mL	4-7 mL/sec	50 mL	150 mL

[1]For pediatric patients aged 12-17, recommended dose is 1-2 mL/kg.
[2]The main VISIPAQUE volume may be preceded by a test bolus consisting of 20 mL VISIPAQUE, immediately followed by a 20 mL saline flush, both injected at rate of 4-7 mL/sec.
[3]Alternatively, a dose of 1 mL/kg may be used to calculate total VISIPAQUE dose (excluding any test bolus).
[4]For CCTA acquired at < 120 kVp, the dose of VISIPAQUE may be reduced by up to 15% in patients < 85 kg and BMI < 30 kg/m^2. For CCTA acquired on a scanner with more than 64 detector rows, the dose of VISIPAQUE may be reduced in proportion to the scan duration.

4. Clinical/Statistical - Efficacy

Highlights of Dr. Bleich's and Misra's efficacy review include the following:

- Outcome-independent consensus around the use of vessel-level[1], original-read[2], per-reader[3], non-visualized-imputed-wrong[4], true-positive-ICA-stenosis≥50%[5], ICA-unevaluable-or-≤2mm-excluded[6] sensitivity/specificity[7] (Sn/Sp) as the co-primary endpoints for quantifying diagnostic performance in the first-pivotal GE-198-002 study. See Dr. Misra's summation (Table 3). Note the lower bound of all 95% confidence intervals (CI) comfortably exceed chance. This experimental design, albeit with ample precedent for imaging drug efficacy evaluation, does not permit inference regarding whether or the degree to which the Sn/Sp of Visipaque CCTA improves the Sn/Sp of referring clinicians in the absence of imaging or compared to competing non-invasive diagnostic procedures.

Table 3: Dr. Misra's summation of all vessels (stenosis ≥ 50%) by reader for original data

	Readers – Original Read Data (Stenosis ≥ 50%)								
	Reader 1			Reader 2			Reader 3		
	CATH +	CATH -	Total	CATH +	CATH -	Total	CATH +	CATH -	Total
CCTA +	57	68	125	67	126	193	58	74	132
CCTA -	14	708	722	8	699	707	14	740	754
Unevaluable	4	55	59	0	6	6	3	17	20
All Total	75	831	906	75	831	906	75	831	906
Sensitivity (%)	57/75 = 76.0			67/75 = 89.3			58/75 =77.3		
95% CI*	(64.8, 85.1)			(80.1, 95.3)			(66.2, 86.2)		
95% CI**	(63.1, 85.5)			(78.8, 95.0)			(64.8, 86.3)		
Specificity (%)	708/831 = 85.2			699/831 = 84.1			740/831 = 89.1		
95% CI*	(82.6, 87.5)			(81.5, 86.5)			(86.7, 91.1)		
95% CI**	(81.1, 88.5)			(80.6, 87.1)			(86.1, 91.4)		

*based on exact binomial confidence interval assuming independent vessels
** logit transform and cluster sampling variance was used for all segments pooled analysis and all vessels pooled analysis to adjust for intra-subject correlation (sponsor provided)

[1] because patient-level analysis negates the localizing value of imaging whereas segment delineation is less anatomically defined/standardized in the coronaries than in arterial regions where we have relied upon segment-level analysis for approval of other MR angiography (MRA) indications;
[2] because of the theoretical potential for bias to improve specificity after failing to meet FDA's 2009-recommended Sp threshold;
[3] DMIP's minimum standard for feasibly assessing generalizability to typical per-reader practice;
[4] because this is most conservative; we have also accepted 50%-wrong-imputation for prior MRA approvals;
[5] historical standard (see Figure 2) and increases feasibility against challenge to power for Sn, though ICA ≥ 70% or FFR is increasingly used to dichotomize PCI decision-making;
[6] too small for PCI;
[7] least dependent of 2x2-table-derivations on population sample variance.

- In second sponsored study GE-012-096, documentation that the 95% (87-99)/87% (84-89) Sn/Sp of Visipaque CCTA "to predict 12-month" major adverse cardiac events (MACE, defined as death, MI, hospitalization for unstable angina, or revascularization) was almost entirely driven by differential rates of revascularization procedures (see pdf page 50 of Dr. Bleich's review). GE-012-096 was a study with control essentially limited to pre-specification of eligibility criteria and a plan for follow-up after CCTA at 1, 6, and 12 months (i.e., a registry study). I appreciate the potential of real-world evidence such as this to improve generalizability compared to controlled trials, especially in the present context of a second/supplement study. However, I would not recommend the use of this design to generate first-pivotal or stand-alone efficacy evidence for diagnostic imaging drugs. To what extent did revascularization depend on CCTA findings? Independence would promote interpretability but is highly unlikely here. Even if assumed as a hypothetical, near-chance diagnostic performance of referring clinicians for prognosis in the absence of imaging is less plausible compared to for the diagnosis of stenosis ≥ 50% at the vessel level (as in GE-198-002), meaning the desirability of comparative design/analysis is even greater. Finally, beyond the challenging-to-quantify point of impacting management, even statistically significant gains in prognostic performance attributable to a diagnostic procedure lose their clinical relevance.

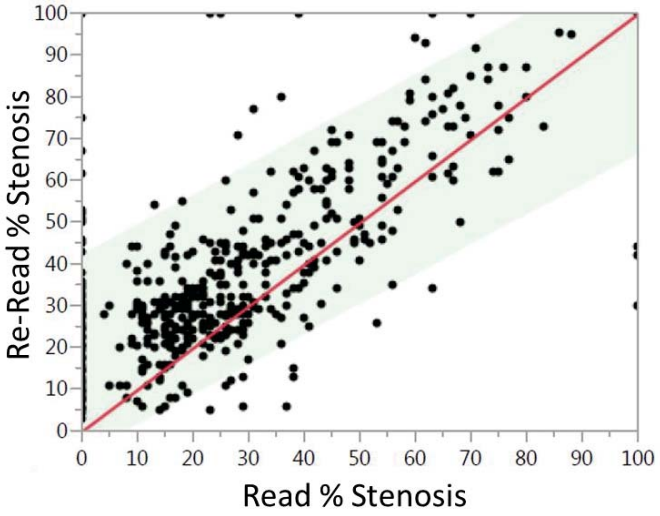
- Dr. Bleich's discussion of leading published ROMICAT and VCT001 (using Visipaque) and PICTURE, PROMISE, and SCOT-HEART (using multiple contrast agents, see pages 51-58) strongly support the generalizability of diagnostic efficacy for Visipaque CCTA found in GE-198-002 and GE-012-096.

A couple of additional observations of personal interest:

- In powering its studies, the sponsor anticipated per-patient ICA ≥ 50% stenosis rates of 50% for GE-198-002 and 12-month event rates of 25% for GE-198-096. The observed rates were 21% and 9%, respectively, suggesting CCTA was primarily studied in patients with low-to-intermediate (mostly low) global risk for 10-year MI or cardiac death.

- Reviewer's analysis of standard-of-reference (quantitative ICA or QCA) maximum per-vessel stenosis as measured in the GE-198-002 read and re-read studies supports the review team's decision to rely on the original read data (see Figure 4).

Figure 4: Reviewer's analysis of read vs. re-read reference standard
Note systematic deviation from the unity line and the wide shaded area containing 95% of individual vessel measurements, both serving as a reminder that term "truth standard" may mislead if interpreted uncritically.



5. Safety

Highlights of Dr. Bleich's review of Visipaque CCTA safety include the following:

- Documentation of one patient who experienced a coronary artery dissection during ICA in Study GE-189-002 (245 enrolled). I mention this event not as an adverse reaction to Visipaque, but as an example of the risk of ICA and an illustration of a difficult-to-quantify potential safety benefit from non-invasive ICA gatekeeping.

- Review strategy accounting for limitation of sponsor's safety data collection protocol. In its two pivotal studies, the sponsor reported only serious and unexpected adverse events, none of which appear to represent reactions to Visipaque.

- Reassuring finding of zero and symmetrically distributed 48-hour-change-in-creatinine post Visipaque in the n=232 GE-189-002 safety population, given plausibly increased risk of contrast-induced nephropathy. Note that patients with serum creatinine ≥ 1.7 mg/dL were excluded from Visipaque CCTA, reasonably representative of typical practice.

- Rationale for addition of new CCTA-pertinent language to labeling section 7.1 (Drug-Drug Interactions): "The use of beta-adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions, and reduces the responsiveness of treatment of hypersensitivity reactions with

epinephrine. Because of the risk of hypersensitivity reactions, use caution when administering iodinated contrast agents to patients taking beta-blockers."

- Sensitive identification of thrombocytopenia safety signal from sponsor's large post-marketing database, as well as insightful explanation plausibly implicating heparin and without new labeling implications.

- No identification of additional CCTA-specific new safety signals.

6. Pediatrics

Dr. Bleich reviewed published evidence on the use of CCTA in patients with Kawasaki disease. Her review suggests a reasonable basis to extrapolate the efficacy and dosing of Visipaque CCTA as established in GE-189-002 and GE-012-096 down to age 12 (see Table 3).

7. Labeling

Dr. Bleich summarizes recommended new labeling downstream of the Visiapque CCTA supplement in the following review excerpt (page 80):

- 2.3 Intravenous Dosage and Administration:
  - Pediatric dosing: CCTA dosing recommendation for pediatric patients over 12 years of age (1-2 mL/kg).
  - Contrast dilution: Inclusion of guidance for variations in the dosing scheme related to the use of dilute contrast administration.
  - Main bolus Visipaque dose: adjusted to reflect the prescribed protocol dose in study GE-189-002, 70-80 mL.
- 7.1 Drug-Drug Interactions: Inclusion of beta-adrenergic blocking agents.
- 14.2 Intravenous Administration Studies: CCTA portion rewritten to reflect most robust analysis of results from the CCTA clinical trials.

The reader is referred to separate labeling reviews by Drs. Fedowitz and Patel for additional information about the concurrent PLR conversion overseen by Dr. Fedowitz.

8. Recommendations

The involved Clinical, Biometrics, and Clinical Pharmacology review teams unanimously find favorable benefit-risk for Visipaque 320 mgI/mL for coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease. I concur.

9. References

Achenbach 1998 value of electron-beam CT for the noninvasive detection of high-grade coronary artery stenosis and occlusions.pdf
CMS 2008 decision memo for computed tomographic angiography.pdf
Daeichin 2016 live observation of atherosclerotic plaque disruption in apolipoprotein E-deficient mouse.pdf
De Bruyne 2012 fraction flow reserve-guided PCI versus medical therapy in stable coronary disease.pdf
Elgendy 2016 meta-analysis of randomized trials of long-term all-cause mortality in patients with NSTEMI managed with routine invasive
Fishbein 2006 how big are coronary atherosclerotic plaques that rupture.pdf
Levin 2016 recent trends in imaging for suspected coronary artery disease what is the best approach.pdf
Mancini 2014 predicting outcome in the COURAGE trial coronary anatomy vs ischemia.pdf
Nakaura 2008 contrast injection protocol for coronary CTA using 64-detector scanner comparison between patient weight-adjusted and f
Niccoli 2013 are the culprit lesions severely stenotic debates in imaging.pdf
NICE 2016 chest pain of recent onset assessment and diagnosis guidelines.pdf
Riley 2011 trends in coronary revascularization in the United States from 2001 to 2009 recent declines in percutaneous coronary interventic
Rumberger 2017 coronary artery disease a continuum not a threshold.pdf
Shaw 2017 comparative effectiveness trials of imaging-guided strategies in stable ischemic heart disease.pdf
Simoons 1989 long-term benefit of early thromboytic therapy in patients with acute MI 5 year follow-up Interuniversity Netherlands trial.p
Wallentin 2016 early invasive vs non-invasive treatment in patient NSTEMI FRISC-II 15 year follow-up.pdf
Wright 1998 gains in life expectancy from medical interventions standardizing data on outcomes (1).pdf
Yeh 2015 population trends in rates of coronary revascularization.pdf

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/s/

ANTHONY F FOTENOS
03/22/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020351/S-044
020808/S-025

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Supplemental New Drug Application
Application Number(s)	NDA 020351 s44
Priority or Standard	Priority
Submit Date(s)	October 6th, 2016
Received Date(s)	October 18th, 2016
PDUFA Goal Date	April 5th, 2017
Division/Office	Division of Medical Imaging Products/Office of Drug Evaluation IV
Reviewer Name(s)	Karen Bleich, MD
Review Completion Date	March 10th, 2017
Established Name	Iodixanol
(Proposed) Trade Name	Visipaque Injection
Applicant	GE Healthcare
Formulation(s)	320 mgI/mL
Dosing Regimen	70-80 mL main bolus volume (does not include optional test bolus volume of 20 mL) at a flow rate of (b)(4) mL/s, followed by 20 mL saline flush
Applicant Proposed Indication(s)/Population(s)	For use in coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For use in coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease.

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Glossary

AC	advisory committee
ACS	acute coronary syndrome
ADR	adverse drug reaction
AE	adverse event
BRF	Benefit Risk Framework
CAD	coronary artery disease
CCTA	Coronary Computed Tomography Angiography
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
DMC	data monitoring committee
DMIP	Division of Medical Imaging Products
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICA	Invasive coronary angiography
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mITT	modified intent to treat
MPI	myocardial perfusion imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SCCT	Society of Cardiovascular Computed Tomography
SOR	standard of reference
SOC	standard of care
TEAE	treatment emergent adverse event
UAP	unstable angina pectoris

1 Executive Summary

1.1. Product Introduction

Visipaque (iodixanol) Injection is a dimeric, isosmolar, nonionic, water-soluble iodinated radiographic contrast medium. Visipaque is approved for intra-arterial administration for angiography and angiocardiography, and for intravenous administration for CT of the head and body, excretory urography and peripheral venography. GE Healthcare proposes to add a coronary CT angiography (CCTA) indication, for the evaluation of patients with suspected coronary artery disease. CCTA is an intravenous CT study in which the images are acquired during the arterial phase of contrast enhancement, in order to visualize the coronary arteries. Visipaque Injection is available in concentrations of 270 and 320 mg of organically bound iodine per mL. The current efficacy supplement is exclusively for the 320 mg I concentration. The proposed dose of (b)(4) mL is similar to the dose for other Visipaque CT indications. The proposed injection rate is (b)(4) mL/s. Current labeling does not include an injection rate for the approved indications.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The sponsor has provided adequate evidence to support the following conclusion: Visipaque CCTA can assist in the diagnostic evaluation of patients with suspected coronary artery disease. The data is strongest in supporting the clinical benefit of Visipaque CCTA in the triage of patients with low to intermediate pre-test probability of coronary artery disease (CAD), by reliably determining the absence of significant CAD and thus avoiding needless invasive coronary angiography (ICA) procedures for many patients. Sensitivity and specificity results for the detection of significant coronary obstruction were adequate in two pivotal GE-sponsored studies, in the first study as compared to the reference standard ICA, and in the second study as compared to clinical outcomes over one year.

Table 1 Reviewer's executive summary of efficacy

STUDY	REFERENCE STANDARD	SENSITIVITY (SUBJECT LEVEL, %)	SPECIFICITY (SUBJECT LEVEL, %)
GE-189-002/GE012-101	ICA	90, 90, 98[1]	70, 76, 81[1]
GE-012-096	12 month clinical outcomes	95	87

[1]The three values are for study reader 1, 2, and 3, respectively.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Coronary artery disease is a leading cause of morbidity and mortality in the United States. Coronary CT angiography (CCTA) already plays an important role in the evaluation of patients with suspected coronary disease in routine clinical practice, particularly as a "gate-keeper" to the more invasive conventional coronary angiography (ICA) procedure. Despite widespread clinical use of iodinated contrast agents for CCTA, none of the agents are currently approved in the US for CCTA. In this primary clinical review, Visipaque CCTA has been found to be effective in the evaluation of patients with suspected coronary disease, particularly for accurately demonstrating the absence of significant coronary disease, thereby allowing for significant numbers of patients with chest pain to avoid the morbidity, mortality, and inconvenience associated with ICA procedures, as well as unnecessary hospitalizations for suspected coronary disease. The most important risks associated with Visipaque usage are class-wide, likely independent of efficacy supplement approval, and outweighed by benefit. Approval of Visipaque for CCTA is thus adequately supported by the available evidence of efficacy and safety.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Coronary artery disease is a leading cause of morbidity and mortality in the United States • Medical interventions and surgical revascularization procedures are effective for treating patients with coronary artery disease • Evaluating the presence or absence of significant coronary artery disease in patients with chest pain or other cardiac symptoms requires imaging.	**Imaging the coronary arteries plays an important role in guiding patients toward appropriate interventions.**
Current Treatment Options	• The diagnostic standard for the evaluation of CAD is ICA. • Commonly used non-invasive tests include echocardiography, myocardial perfusion imaging, and CCTA. Cardiac MRI is currently less common. • Contrast-enhanced CCTA is the only non-invasive test that allows for anatomic assessments of coronary arteries and is now a routine medical test for which several medical societies have issued guidelines.	Approval of Visipaque "to assist in the diagnostic evaluation of patients with suspected CAD" addresses an unmet need whereby CCTA is not addressed in the current labeling of any iodinated contrast agent despite widespread off-label usage of contrast-enhanced CCTA in everyday clinical practice.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The strongest evidence for the benefit of Visipaque comes from the high sensitivity with which it can exclude significant coronary artery disease and thus accurately triage patients to prevent unnecessary invasive procedures. In the prospective clinical trial comparing Visipaque CCTA to ICA, Visipaque CCTA was able to exclude stenosis of ≥50% at the subject level with ≥90% sensitivity.	Patients with chest pain without a known history of CAD can undergo Visipaque enhanced CCTA which may exclude the presence of significant coronary artery disease, precluding the need for an invasive angiogram, and allowing for more timely discharge of ED patients.
Risk	• This review is for an efficacy supplement; Visipaque has already been approved for general CT and intra-arterial indications. It has been safely used in the U.S. post-market setting since 1996, and in Europe since 1993. • The most important risks associated with the use of Visipaque are class-wide. The most common adverse reactions are anaphylactoid reactions. There is a potential risk for interactions between beta blockers and iodinated contrast agents, which is newly incorporated into the label. Notably the risk of interaction with beta blockers is likely higher with high osmolar contrast agents, and Visipaque is a low (isosmolar) osmolar contrast agent. Other class-wide risks are adequately addressed in prior reviews and current labeling.	Given current practice patterns, including wide-spread off-label use of iodinated contrast agents for CCTA, approval of a CCTA indication for Visipaque may not lead to any net increase in overall iodinated contrast administration. If approval leads to a small shift from other iodinated contrast agents to Visipaque, this shift would be unlikely to increase net risk, since Visipaque has a similar safety profile as compared to other iodinated contrast agents. The new inclusion into the label of potential risks of interactions with beta blockers is appropriate due to the common use of beta blockers to perform CCTA. Notably, there are no known cases of negative interactions between beta blockers and Visipaque specifically.
Risk Management	• No risk management issues are identified related to the specific indication for CCTA	No post-marketing commitment is requested from the sponsor at this time.

2 Therapeutic Context

2.1. Analysis of Condition

Cardiovascular diseases are the leading causes of death worldwide, and the most common type of cardiovascular disease is coronary artery disease. In the United States, coronary artery disease is the number one cause of death in both men and women, with more than 13 million Americans diagnosed with coronary artery disease, accounting for more than 500,000 deaths per year (Mozzafarian 2016). The diagnosis and triage of patients presenting to the ED with suspected acute coronary syndromes (ACS) has a substantial impact on health care utilization. More than 9 million patients are seen each year at EDs in the U.S. for acute chest pain and potential CAD, with related health-care costs of 13 to 15 billion dollars (Bhuiya 2010).

The pathophysiology of CAD involves the narrowing or blockage of the coronary arteries by the accumulation of atherosclerotic plaque. When one or more of the coronary arteries become sufficiently occluded by plaque, or when the plaque ruptures and a blood clot forms, the supply of oxygenated blood and nutrients becomes insufficient to meet the demands of the heart, most commonly resulting in chest pain. With increasing severity, atherosclerosis may lead to myocardial infarction (MI) and eventually to cardiac death.

Characterization of coronary artery disease is critical in patients suspected of coronary artery disease, as effective medical treatments and surgical interventions are available and are often life-saving.

2.2. Analysis of Current Treatment Options

Analysis of current diagnostic options can be considered in the context of other CT contrast agents which can be used for CCTA, and also in the context of other diagnostic tests available for the evaluation of CAD.

Of the seven iodinated contrast agents approved for CT and available in the United States, none are currently approved for CCTA, although off-label use of iodinated contrast for CCTA is widespread. Current practice is supported by performance and appropriateness guidelines issued by several notable medical societies, as well as vast numbers of published clinical trials. In general, guidelines and other publications do not favor one iodinated contrast agent over another. For example, the recent Society of Cardiovascular Computed Tomography (SCCT) guidelines for the performance of CCTA do not specify any particular iodinated contrast agent, other than to recommend contrast agents with high iodine concentrations (Abbara 2009). Most of the commonly used CT contrast agents are available in high concentration formations

(320mgI/mL – 370 mgI/mL) and are largely considered interchangeable in regards to effectiveness of contrast-enhanced CCTA.

Current options for the diagnosis of CAD certainly include invasive angiography; however, ICA and CCTA are not currently considered analogous options, in terms of clinical applicability. Specifically, CCTA in practice (and as presented in this efficacy supplement) is optimally suited to the patient population with low or intermediate risk of coronary artery disease. ICA, on the other hand, is no longer widely used for the low or intermediate risk group because of the availability of less invasive tests. A patient with a high likelihood of coronary artery disease (based on some combination of clinical history, family history, ECG, stress testing, and blood tests) is ideally managed with ICA because of the ability to concurrently perform intravascular treatments such as angioplasty and stenting.

A more meaningful consideration of current options involves a discussion of the non-invasive tests that are commonly used for the low and intermediate probability patients, all of which like CCTA are considered gatekeepers to the more invasive ICA. These include the category of stress tests, most commonly exercise ECG, stress echocardiography, and stress radionuclide myocardial perfusion imaging (MPI). These tests differ in terms of their diagnostic accuracy and relative advantages and disadvantages, and they can all provide robust information regarding the presence or absence of ischemia. MPI is generally considered to have higher sensitivity for the detection of ischemia, as compared to ECG and echocardiography.

Notably, none of the functional techniques directly visualize the coronary arteries, which is unique to CCTA among the noninvasive options. Functional data regarding the heart is critical in the CAD population and stress testing is often done in conjunction with anatomic imaging to provide a more complete diagnostic assessment. Indeed, hybrid imaging combining CCTA and MPI, while not currently widely available, will likely be of benefit to many cardiac patients in the future by combining critical anatomic and functional information.

Finally is a brief consideration of cardiac MRI. While there are no gadolinium products approved for coronary or cardiac MRI in the U.S., gadolinium contrast agents are used off-label for cardiac imaging, predominantly for functional stress imaging, demonstrating ischemic and nonviable myocardium. Cardiac MRI is less widely available than the more commonly used modalities, but may rise to prominence in the future for the assessment of CAD.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The indicated uses for Visipaque included in the current product label include a variety of intra-

arterial and intravenous procedures including: angiocardiography; cerebral, peripheral, and visceral angiography; excretory urography; CT of the head and body; and peripheral venography. The indication statement on the current label is not substantially changed from the original labeling at the time of the initial approval in 1996. The current CCTA application represents the first efficacy supplement to propose a new indication for Visipaque. Table 2 itemizes major milestones in Visipaque's overall U.S. regulatory history from a primary clinical reviewer perspective.

Table 2 Reviewer's tabulation of regulatory history underlying approved new indications

Date	Application	Description
3/22/1996	NDA 020351	Original NDA approval included the current approved indications.
12/18/2003	NDA 020351	Approval granted for addition of a "Geriatric Use" subsection

Source: DARRTS

3.2. Summary of Presubmission/Submission Regulatory Activity

Regulatory guidance from the FDA regarding the coronary CTA indication began in 2009 and continued until the current submission was received in 2016, as summarized in Table 3.

Table 3 Reviewer's tabulation of regulatory milestones leading up to the current submission

Date	Application	Description
8/27/2009	IND 034585	Meeting minutes (3/22/2009) from face-to-face meeting regarding sponsor's submitted clinical trial results. FDA concluded "given the inadequacy of the reviewed study data to form the basis for an approvable NDA submission, FDA recommends that additional pivotal studies are needed to support the use of Visipaque as an imaging agent in CCTA for diagnosis and exclusion of CAD."
6/16/2015	IND 034585	Sponsor submitted correspondence requesting a meeting to discuss Phase 3 study design and clinical program to support a coronary CTA indication for Visipaque
11/10/2015	IND 034585	Face-to-face meeting for re-positioning of sponsor's request based on newly available information and guidelines. The sponsor-proposed Phase 3 study was deemed unnecessary by FDA. FDA suggested a future pre sNDA meeting for presentation of the relevant studies and publications.
5/13/2016	IND 034585	Pre-sNDA meeting requested by sponsor to discuss the studies

		and publications for an sNDA filing for CCTA.
6/13/2016	IND 034585	Meeting package was submitted by the sponsor.
7/11/2016	IND 034585	Written responses were provided by DMIP
7/13/2016	IND 034585	Face-to-face meeting in which FDA agreed that the currently proposed indication "to assist in the diagnostic evaluation of patients with suspected CAD" appeared sufficiently supported for sNDA filing review.
10/6/2016	NDA 020351	Receipt of sNDA 44

Source: DARRTS

3.3. Foreign Regulatory Actions and Marketing History

Visipaque was first approved for marketing in Sweden for intra-arterial use (150 mgI/mL, 270 mgI/mL and 320 mgI/mL) in February 1993 and for intravenous use (270 mgI/mL and 320 mgI/mL) in 1994. The sponsor states that "worldwide, particularly in Europe, CCTA is considered an approved indication under the assumption that examination of the coronary artery system is covered under the CT body indication" (2.5 Clinical Overview).

In the UK, the Visipaque Summary of Product Characteristics states the following indications (quoted in the indented text):

> This medicinal product is for diagnostic use only. X-ray contrast medium for cardioangiography, cerebral angiography (conventional), peripheral arteriography (conventional), abdominal angiography (i.a. DSA), urography, venography, CT enhancement. Lumbar, thoracic and cervical myelography. Arthrography, hyersterosalpingography (HSG) and studies of the gastrointestinal tract. In children it is used for cardioangiography, urography, CT enhancement and studies of the upper gastrointestinal tract.
> *Source: https://www.drugs.com/uk/visipaque-injection-320mg-i-ml-leaflet.html*

Reviewer comment: With respect to Visipaque CCTA, the UK label includes no specific reference to CCTA.

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

After initial review of the sNDA submission by all review disciplines, it was agreed that reviewers from the Office of Clinical Pharmacology (OCP, Christy John) and the Office of

Surveillance and Biometrics (OSB, Satish Misra) would write primary reviews in addition to this clinical review.

A primary review was not provided from the Division of Pediatric and Maternal Health (DPMH) because the supplement was proposed for adult usage only. DPMH was, however, involved in the concurrent PLR conversion (Erica Radden). Reviews were also not included from the Office of Scientific Investigations (OSI) and the Office of Product Quality (OPQ).

4.1. Office of Scientific Investigations (OSI)

An OSI audit was not requested as part of this review.

4.2. Product Quality

The sponsor reports that no changes have been made to the formulation of the product throughout the entire clinical development program. There was no new chemistry, manufacturing, or control (CMC) information in the submission.

4.3. Clinical Microbiology

The sponsor submitted no new clinical microbiology information.

4.4. Nonclinical Pharmacology/Toxicology

The sponsor submitted no new nonclinical pharmacology/toxicology information.

4.5. Clinical Pharmacology

The sponsor submitted no new clinical pharmacology.

4.5.1. Mechanism of Action

Visipaque is a dimeric, isosmolar, nonionic, water soluble, iodinated contrast agent. Intravascular injection of Visipaque opacifies those vessels in the path of flow of the contrast agent, permitting radiographic visualization of the internal structures until significant dilution and elimination occurs.

4.5.2. Pharmacodynamics

As with other iodinated contrast agents, the degree of enhancement following Visipaque injection is directly related to the iodine content in the administered dose. Peak iodine plasma levels occur immediately following rapid intravascular injection. Iodine plasma levels fall rapidly within 5 to 10 minutes.

4.5.3. Pharmacokinetics

Visipaque is predominantly non-metabolized, and is predominantly renally excreted. In adults, approximately 97% of the injected dose is excreted unchanged in the urine within 24 hours, with less than 2% excreted in feces within 5 days post-injection.

4.6. Devices and Companion Diagnostic Issues

The sponsor includes no companion device or diagnostic in the submission.

4.7. Consumer Study Reviews

The sponsor submitted no label comprehension, patient self-selection, or other human factors studies in the submission.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 4 Reviewer's tabulation of clinical trials relevant to this supplement

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Main Evaluation	No. of patients enrolled	Study Population	No. of Centers
GE-Sponsored Studies							
GE-189-002 (VCT002)	Open-label, prospective, multi-center, non-randomized	Test bolus: 20 mL at 4-5 mL/s Main injection: 70-80 mL Visipaque at 3.5-5 mL/s	Diagnostic performance of CCTA using LightSpeed VCT scanner for detection of presence or absence of coronary artery obstruction in subjects with chest pain when compared against ICA as SOR	Blinded CCTA image evaluation using AHA 15 coronary segmental model	245	Outpatients with chest pain, scheduled for ICA	16
GE-189-002 reread (GE-012-101)	Open-label, prospective, multi-center, non-randomized, re-read	Re-read (n/a)	Same as above, with re-interpretation ICA and CCTA images from GE-189-002 according to new standards	Blinded CCTA image evaluation using SCCT 18 coronary segment model	232	Data from subjects previously dosed with Visipaque and imaged in GE-189-002	16
GE-012-096	Prospective, multi-center, registry	Not pre-specified, mean dose of 91.5 mL Visipaque, range of 30-180 mL	Prognostic value in terms of sensitivity, specificity, PPV, and NPV of CCTA compared to subsequent ICA findings or binary subject outcomes	CCTA compared to clinical outcomes or ICA up to 12 months	885	Outpatients with chest pain scheduled to undergo CCTA	17
Published Visipaque-only Studies							
ROMICAT	Prospective, single-center	80-100 mL Visipaque	Prognostic value of CCTA compared to occurrence of ACS during index	Blinded CCTA evaluation compared to	368	ED patients with chest pain, normal initial	1

			hospitalization, MACE during 6-month follow-up	ACS and MACE outcomes		troponin, and ECG.	
VCT001	Prospective, multi-center, non-randomized	50-150 mL Visipaque at 4-5 mL/s	Diagnostic performance of CCTA in terms of per patient and per vessel level analysis of stenosis ≥ 50% and ≥ 70% using QCA as SOR	Blinded image evaluation using AHA 15-segment coronary artery model	77	Outpatients with chest pain referred for ICA	3
PICTURE	Prospective, multi-center, non-randomized	Timing bolus: 10-20 mL at 4-5 mL/s. Main injection:80 mL Visipaque at 3.5-5 mL/s.	Diagnostic performance of CCTA and MPI SPECT in terms of sensitivity, specificity, NPV, and PPV of stenosis ≥50% and ≥70% using QCA as SOR	Blinded evaluation of CCTA and ICA images using the AHA 15-segment coronary artery model; and MPI	230	Outpatients with chest pain referred for nuclear MPI	12
Published Studies with Multiple Agents							
PROMISE	Prospective, randomized, multi-center	Multiple contrast agents/protocols	Comparison of CCTA to functional imaging for chest pain assessment	Clinical outcomes over 25 months	10,003	Symptomatic outpatients	68
SCOT-HEART	Prospective, randomized, multicenter	Multiple contrast agents/protocols	Comparison of CCTA with standard work-up, to standard work-up alone	Clinical outcomes over 1.7 years	4,142	Symptomatic outpatients	12

5.2. Review Strategy

This primary clinical review is focused on the question of whether Visipaque's approved intravenous CT indications (currently for head and body) should be expanded to include a new indication for coronary CTA. My review strategy was primarily governed by DMIPs concurrence at the meeting held between GE and DMIP on 7/13/2016 that the GE sponsored studies GE-189-002 and GE-101-096 were sufficient for the pursuit of an efficacy supplement as a 505b1 application, and that the Visipaque-only published literature reports and the published studies with multiple contrast agents would provide supportive data.

Table 5 summarizes regulatory milestones occurring between the sponsor's October 6th, 2016 submission and mid-March, 2017.

Table 5 Reviewer's tabulation of post-submission regulatory milestones

Date	Description
10/6/2016	Receipt of sNDA 44 and start of 21st Century Review Clock
11/2/2016	Filing meeting
11/29/2016	Fast-track designation granted for unmet medical need
1/5/2017	Mid-cycle meeting
1/25/2017	Labeling meeting #1
1/31/2017	Labeling meeting #2
2/13/2017	Response to 1/30/2017 IR received, three questions on post-marketing experience with peds and ADRs, as well as packaging issue
3/1/2017	PeRC meeting for requested full waiver
3/1/2017	Response to 2/17/2017 IR received, regarding use in patients < 1 year of age
3/7/2017	Labeling meeting #3

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. GE-189-002 and Re-read GE-012-101

6.1.1. Study Design

Overview and Objective

Study GE-189-002 was designed to evaluate the diagnostic performance of CCTA using the 64-detector row GE LightSpeed VCT scanner with Visipaque Injection (320 mgI/mL) for detecting the presence or absence of significant coronary artery obstruction in patients suspected of having CAD, when compared to ICA, as the standard of reference. The study was not conducted under the IND for Visipaque. GE states that "the study was originally designed to support the body of evidence around usability of the GE Lightspeed VCT scanner and therefore was not filed to the Visipaque IND at the time (Module 2.7.3 Summary of Clinical Efficacy)." The study was published as the ACCURACY trial (Budoff 2008).

GE-189-002 was conducted from 2006-2007. In 2015, a full re-read of the study data from GE-189-002 was performed, including a re-read of both the CCTA images and the ICA images, as study GE-012-101. GE states that "the purpose of the re-read was to assess the Visipaque-enhanced CCTA images in accordance with current published guidelines and clinical practice, and to address various aspects of the original image reading and assessment methodology that were judged to be suboptimal by the FDA."

The two studies are presented together because they are two interpretations of one set of imaging data from one clinical trial. The notable differences between the studies are that they used different coronary segmental anatomy models to subdivide the coronary arteries and that the re-read study included a more robust statistical analysis plan. As with the original study, the re-read study was not conducted under the IND for Visipaque. Thus there was no input or guidance provided from DMIP for the re-read study.

Reviewer comment: The rationale for the undertaking of the re-read study can be considered in the context of the regulatory history of this application. In 2009, at a face-to-face meeting between DMIP and GE, DMIP concluded that the GE-189-002 study was "not adequate as confirmatory or pivotal study forming (in part or in isolation) the basis of an approvable NDA submission" (meeting minutes IND 34585, 9/28/2009). In particular, DMIP expressed concerns about the reporting of the CCTA results as a consensus read by three readers, and about the lower than expected specificity result, in terms of the pre-specified win criteria. There is no evidence that DMIP recommended a re-read of the study data.

Trial Design

The trial design was prospective, multi-center, and open-label. CCTA images were compared to invasive coronary angiography as the standard of reference, in a population of stable

outpatients with symptoms suggestive of coronary artery disease, but without a known history of CAD. The primary endpoint was the diagnostic performance of CCTA for the detection of the presence or absence of significant coronary artery obstruction when compared against ICA.

Subjects who were scheduled to undergo outpatient evaluation of typical or atypical chest pain by ICA were screened for study enrollment in 16 centers in the U.S. Subjects with a history of known cardiac disease were excluded. The study involved blinded reading in that the CCTA interpretations were performed by independent readers who were blinded to the subjects' medical histories, as well as to the results of the other modalities. The study was "open-label" in terms of the awareness of CCTA readers that all subjected received Visipaque.

The main inclusion criterion was that subjects were referred for an elective ICA for typical or atypical chest pain. Additional inclusion criteria specified age ≥18 years of age, the presence of sinus cardiac rhythm, and the willingness to use beta blockers to achieve a heart rate of ≤ 65 beats per minute, if needed. The sponsor itemized 12 exclusion criteria, notably any history of CAD, allergy to iodinated contrast, serum creatinine of ≥1.7 mg/dL, resting heart rate >100 beats per minute, contra-indications to beta blockers or verapamil, and contra-indications to nitroglycerin.

Reviewer comments: Notably, patients in this study were not excluded based on elevated coronary artery calcium score or elevated body mass index, both factors that have been suggested previously to limit the accuracy of CCTA. Also notable is the necessity for heart rate control for CCTA, and the exclusion of subjects who could not, for various reasons, achieve a heart rate of ≤65 beats per minute. Heart rate control is not generally considered necessary for the performance of ICA.

The sponsor's detailed schedule of evaluations is provided below in Table 6.

Table 6 Sponsor's schedule of evaluations, GE-189-002

	Preprocedure		CCTA*	Post-administration		
Variables	Screening (0 - 7 days prior)	Baseline (Day 0)	Exam (Time 0)	5-15 min*	30 min* -1 hr*	48 hrs* (±4 hrs)
Informed Consent	X					
Entry Criteria	X	X				
Demographics, Height/Weight	X					
General Medical/Surgical History	X					
Cardiac History/Risks	X					
Seattle Angina Questionnaire	X					
Laboratory Evaluations	X[a]					X[d]
Concurrent Medications	X	X	X	X	X	X
Beta-Blocker Administration		X[b]	X[b]			
Nitroglycerin Administration			X			
Urine Pregnancy Test (Women Only)		X				
Vital Signs (heart rate, blood pressure, respiration rate)	X	X[b]	X[c]	X	X	X
Calcium Scan			X			
Contrast (VISIPAQUE) Administration			X			
Image Acquisition			X			
CCTA Image Interpretation (Incidental Findings / Non-Coronary Abnormalities)						
Adverse Event Recording (Continuous Monitoring)			X	X	X	X

* CCTA = coronary computed tomography angiography, min = minute, hr = hour
[a] Standard of care (historical) lab values may be used within 14 days of the CCTA procedure to meet inclusion/exclusion criteria for a potential subject.
[b] beta-blocker administration as necessary
[c] Vital signs must be taken just prior to nitroglycerin administration.
[d] Serum creatinine measurement must be performed before the CATH procedure and result should not be >0.3mg/dL above the pre-CCTA (screening) value.

Source: pg 21 ge 189-002-Study Report Body

All CCTA procedures were performed using the GE Healthcare LightSpeed VCT scanner with 64-detector rows. All study sites followed a study-specific CT imaging manual detailing patient preparation, patient positioning, contrast injection, and scan parameters.

With respect to study drug administration, the sponsor's protocol included two options for the dosing of Visipaque for CCTA. Both protocol options began with a test bolus in order to determine the scan delay time. The test bolus consisted of 20 mL Visipaque, followed by 20 mL saline flush, at an injection rate of 4-5 mL/sec. Instructions for the determination of the scan time delay were specified in the Cardiac CT Imaging Manual.

Table 7 Contrast administration protocols – Option #1

Phase	Product Name	Main Volume (mL)	Injection Rate (mL/Sec)
1st phase contrast	VISIPAQUE 320 mg-I/mL	70 - 80	4 – 5
2nd phase saline	0.9% sodium chloride solution	40 – 50	4 – 5

Table 8 Contrast administration protocol -Option #2

Phase	Product Name	Main Volume (mL)	Injection Rate (mL/Sec)
1st phase contrast	VISIPAQUE 320 mg-I/mL	50 - 60	4 – 5
2nd phase contrast + saline	VISIPAQUE SALINE	20 30	4 – 5
2nd phase saline	0.9% sodium chloride solution	20	4 – 5

Source: pg 27-28 ge 189-002 Protocol and Amendments

Reviewer comment: The study design does not include dose optimization of Visipaque for the performance of CCTA studies. The specified contrast administration protocol including contrast dose is reflective of common clinical practice for CCTA.

Concurrent administration of medications to achieve heart rate control was administered as needed. The protocol called for the administration of nitroglycerin for vasodilation to all study subjects. Vital signs were assessed regularly as delineated in the schedule of events.

While the study sites followed specific protocol instructions for the performance of the CCTA examinations, the invasive coronary procedures (SOR) were part of each subject's routine clinical care and were performed according to each study site's clinical standard of practice. The sponsor notes that the angiography procedures were performed using digital angiographic systems, and in accordance with the imaging standard set by the American College of Cardiology/Society for Cardiac Angiography and Interventions Expert Consensus Document. The contrast agents for the ICA were not prescribed, other than that the contrast agents used were FDA approved. The dose of the contrast agent was determined by procedure needs but

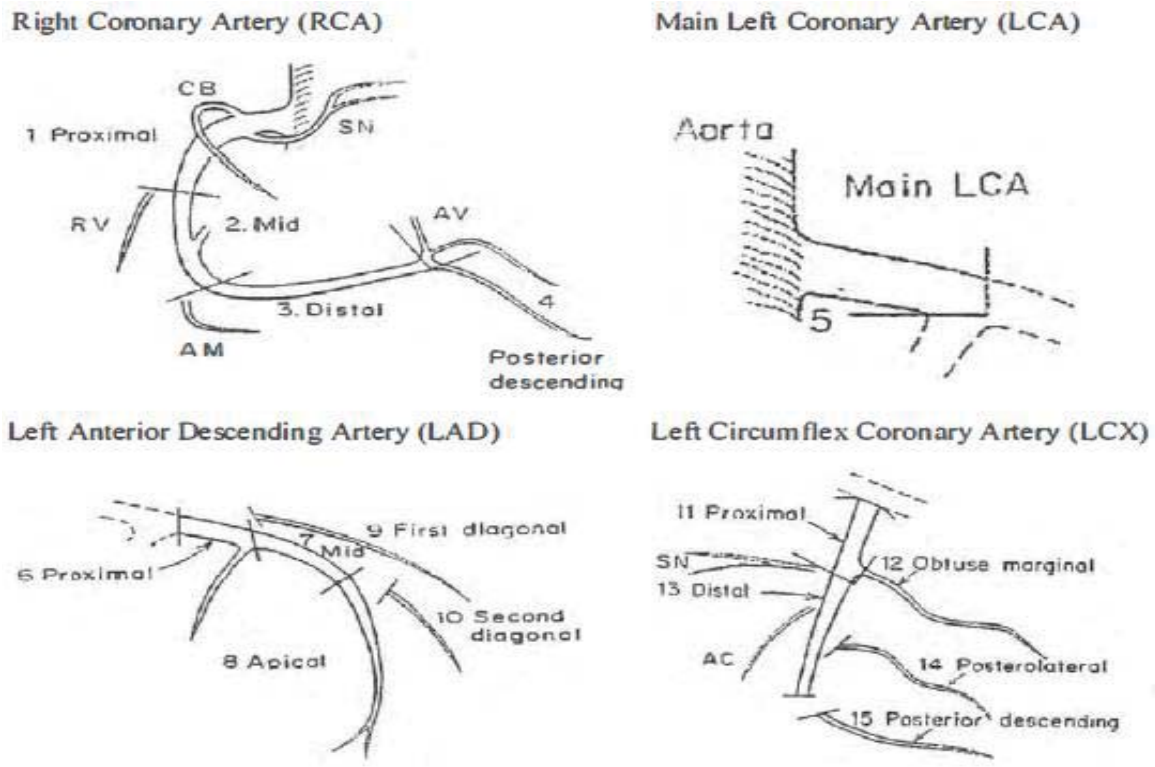
did not exceed the maximum volume specified in the product package insert.

Image Interpretation
There are four coronary arteries (left main, left anterior descending, left circumflex, and right coronary artery) and each coronary artery can be divided into standardized models of segmental coronary artery anatomy for the localization of stenoses. Both the CCTA studies and the ICA studies were evaluated by assessing each coronary artery segment individually for stenosis.

Two different models of coronary segmental anatomy are the American Heart Association (AHA) model, and the Society of Cardiovascular Computed Tomography (SCCT) model. The AHA coronary arterial segmental model includes 15 coronary segments (Austen 1975), and the SCCT coronary segment model includes 18 coronary artery segments (Raff 2009).

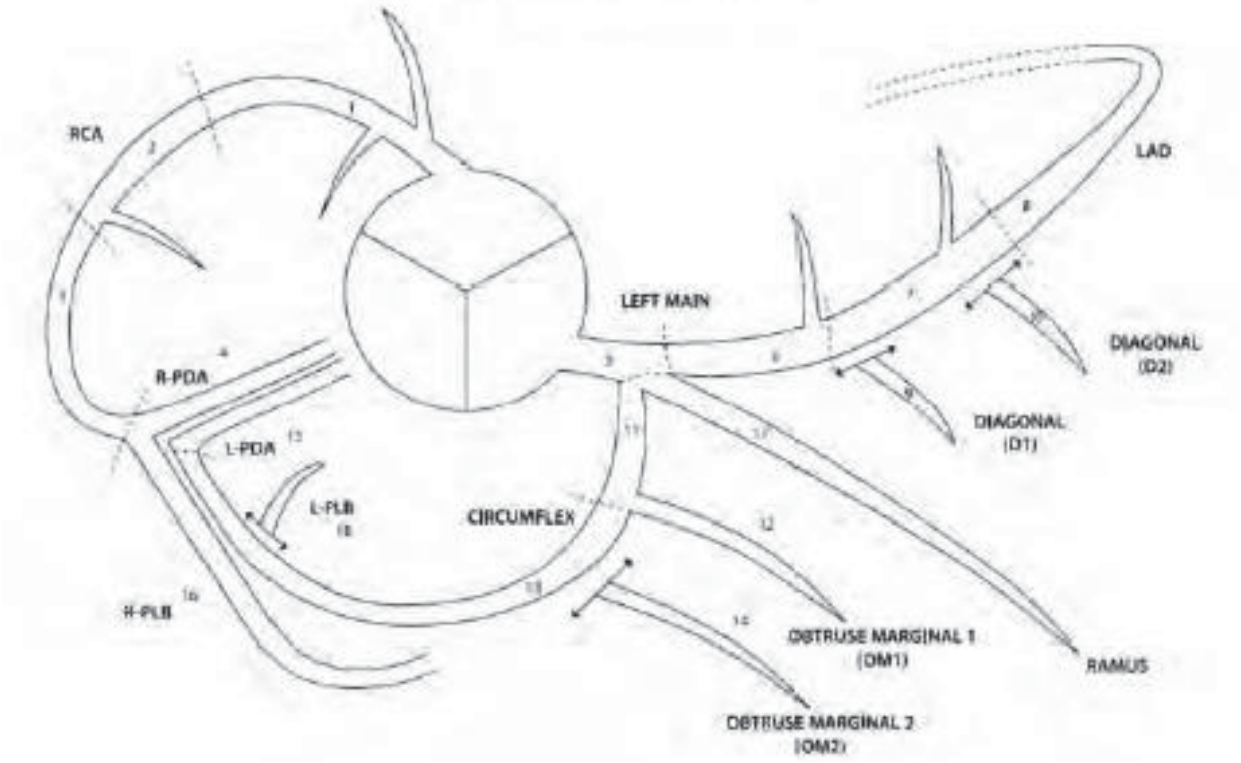
In the original read study, the CCTAs and ICAs were interpreted in terms of the degree of stenosis at each of 15 coronary artery segments (AHA model). In the re-read study, the same set of CCTAs and ICAs were re-interpreted with the results reported at each segment, based on the subdivision of the coronary arteries into 18 segments (SCCT model). Diagrams of the two coronary segmental models are provided below. Following the images is a table listing all of the segments for each model, highlighting the differences between the two models.

Figure 1 AHA 15 segment coronary artery model



Source: pg 17 ge 189-002-16-1-13 indep review ct manual

Figure 2 SCCT 18 segment model



Source: pg 49 ge012-101-16-1-1 protocol amend

Table 9 Coronary artery segment model comparison: AHA and SCCT

Coronary Artery	AHA 15 Segments		SCCT 18 Segments	
RCA	1	Proximal RCA	1	Proximal RCA
	2	Mid RCA	2	Mid RCA
	3	Distal RCA	3	Distal RCA
	4	PDA (posterior descending)	4	PDA
			16	R-PLB (posterior-lateral)
Left main	5	LM	5	LM
LAD	6	Proximal LAD	6	Proximal LAD
	7	Mid LAD	7	Mid LAD
	8	Apical (distal) LAD	8	Distal LAD
	9	1st diagonal	9	Diagonal 1
	10	2nd diagonal	10	Diagonal 2
LCx	11	Proximal Cx	11	Proximal Cx
	12	OM (obtuse marginal)	12	OM 1
	13	Distal Cx	13	Mid and distal LCx
	14	PL LCx (postero lateral)	14	OM 2
	15	PDA LCx (posterior descending)	15	PDA LCx
			17	RI (Ramus intermedius)
			18	L-PLB (posterolateral branch)

Image Interpretation – CCTA

For both the original read study and for the re-read study, each CCTA examination was independently read by three readers. CCTA readers were instructed to evaluate each coronary segment individually, as shown below in the sample portion of the case report form. The name of each coronary segment is listed in the left hand column. The row of text beneath "EVALUATION OF CTA" demonstrates the information that was obtained for each segment.

Figure 3 Demonstrative portion of CRF

(b)(4)

Source: pg 11 ge 189-002-16-1-2-crfs

Each coronary segment was first determined to be evaluable or not evaluable. Segments categorized as not evaluable were further categorized as either not seen, or poorly seen due to vessel motion, banding artifact, or calcification. The diameter of the vessel segment was then recorded as less than 2 mm or ≥ 2mm. Next, the degree of stenosis was assessed. Readers could either calculate an exact percentage of stenosis based on their own vessel measurements, or they could visually estimate each segment into one of the following

categories: no stenosis, ≤29% stenosis, 30-49% stenosis, 50-69% stenosis, 70-99% stenosis, or 100% stenosis. Lastly, the segment was evaluated for the presence or absence of plaque, and the impact the plaque had on evaluation.

Reviewer comment: The representative CRF portion shown here is from the original read study (GE-189-002). The re-read study (GE-012-101) used a different CRF which directed the radiologist or cardiologist to collect the same information described above.

Image Interpretation – ICA

The standard of reference ICA images were interpreted by a single independent blinded reader using commercially-available quantitative coronary analysis (QCA) software. QCA is an automated vessel border detection program that determines the vessel contours and calculates the percentage of stenosis. For both studies, only coronary artery segments that were evaluable by QCA were included in the analysis.

For the original read study, the QCA reader performed the automated QCA assessment on each coronary segment that was deemed to be >30% stenosed by visual inspection. For the re-read study, the QCA reader performed the QCA assessment on every coronary segment. As with the CCTA interpretations, the AHA 15 segmental model was used for the original read study, and the SCCT 18 segmental model was used for the re-read study.

The CRF for the ICA interpretation was almost identical to the CRF for the CCTA interpretation, except that there was no evaluation of plaque on the ICA CRF because of the inability to visualize the vessel wall with ICA.

Reviewer comment: The QCA reader for the original read study and the QCA reader for the re-read study were two different physicians, trained in interpretation of ICA.

Study Endpoints

The primary endpoint for both the original study and for the re-read study was the sensitivity and specificity of Visipaque-enhanced CCTA to detect significant stenosis (defined as luminal narrowing greater than or equal to 50%) as compared to ICA, with vessel segments < 2 mm by ICA excluded.

Based on the data collected on the CRFs, the sensitivity and specificity of CCTA could be calculated at the segment level, the vessel level or the subject level. For example, in a segment level analysis, a segment is categorized as true positive if there is significant stenosis by CCTA and also significant stenosis of the same segment by ICA. In a vessel level analysis, a vessel is categorized as true positive if there is significant stenosis in any segment within the vessel by CCTA, and also significant stenosis in any segment within that same vessel by ICA. In a subject

level analysis, a subject would be categorized as true positive if there is a significant stenosis in any segment of any vessel, and also significant stenosis in any segment of any vessel by ICA.

The pre-specified study endpoint for the original read study was the sensitivity and specificity of CCTA as determined at the subject level; for the re-read study the primary endpoint was determined at the vessel level.

Reviewer comment: Both subject level and vessel level analyses have merits. A vessel level analysis is more robust in terms of evaluating the anatomic accuracy of CCTA, which is a reasonable expectation of a CT-based test. While subject level analyses do not allow for disease localization, there is clinical benefit to the evaluation of CCTA in terms of the ability of the test to reliably "rule-out" any significant coronary stenosis at the subject level.

In both studies, the primary endpoint defined significant stenosis as ≥ 50% luminal narrowing based on the degree of stenosis entered into the CRF. Thus, all segments categorized as having 50-69% stenosis, 70-99% stenosis, and 100% stenosis were counted as significantly stenosed. Both studies included an additional endpoint using ≥70% luminal narrowing as the definition of significant stenosis.

Reviewer Comment: Determination of coronary artery stenosis in terms of the presence or absence of ≥ 50% stenosis and ≥ 70% stenosis are commonly accepted reference points for the interpretation of CCTA examinations and are used to guide management decisions. For example, the following table is taken from the 2014 SCCT Guidelines on the use of CCTA for ED patients and demonstrates the clinical practice recommendations based on the degree of stenosis.

Table 10 SCCT Sample Management Recommendations to ED Physicians

Degree of maximal coronary stenosis	Management recommendation
0%–25%	ACS unlikely; discharge is reasonable. Follow-up for minimal CAD at physician discretion
26%–49%	ACS unlikely; discharge is reasonable. Outpatient follow-up recommended for preventive measures
50%–69%	ACS possible; further evaluation indicated before discharge
>70%	ACS likely; admit for further evaluation

ACS, acute coronary syndrome, CAD, coronary artery disease.

Source: Raff 2014

Below 50% stenosis, acute coronary syndrome is considered unlikely. Above 70% stenosis, ACS is considered likely. Between 50% and 70% stenosis is considered indeterminate and requires further evaluation.

Finally, a comment about vessel size in terms of the primary endpoint. All segments were categorized as < 2 mm or ≥ 2 mm in diameter on the CRFs. The pre-specified study endpoint excluded segments < 2 mm from the analysis in both the original read and the re-read analyses. Additionally, all segments that were unevaluable (anatomically missing, distal to occlusion, or non-diagnostic) by ICA were excluded.

The measurement cut-off used was 2 mm, because vessels with a diameter of less than 2 mm are generally considered too small for intravascular intervention (such as stenting or angioplasty) and are thus not considered clinically relevant in terms of evaluating the sensitivity and specificity of CCTA vs ICA (Hausleiter 2007).

Statistical Analysis Plan

Unevaluable segments
Within the context of a diagnostically adequate CCTA study, individual coronary artery segments could be categorized as unevaluable by the readers. The SAP differed between the original read study and the re-read study in terms of the disposition of these segments in the analysis.

In the original read study, segments that were non-evaluable on CCTA were assigned the same result as the adjacent evaluable segment. In the re-read study, segments that were unevaluable by CCTA were assigned as false negative or false positive, depending on the SOR result. (I.e. If the ICA result in any given segment was ≥50% stenosis, and the CCTA result in that same segment was unevaluable, then the result was included as a false negative. Alternatively, if the ICA read was no significant stenosis, and the CCTA result was unevaluable, then the result was included as a false positive.)

Reviewer comment: Segments that could not be evaluated on the SOR ICA images were necessarily excluded from the analysis.

Majority reads
The SAP specified the use of majority reads for the original read study, in which the CCTA results were based on the consensus of two of the three CCTA readers. (The consensus rules were applied to the results of independent interpretations of the studies; the studies were not read collectively.) Discordant results, in which the three reads on any given segment consisted

of all possible results (stenosis, no stenosis, unevaluable) were excluded from the analysis.

The re-read study reported the results in terms of each reader independently.

Win criteria
For the original study, the sponsor specified that the subject level sensitivity and specificity would be estimated with exact two-sided 95% confidence intervals. The null and alternative hypotheses to be tested are:

H_0 Sensitivity ≤ 0.80 verses H_0: Sensitivity > 0.80, and
H_0 Specificity ≤ 0.80 versus H_0: Specificity > 0.80.

The initial plan was to enroll a total of 304 subjects, with target number of 258 evaluable subjects. The sample size estimation was based on the assumption that subjects would have a 50% probability of having significant luminal obstruction by ICA and 15% of the subjects being non-evaluable. For the re-read study, no win criteria were specified.

Reviewer comment: Additional evaluation of the statistical analysis plan is provided separately by the statistical review team.

Protocol Amendments

GE-189-002 was initially planned to include outcomes information for the study subjects over one year of follow-up. The outcomes portion of the study was later abandoned, after outcome data for a total of 53 of the study subjects was collected up to 6 months. The outcome data is not included with the submission. Additionally, enrollment in the study was terminated early, prior to enrollment of the pre-specified 258 study subjects.

The re-read study included no protocol amendments.

Data Quality and Integrity: Sponsor's Assurance

The sponsor's documentation and conduct throughout the review period attest to adequate data quality and integrity.

6.1.2. Study Results

Compliance with Good Clinical Practices

The sponsor states: "this study was conducted in full accordance with the Declaration of Helsinki, the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonization (ICH) and any applicable national and local laws and regulations" (pg 15, ge 189-002-study report body).

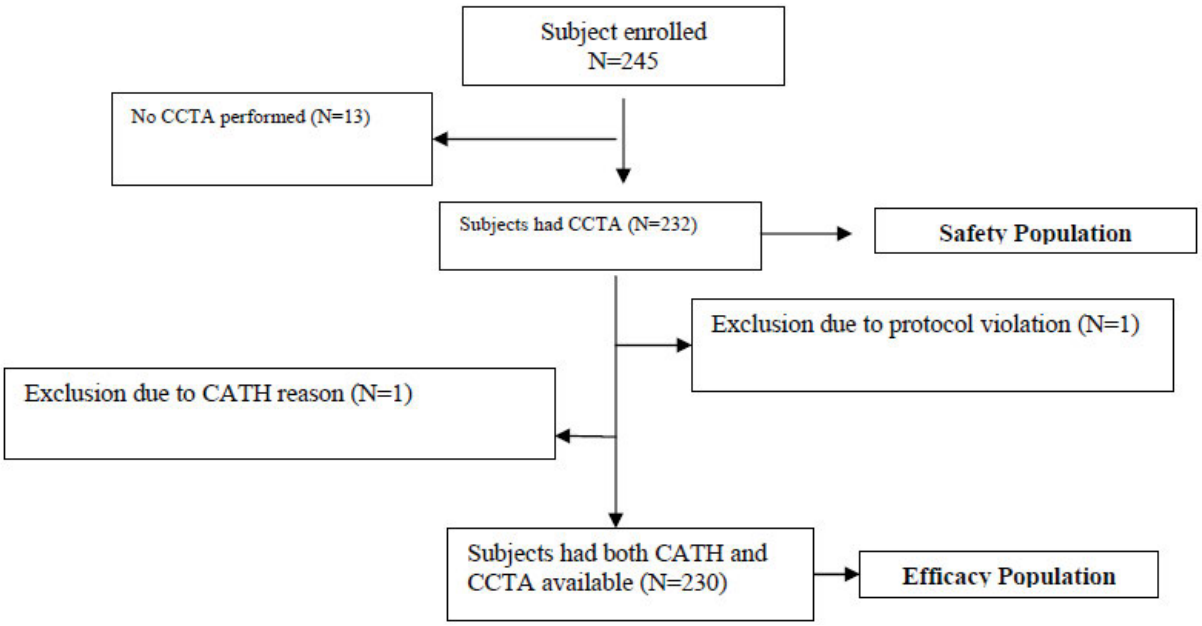
Financial Disclosure

The sponsor provides adequate documentation of having collected or attempted to collect disclosure forms from all study personnel. Disclosure forms included payments from the sponsor to three of the clinical investigators, two of which were in the form of research grants. One investigator was paid a retainer as a speaker/trainer for GE. The absence of financial disclosure forms for two study personnel and the disclosed details of financial interests of three of the study personnel do not raise significant questions about the integrity of the data.

Patient Disposition

A total of 245 subjects were enrolled in the study. 232 of the enrolled subjects underwent CCTA and comprised the safety population. Two of the 232 subjects who underwent CCTA were excluded from the efficacy population, one because of a protocol violation in which the CCTA was performed with non-study contrast, and the other because the ICA data was lost. Thus, 230 of the enrolled subjects completed both CCTA and ICA procedures and were included in the efficacy analysis.

Figure 4 Sponsor's diagram of subject disposition



Source: pg 40 ge 189-002-study report body

Reviewer comment: Note that in the diagram the word "CATH" refers to invasive coronary angiography (ICA).

Protocol Violations/Deviations

Only one protocol deviation was reported that required exclusion from the study, as commented upon earlier (non-study drug used for CCTA). There were minor protocol violations in terms of study drug dosing deviations from the study protocol instructions.

One subject experienced a coronary artery dissection during the ICA procedure and therefore showed artificially induced results in the first two RCA segments. For this subject, the results from these segments were not included in any efficacy analyses.

Table of Demographic Characteristics

The study was performed entirely in the U.S., at a total of 16 study centers. The study included an adequate representation of women (41%), a high percentage of Caucasians (88%), and a relatively high mean body mass index (BMI) of 31.4. The demographics of all 230 subjects included in the efficacy population are detailed in Table 11.

Table 11 Demographic characteristics of the primary efficacy analysis

Demographic Parameters	**Treatment Group** (N=230) n (%)
Sex	
Male	136 (59.1)
Female	94 (40.9)
Age	
Mean years (SD)	57.1
Min, max (years)	31, 82
Race[1]	
Caucasian	202 (87.8)
Black or African American	13 (5.7)
Other	15 (6.5)
Weight (kg)(mean)	92.5
BMI (kg/m^2)(mean)	31.4
Coronary Artery Calcium score (mean)	284.0

[1] Data on race and/or ethnicity other than "Causasian, Black, or other" not provided by study sponsor.

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

There was a high prevalence of risk factors for heart disease among the study subjects, including: family history of CAD (73%), hyperlipidemia (68%), hypertension (67%), obesity (39%), and diabetes (24%). Over half of the study subjects were current or ex-smokers, and $1/3^{rd}$ reported a sedentary lifestyle. Many study subjects were receiving cardiovascular medications including: ACE inhibitors (24%), angiotensin II antagonists (22%), beta blockers (51%), organic nitrates (21%), and platelet aggregation inhibitors (72%). These are detailed in Table 12.

Table 12 Sponsor's summary of cardiac medical history and prior cardiac tests

	All Subjects N=231 n (%)
Cardiac Risk Factors	
No risk factors	2 (0.9)
Hyperlipidaemia	158 (68.4)
Hypertension	155 (67.1)
Diabetes	56 (24.2)
Positive family history of CAD	169 (73.2)
Obesity	90 (39.0)
Lack of physical activity/sedentary lifestyle	78 (33.8)
Smoking	
Current smoker	46 (19.9)
Ex-smoker	82 (35.5)
Prior Non-invasive Cardiac Tests	
Stress ECG (no imaging)	26 (11.3)
SPECT MPI	102 (44.2)
Stress echo	27 (11.7)
Other[a]	99 (42.9)

CAD = Coronary artery disease; ECG = Electrocardiogram; MPI = Myocardial perfusion imaging; SPECT = Single photon emission computed tomography.
N = Total number of subjects in the safety population.
n = Number of subjects (out of N) that had an abnormal history for that body system.
Note: Cardiac medical history data were collected in Study GE-189-002.
[a] If a subject had more than one record of other prior non-invasive cardiac tests, he/she was counted once.

Source: pg 37 ge012-101-study report body

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The study involved a one-time administration of Visipaque, injected intravenously by the physicians and/or technologists at the study sites according to the protocol for the performance of the CCTA, as directed by the sponsor in the CT manual provided to the study sites.

The specified Visipaque dose included a main volume injection of 70-80 mL. The mean administered main volume dose of Visipaque was 73 mL, with a range of 50.0 – 106.0 mL. GE reports that one subject received more than the specified dose, 106 mL Visipaque, and 4 subjects received lower volumes than specified (one subject received 62 mL, and 3 subjects received 50 mL).

The protocol also included a test bolus of 20 mL of Visipaque as part of the dosing protocol, given immediately prior to the main injection in order to determine the scan time delay. GE reports that the majority of the subjects received a test bolus of 20 mL of Visipaque, with a range of 2 mL – 40 mL.

The administered doses and injection rates are captured in Table 13. Note that the table does not include the test bolus.

Table 13 Sponsor's summary of main volume dose, efficacy population

Dosing Parameter		All Subjects (N = 230)
VISIPAQUE™ administered	n (%)	230 (100%)
Administration performed per protocol	n (%)	216 (93.9)
Volume of VISIPAQUE™ administration (mL)	n	230
	Mean	72.76
	SD	(6.030)
	Min, Max	50.0, 106.0
Injection rate of main VISIPAQUE™ administration (mL/sec)	n	230
	Mean	4.97
	SD	(0.221)
	Median	5.00
	Min, Max	3.5, 5.5

Min = minimum; Max = maximum; SD = standard deviation
N = Total number of subjects in the efficacy population.
n = Number of subjects that had non-missing values for that parameter.
Note: Contrast medium data were collected in Study GE-189-002.

Source: pg 40 ge012-101-study report body

Procedural medications for heart rate control and vasodilation were given to nearly all of the study subjects: 78% of the subjects received metoprolol, and 98% received nitroglycerin. Table 14 summarizes the concomitant medications given during the study.

Table 14 Sponsor's tabulation of administered procedural medications - safety population

Medication	N=232 n (%)
IV beta-blocker or calcium channel blocker received	144 (62.1)
Beta-blocker administered	
Metoprolol oral	113 (48.7)
Metoprolol IV	69 (29.7)
Other beta-blockers	0 (0.0)
Calcium channel blocker administered	0 (0.0)
Nitroglycerin received	
Spray	187 (80.6)
Tablet	41 (17.7)

Source: pg 45 ge 189-002-study report body

Efficacy Results – Primary Endpoint

Original read results (GE-189-002)

The results for the primary endpoint were initially provided in terms of a majority read of the CCTA results. The majority read CCTA results for the sensitivity and specificity of the primary endpoint (≥ 50% stenosis threshold, subject-level analysis, vessels < 2 mm excluded) were reported as 96% and 83%, respectively.

The sponsor provided a post-hoc analysis of the original read results in terms of reporting the CCTA results per CCTA reader, instead of as a majority read. Additionally, the sponsor's post-hoc analysis adopted the more conservative method of categorizing unevaluable segments as "incorrect" (either false positive or false negative, depending on the SOR).

Reviewer comment: The post-hoc analysis described above was not included with the original presentation of the study data in 2009.

In the post-hoc analysis, the sensitivity results for the primary endpoint were 90%, 90%, and 98%, for readers, A, B, and C, respectively, and the specificity results were 70%, 76%, and 81%, as shown in the 2x2 tables below.

Table 15 2x2 tables of subject-level results per reader

	ICA +	ICA -	Total
CCTA +	44	33	77
CCTA -	2	137	139
Un-evaluable	3	11	14
Total	49	181	230

Reader 1: Sn, Sp = 90%, 76%

	ICA +	ICA -	Total
CCTA +	48	54	102
CCTA -	1	126	127
Un-evaluable	0	1	1
Total	49	181	230

Reader 2: Sn, Sp = 98%, 70%

	ICA +	ICA -	Total
CCTA +	44	33	77
CCTA -	4	147	151
Un-evaluable	1	1	2
Total	49	181	230

Reader 3: Sn, Sp =90%, 81%

The comparative results of the subject-level, vessel-level, and segment-level analyses are shown in Table 16, for the primary endpoint (in terms of definition of stenosis ≥ 50%, and small vessels excluded), according to the post-hoc analysis parameters, with confidence intervals included.

Table 16 Summary of sponsor's original read post-hoc results, for subject-, vessel-, and segment-level analysis, with ≥ 50% stenosis threshold, and segments < 2mm by ICA excluded

	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Subject-level				
Reader A	89.8 (77.8, 96.6)	75.7 (68.8, 81.8)	57.1 (45.4, 68.4)	98.6 (94.9, 99.8)
Reader B	98.0 (89.2, 100)	69.6 (62.4, 76.2)	47.1 (37.1, 57.2)	99.2 (95.7, 100)
Reader C	89.8 (77.8, 96.6)	81.2 (74.8, 86.6)	57.1 (45.4, 68.4)	97.4 (93.4, 99.3)
Vessel-level (summation of all vessels)				
Reader A	76.0 (63.1, 85.5)	85.2 (81.1, 88.5)	45.6 (36.1, 55.4)	98.1 (96.3, 99.0)
Reader B	89.3 (78.8, 95.0)	84.1 (80.6, 87.1)	34.7 (27.4, 42.8)	98.9 (97.6, 99.5)
Reader C	77.3 (64.8, 86.3)	89.1 (86.1, 91.4)	43.9 (35.1, 53.2)	98.1 (96.6, 99.0)
Segment-level (summation of all segments)				
Reader A	62.1 (50.5, 72.4)	87.6 (83.6, 90.7)	39.1 (31.4, 47.5)	98.6 (97.7, 99.1)
Reader B	77.0 (66.9, 84.7)	89.4 (87.0, 91.4)	30.3 (23.9, 37.6)	99.0 (98.3, 99.4)
Reader C	55.2 (43.8, 66.0)	91.4 (89.3, 93.1)	32.9 (25.9, 40.8)	98.3 (97.4, 98.9)

Source: pg 9 Summary of Clinical Efficacy

Reviewer comment: Only the results per reader are included in the table, as the majority read results were considered to be less relevant by the clinical and statistical review team.

Re-read results (GE-012-010)
The following table summarizes the sensitivity and specificity results, as well as PPV and NPV results, including confidence intervals for the results at the subject-level, vessel-level, and segment-level of the re-read study.

Table 17 Summary of sponsor's re-read results, for subject-, vessel-, and segment-level analysis, with ≥ 50% stenosis threshold, and segments < 2mm by ICA excluded

	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Subject-level				
Reader 1	67.6 (55.5, 78.2)	96.2 (91.9, 98.6)	88.9 (77.4, 95.8)	86.9 (80.9, 91.5)
Reader 2	78.9 (67.6, 87.7)	89.2 (83.3, 93.6)	76.7 (65.4, 85.8)	90.4 (84.6, 94.5)
Reader 3	88.7 (79.0, 95.0)	87.3 (81.1, 92.1)	75.9 (65.3, 84.6)	94.5 (89.5, 97.6)
Vessel-level (summation of all vessels)				
Reader 1	57.0 (46.5, 66.9)	96.5 (94.6, 97.8)	70.7 (59.7, 79.7)	93.9 (91.7, 95.5)
Reader 2	63.2 (52.5, 72.7)	94.9 (93.0, 96.2)	64.3 (54.3, 73.1)	94.6 (92.5, 96.2)
Reader 3	79.8 (70.8, 86.6)	91.2 (88.5, 93.4)	57.2 (48.6, 65.5)	96.9 (95.3, 97.9)
Segment-level (summation of all segments)				
Reader 1	40.0 (31.4, 49.3)	95.5 (94.1, 96.5)	34.2 (27.4, 41.7)	96.5 (95.3, 97.3)
Reader 2	47.4 (37.7, 57.4)	95.6 (94.5, 96.5)	38.8 (31.3, 46.8)	96.9 (95.8, 97.7)
Reader 3	60.0 (50.9, 68.4)	93.8 (92.1, 95.2)	36.2 (29.4, 43.6)	97.6 (96.7, 98.2)

Reviewer comment: The readers in the re-read study are called "1, 2, and 3" to differentiate them from the readers in the original read study ("A, B, and C"), because different radiologists and cardiologists interpreted the CCTAs for the two studies.

Data Quality and Integrity – Reviewers' Assessment

No significant quality/integrity review issues were identified that would undermine the sponsor's reported results.

Efficacy Results – Secondary and other relevant endpoints

Both the original read and the re-read studies included secondary endpoint analyses with ≥70% as the threshold for significant stenosis. For both studies, the results at the ≥70% stenosis threshold were similar to those at the ≥50% threshold.

An additional secondary endpoint was an analysis of the results with vessels segments <2 mm included. The analyses with the small vessels resulted in similar results for both the original read and the re-read studies, as compared to the analyses without the small vessels.

Additional Analyses Conducted on the Individual Trial

Given two sets of interpretations (original read and re-read) of the same sets of CCTA and ICA images, yielding two sets of study results, the clinical and statistical review teams concluded that the most valid analysis consisted of the application of the more robust statistical rules specified in the re-read study, to the imaging interpretation data of the original read study. The presence of an unintentional bias in the re-read results, based on the knowledge of the results of the original read study, could not be excluded. The statistical review team reanalyzed the data from the original read study, applying the more robust statistical rules from the re-read study. The results were identical to the sponsor's post-hoc analysis of the original read data, as provided above.

Finally, while the results were presented at the subject-level, at the vessel-level, and at the segment-level, the clinical review team determined that the vessel-level analysis reflected the most useful data clinically, in terms of providing some anatomic localization of disease, without the confounding errors inherent in classifying stenosis to belong to a specific portion of a vessel by imposing anatomic models of segmental anatomy.

The Table 18 below summarizes the data reflecting the review team's preference in terms of conveying the study results in the Clinical Trials section of the product label.

Table 18 Summary of most relevant results of Visipaque-enhanced CCTA, compared to ICA, at the vessel-level, with ≥ 50% stenosis threshold, and with segments < 2 mm by ICA excluded

Vessel-level (summation of all vessels)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Reader A	76.0 (63.1, 85.5)	85.2 (81.1, 88.5)	45.6 (36.1, 55.4)	98.1 (96.3, 99.0)
Reader B	89.3 (78.8, 95.0)	84.1 (80.6, 87.1)	34.7 (27.4, 42.8)	98.9 (97.6, 99.5)
Reader C	77.3 (64.8, 86.3)	89.1 (86.1, 91.4)	43.9 (35.1, 53.2)	98.1 (96.6, 99.0)

Reviewer comment: Note that these figures are the same as the vessel-level results in Table 16. The sponsor's post-hoc analysis of the data was identical the statistical review team's re-analysis of the data.

6.2. GE-012-096 "A prospective, multicenter registry study for clinical outcomes in subjects undergoing coronary CTA examination"

6.2.1. Study Design

Overview and Objective

GE-012-096 was a registry study designed to prospectively assess the value of Visipaque-enhanced CCTA findings in predicting the occurrence of downstream adverse cardiac events in stable patients with chest pain. Outpatient subjects who were referred to undergo a CCTA examination as part of their medical care were enrolled into the registry. Prognostic value was assessed in terms of the sensitivity, specificity, PPV and NPV of CCTA as compared to subjects' subsequent ICA findings (if performed) or binary subject outcomes during each follow-up period.

Trial Design

The trial design was a prospective and multicenter registry study. The study was conducted at 17 sites in the U.S. and Canada from 2008-2010. Subject information was collected at baseline, during and after Visipaque administration for CCTA, and at 1, 6 and 12 months after the Visipaque-enhanced CCTA procedure. The diagnostic efficacy of Visipaque-enhanced CCTA was measured in terms of sensitivity and specificity against patient outcomes as the SOR.

The CCTA images were interpreted by the site investigators as part of the subjects' routine medical care. The definition of a positive CCTA result was the presence of ≥50% luminal diameter reduction in at least one coronary artery segment.

Male and female patients over the age of 18 referred for CCTA at the study centers were screened for enrollment. The inclusion and exclusion criteria are summarized below.

Inclusion criteria:

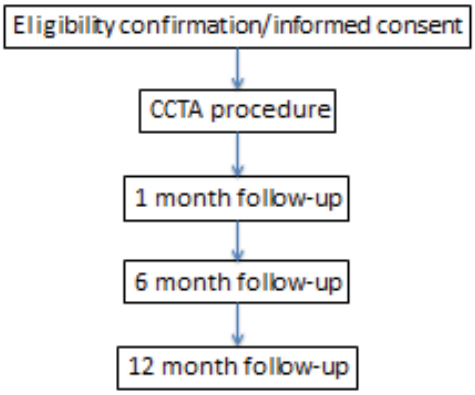
- Subjects with chest pain syndrome scheduled to undergo a Visipaque-enhanced CCTA examination for 1 of the following reasons:
    - Intermediate pre-test probability of CAD
    - An uninterpretable/equivocal stress test (exercise, perfusion, or stress echo).
- The subject was willing to allow the study doctor to make their medical records available to GE Healthcare.
- The subject agreed to be called at 1, 6, and 12 months for follow-up data.

Exclusion criteria:

- Subjects with known CAD confirmed by 1 of the following:
    - Previously myocardial infarction;
    - Pervious cardiac catheter angiography showing ≥50% obstruction;
    - Previous coronary revascularization, such as percutaneous coronary intervention or coronary artery bypass placement.
- Contraindications to receiving Visipaque.

The planned enrollment was 1000 study subjects at 20 centers. The actual enrollment was 885 subjects at 17 centers. The following is a simple overview demonstrating the linear nature of the registry study design, with no comparator arm.

Figure 5 Schedule of Events GE-096-101



While Visipaque 320 mgI/mL was exclusively used as the study drug, the protocol for Visipaque administration, including total dose and injection parameters, was not pre-specified, and was at the discretion of the prescribing physician based on the local clinical standards. Accordingly, there was variation in Visipaque dose and CCTA techniques. The minimum requirement for the CT scanner was 64-slice technology.

The standard of reference was either the subject's subsequent coronary artery angiography findings (if performed) or binary subject outcomes during each follow-up period. A clinical outcome consisted of the presence of 1 or more of the following events:

- MACE: cardiac death, non-fatal myocardial infarction, or unstable angina requiring hospitalization.
- All causes of death.
- Coronary revascularization: PCI, CABG.

Subject information captured for the trial on the CRFs included baseline demographics, CCTA dosage and results, adverse events, and subject outcomes at multiple follow-up time points. In the event that a subject reached an endpoint (death, MACE, or coronary revascularization), the subject was deemed to have completed the study with no further follow-ups obtained. An independent adjudicator who was not blinded to the results of the CCTA performed a review of all patient clinical information from subjects who had a coronary revascularization, MACE or death to determine if a qualified clinical outcome had occurred.

Study Endpoints

The primary study endpoint was the sensitivity and specificity of Visipaque-enhanced CCTA for the detection of downstream cardiac events (SOR) in subjects who were clinically referred to undergo CCTA.

Statistical Analysis Plan

The statistical analysis plan included information regarding sample size and power analysis, and definitions of the analysis endpoints and the analysis populations, most of which is covered in the trial design. In determining the sample size, the sponsor anticipated that 25% of the subjects would have disease. It was also estimated that the sensitivity would be about 90% and the specificity about 80%.

Reviewer comment: Additional evaluation of the statistical analysis plan is provided separately by the statistical review team.

Protocol Amendments

There were no protocol amendments during the study.

Data Quality and Integrity: Sponsor's Assurance

The sponsor states that the handling of data, including data quality control, complied with all applicable regulatory guidelines. No concerns regarding the sponsor's documentation were identified during the review.

6.2.2. Study Results

Compliance with Good Clinical Practices

The study was not conducted under the IND for Visipaque. The sponsor states that the study was conducted in full accordance with the Declaration of Helsinki and the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonization.

Financial Disclosure

The sponsor provides adequate documentation of financial disclosure forms and reports no disclosable information for any investigator.

Patient Disposition

Subject disposition is summarized in Table 19, which includes the primary indications for the referral for CCTA. Multiple indications could be included for a single patient.

Table 19 Sponsor's summary of subject disposition by primary indication

Disposition of Subjects	Overall	Primary Indication[a]						
		Chest Pain	Shortness of Breath	Dyspnea on Exertion	Post-MPI	Stress ECG	Stress Echo Test	Other
Number of Enrolled Subjects, N	885	723	312	182	311	100	56	174
Subjects in Safety Population[b], n (%)	874 (99)	715 (99)	304 (97)	178 (98)	308 (99)	98 (98)	56 (100)	173 (99)
Subjects in Efficacy Population[c], n (%)	857 (97)	701 (97)	299 (96)	175 (96)	302 (97)	95 (95)	55 (98)	170 (98)
Subjects Completing the Study[d], n (%)	850 (96)	694 (96)	292 (94)	174 (96)	303 (97)	95 (95)	54 (96)	166 (95)
Subjects Prematurely Discontinuing the Study[e], n (%)	35 (4)	29 (4)	20 (6)	8 (4)	8 (3)	5 (5)	2 (4)	8 (5)

N = number of subjects enrolled; n = number of subjects in the category; % = n/N*100%;
ECG = electrocardiogram. MPI = Myocardial perfusion imaging; Echo = echocardiography.
[a] Subjects may have more than one primary indication for CCTA.
[b] Subjects who were administered VISIPAQUE.
[c] Subjects in the safety population without any major protocol violation, and with evaluable baseline CCTA images and at least 1 follow-up assessment, except for subjects with an event (death, major adverse cardiac event [MACE], or coronary revascularization), in which case, no follow-up assessment is required.
[d] A subject is considered to have completed the study if the subject has had an event or has completed 12 months follow-up.
[e] Percentages based on the number of prematurely discontinued subjects.

Source: Source: pg 31 ge012-096-study report body

A total of 885 subjects were enrolled in the study. The safety population consisted of 874 subjects who were administered Visipaque. The efficacy population consisted of 857 subjects who had completed at least one follow-up evaluation. Within the efficacy population, 857, 853, and 843 subjects completed follow-up at 1 month, 6 months, and 12 months, respectively. Notably, 95% of the enrolled subjects completed the 12 month follow-up evaluation.

Nine subjects did not have at least one follow-up evaluation. Seven subjects (0.8%) were discontinued from the study because of too much calcium in the arteries, and two subjects (0.2%) were discontinued because of failure to achieve adequate heart rate control. As detailed in the next section, eight subjects were discontinued due to protocol violations.

Protocol Violations/Deviations

Eight protocol deviations occurred in 8 subjects; the data for all 8 subjects were excluded from the efficacy analysis. The most common deviation involved the discovery of a history of CAD (thus meeting exclusion criteria) after enrollment. Table 20 summarizes the protocol deviations.

Table 20 Sponsor's summary of protocol deviations by subject

Subject Number (b)(6)	Deviation Type	Actual Deviation
	minor	After the subject signed the informed consent, it was discovered that the subject did not meet the inclusion criteria.
	major	Prior catheterization documents coronary calcification.
	minor	Subject did not mention history of CABG during interview.
	major	Left heart catheterization procedure performed 1997, mild CAD of LAD.
	major	Left heart catheterization less than 50% plaque found in LAD.
	major	Left heart catheterization done in 2006, less than 30% disease in LAD.
	major	Left heart catheterization done in 2001, no intervention done, less than 50% CAD.
	minor	Informed consent signed after VISIPAQUE administered.

Source: pg 32 ge012-096-study report body

Table of Demographic Characteristics

The overall mean age of the study subjects was 58.8 years, with a range from 19-89 years. 51% were males and the subjects were predominantly white (78%). The subject demographics are summarized in Table 21 below.

Table 21 Sponsor's summary of subject demographics (safety population)

Variable		Overall N=874
Age at Consent (yrs)	Mean (SD)	58.8 (11.96)
	Range (min–max)	19 – 89
Age category	< 65 years, n (%)	568 (65)
	≥ 65 years, n (%)	306 (35)
Gender	Male, n (%)	443 (51)
	Female, n (%)	431 (49)
Race, n (%)	White, n (%)	684 (78)
	Black or African American, n (%)	86 (10)
	Asian, n (%)	38 (4)
	American Indian or Alaska Native, n (%)	5 (1)
	Other, n (%)	61 (7)
Height (cm)	Mean (SD)	169.9 (10.28)
	Range (min–max)	122-198
Weight (kg)	Mean (SD)	86.0 (20.41)
	Range (min–max)	45-177
BMI[b] (kg/m^2)	Mean (SD)	29.7 (6.39)
	Range (min–max)	15.2-71.0

N = number of subjects in the population; n = number of subjects in the category; SD = standard deviation; % = n/N*100%; ECG = electrocardiogram.
[a] Subjects may have more than one primary indication for CCTA.

Source: pg 33 ge012-096-study report body

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

The most common indications for CCTA were chest pain (82%), post-myocardial perfusion imaging (35%), shortness of breath (35%), and dyspnea on exertion (20%). Study subjects could have more than one primary indication for CCTA. 95% of the study subjects had one or more risk factors for CAD. The most common were hyperlipidemia (62%), HTN (60%), and positive family history of CAD (49%). The primary indications for the CCTA examination and the cardiac risk factors at baseline are summarized in Table 22.

Table 22 Sponsor's summary of primary indications for CCTA and cardiac risk factors at baseline

Baseline Characteristics	Overall (N=874)
Primary Indications for CCTA[a]	
Chest pain	715 (82%)
Shortness of breath	304 (35%)
Dyspnea on at exertion	178 (20%)
Post myocardial perfusion imaging	308 (35%)
Stress ECG	98 (11%)
Stress echocardiography test	56 (6%)
Others	173 (20%)
Risk Factor[a]	
Subjects with at least 1 risk factor, n (%)	834 (95%)
Hyperlipidemia, n (%)	538 (62%)
Hypertension, n (%)	522 (60%)
Positive Family History of CAD, n (%)	426 (49%)
Smoking - Ex, n (%)	272 (31%)
Sedentary Lifestyle, n (%)	251 (29%)
Obesity, n (%)	244 (28%)
Diabetes, n (%)	166 (19%)
Smoking - Current, n (%)	112 (13%)

N = number of subjects in the population; n = number of subjects in the category; % = n/N*100%;
CAD = coronary artery disease.
[a] Subjects may have more than 1 primary indication for CCTA or risk factor.

Source: pg 34 ge012-096-study report body

The presence of significant calcifications in the coronary arteries can create artifacts that can limit visualization of the vessels on CCTA. Coronary artery calcium levels on CT are graded and categorized into a standardized calcium score measurement in which less than 100 is considered normal or mild calcification, and over 400 is considered extensive calcification.

In the registry study population, the mean coronary calcium score was 216. The median calcium score was 15, indicating that the majority of the subjects had mild calcification in their coronary arteries. The calcium scores are summarized in Table 23.

Table 23 Sponsor's summary of coronary calcium score

Calcium Score – Overall	n	829
	Mean (SD)	216.4 (527.01)
	Range (min–max)	0 – 5077
	Median	15.0

Source: pg 35 ge012-096-study report body

Reviewer comment: Note that seven subjects (0.8%) were eliminated from the study because of too much calcium in the arteries to perform CCTA. Directions to exclude patients based on calcium scores was not specified in the protocol, but rather reflected individual site practices. Also note that in the GE-189-101 study, subjects were specifically not excluded on the basis of calcium scoring.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There are no concerns regarding treatment compliance given single dose protocol administered by study personnel.

Efficacy Results - Primary Endpoint

The sensitivity of Visipaque-enhanced CCTA for the detection of downstream cardiac events was 96.1%, 95.8%, and 94.7% at the 1-, 6-, and 12—month follow-up time points, respectively, and the specificity was 84.5%, 86.6%, and 87.0%. Fifty-one (6%) of the subjects developed one or more MACE-related clinical outcomes by 1 month, 71 (8%) by 6 months, and 76 (9%) by 12 month (76 subjects with events in total). At the 12-month follow-up, rate of MACE was 5.7% vs 0.1%, revascularization 39.7% vs 0.6%, and any cardiac event 41.4% vs 0.6% for patients with a positive CCTA finding versus those with a negative CCTA finding at baseline. The results are summarized in the Table 24, with the sensitivity and specificity (with confidence intervals) at 12 months highlighted.

Table 24 Summary of diagnostic efficacy of Visipaque-enhanced CCTA, compared to the SOR

Follow-up Period	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
1 month	49/51	681/806	49/174	681/683
	96.1% (86.5, 99.5)	84.5% (81.8, 86.9)	28.2% (21.6, 35.5)	99.7% (98.9, 100.0)
6 month	68/71	677/782	68/173	677/680
	95.8% (88.1, 99.1)	86.6% (84.0, 88.9)	39.3% (32.0, 47.0)	99.6% (98.7, 99.9)
12 month	72/76	667/767	72/172	667/671
	94.7% (87.1, 98.5)	87.0% (84.4, 89.3)	41.9% (34.4, 49.6)	99.4% (98.5, 99.8)

Source: pg 38 ge012-096-study report body

Reviewer comment: The PPV was notably low at all follow-up time points (28.2% - 41.9%), reflecting the high number of cases with positive CCTA findings at baseline but no subsequent cardiac events during the follow-up period.

Data Quality and Integrity - Reviewers' Assessment

No significant quality or integrity review issues were identified.

Dose/Dose Response

[Visipaque was administered intravenously at the discretion of the prescribing physician based upon institutional requirements for the CCTA procedures. The sponsor's rationale for the dose selection is "the Visipaque product package insert was to be consulted for the prescribing information". The administered doses are summarized in Table 25 below.

Table 25 Sponsor's summary of Visipaque 320 mg I/mL administration

Volume Administered (mL)	Safety Population (N=874)
Mean	91.3
SD	20.50
Minimum	30
Maximum	180
Median	95.0

Source: pg 36 ge012-096-study report body

Reviewer comment: As a registry study, dosing of the study drug and the specification for the performance of the CCTA was as per local clinical practice at the 17 study sites. While the administered doses were reported on the CRFs, the injection rate and protocol specifics such as the use of a dilute contrast phase are not reported. The high sensitivity and specificity of the study results are notable in the context of a wide range of total volume of Visipaque (30 mL – 180 mL) and in the context of studies having been performed as per clinical practice at multiple institutions, rather than with a standardized study protocol.

6.3. Supportive Evidence Based on Published Literature

6.3.1. Literature Review of Visipaque-Only Studies

The sponsor includes the published results from three CCTA studies which were performed exclusively using Visipaque 320 mgI/mL. These are briefly summarized here specifically in the context of the value they add to the pivotal studies performed by the sponsor. Note that only the published reports are available. No primary data is evaluated in this section.

Study #1: ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography)
Hoffmann U, Bamberg F, Chae CU, Nichols JH, Rogers IS, Seneviratne SK, Truong QA, Cury RC, Abbara S, Shapiro MD, Moloo J. Coronary computed tomography angiography for early triage of

patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. Journal of the American College of Cardiology. 2009 May 5;53(18):1642-50.

The ROMICAT study was a prospective, single-center, observational cohort study. The trial was designed to investigate the usefulness of Visipaque-enhanced CCTA in assessing patients with acute chest pain in the emergency department. The ROMICAT study is of particular value to the supplemental NDA application because it involves a critical study population that is not included in the sponsor's pivotal trials, namely ED patients with acute chest pain.

ED patients with acute chest pain represent a significant population both in terms of the frequency of the presentation in the U.S., and because of the potentially dire consequences of a missed diagnosis of ACS. Patients with clear evidence of ACS (positive blood tests, positive ECG findings) are effectively triaged to ICA or other intervention. It is patients without clear ACS (normal initial troponin, normal initial ECG) for whom an accurate non-invasive test with high negative predictive value would be of most use. Traditionally, these patients have been admitted for 24 hours of observation and serial blood work to rule out ACS. The ROMICAT study analyzed the ability of CCTA to effectively exclude coronary disease and allow for more timely discharge of patients without CAD.

The ROMICAT study was conducted from 2005-2007. Enrolled subjects underwent a Visipaque-enhanced CCTA and were then evaluated for the primary endpoint of occurrence of ACS (i.e., acute myocardial infarction or unstable angina pectoris) during the index hospitalization, and MACE during a 6-month follow-up. The CCTA procedure was performed using a 64-slice CT scanner, using 80-100 mL of Visipaque 320 mgI/mL. The images were assessed to detect coronary plaque and significant coronary stenosis, defined as ≥50% luminal narrowing. The evaluation category of "any plaque" referred to "any discernible structure that could be assigned to the coronary artery wall" and could be calcified or non-calcified.

Reviewer comment: The study description of "any plaque" would seem to imply that all stenoses not meeting criteria for ≥ 50% luminal narrowing would be captured in this category.

Among the 368 patients (mean age 53 ± 12 years, 61% men), 31 (8.4%) had ACS (8 had MI and 23 had UAP). After a mean follow-up of 6 months, none of the 337 subjects without ACS had had a MACE. The results are summarized in the following table.

Table 26 Sponsor's tabulation of diagnostic accuracy of CCTA for detection of ACS

Coronary CTA Finding	Sensitivity [95% CI]	Specificity [95% CI]	PPV [95% CI]	NPV [95% CI]	LR +	LR -
Acute coronary syndrome						
Any plaque	31/31 (100%) [89%, 100%]	183/337 (54%) [49%, 60%]	31/185 (17%) [12%, 23%]	183/183 (100%) [98%, 100%]	2.2	0.0
Coronary stenosis	24/31 (77%) [59%, 90%]	293/337 (87%) [83%, 90%]	24/68 (35%) [24%, 48%]	293/300 (98%) [95%, 99%]	5.9	0.3

CI = Confidence interval; CTA = computed tomography angiography; LR + = likelihood ratio given positive test result; LR - = likelihood ratio given negative test result; NPV = negative predictive value; PPV = positive predictive value

Source: 2.7.3 Summary of Clinical Efficacy pg 43

The CCTA finding of "any plaque" was associated with a perfect sensitivity because none of the patients without plaque had ACS. Accordingly, there were many patients who had "any plaque" but also had no ACS, thus leading to a low specificity of 54%. The CCTA finding of "coronary stenosis" was defined similarly to the pivotal GE-sponsored CCTA studies, with a positive test defined as at least one coronary segment with ≥50% luminal narrowing. The sensitivity and specificity results (with CIs) for coronary stenosis were 77% (59, 90) and 87% (83, 90), respectively. Seven of the 31 subjects in whom a significant stenosis was excluded by CCTA had ACS, highlighting the significant limitation of the test in terms of detecting significant stenosis or limitations of the stenosis endpoint.

The study discussion includes the important observation that about the half of the study population (50.3%, 183 out of 368) had no plaque, which was 100% sensitive for the absence of ACS, indicating that early performance of CCTA can significantly improve patient evaluation and management in the ED.

Study 2: VCT001

Budoff MJ, Kalia N, Cole J, Nakanishi R, Nezarat N, Thomas JL. Diagnostic accuracy of Visipaque enhanced coronary computed tomographic angiography: a prospective multicenter trial. Coronary artery disease. 2017 Jan 1;28(1):52-6.

This study was originally conducted from 2005-2006 by GE Healthcare to evaluate the diagnostic performance of Visipaque-enhanced CCTA as compared to ICA. The sponsor terminated the study early, after 99 subjects were enrolled (96 of whom completed the study). The enrolled subjects consisted of patients with typical or atypical chest pain who were referred for ICA. The CCTA studies were interpreted using ≥70% luminal narrowing as the definition of significant stenosis. The original primary study endpoint was accuracy at the subject-level and the threshold for success was >82.5% The results as reported in the statistical report for the original study was 80.2% accuracy of CCTA to detect ≥70% luminal narrowing, as compared to ICA. The result was below the target threshold.

Several years later, a study investigator, Dr. Budoff, proposed to develop a published report of the study's findings, based upon a re-read of the available imaging information. According to GE, the re-read study employed methodology such as consensus reads, which were not intended to verify efficacy in a regulatory submission. Of the 96 subjects who completed the study, the data from 77 of the subjects was available for the re-read, the other data having been lost or deleted. The re-analysis included a re-read of the CCTA images using consensus reads. Both ≥50% and ≥70% stenosis thresholds were evaluated. The results are summarized in the table below. Note that confidence intervals are not provided by the sponsor.

Table 27 Sponsor's tabulation of efficacy of Visipaque-enhanced CCTA vs QCA, based on the re-read study of a portion of the initial study population

	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Per Patient				
≥50%	85%	90%	81%	92%
≥70%	100%	92%	75%	100%
Per Vessel				
≥50%	85%	95%	74%	97%
≥70%	97%	96%	65%	97%

The sensitivity and specificity results are very high for both definitions of significant stenosis (≥50% and ≥70%) and at both the subject-level and at the vessel-level, indicating the utility of CCTA as compared to ICA to identify significant stenoses. While the sensitivity and specificity results are high, there are significant problems in the reanalysis methodology, including the large amount of missing data (20% of the study data was missing at the time of the reanalysis), and the consensus read technique for CCTA interpretation, limiting the value of the results. Additional consideration should include the failure of the initial analysis (which included all of the study data) to succeed on the primary study endpoint.

Study #3: PICTURE study (Perfusion Imaging and CT – Understanding Relative Efficacy)
Budoff MJ, Li D, Kazerooni EA, Thomas GS, Mieres JH, Shaw LJ. Diagnostic accuracy of noninvasive 64-row computed tomographic coronary angiography (CCTA) compared with myocardial perfusion imaging (MPI): the PICTURE Study, a prospective multicenter trial. Academic Radiology. 2017 Jan 31;24(1):22-9.

The PICTURE study was a prospective multicenter trial to evaluate the diagnostic performance of Visipaque-enhanced CCTA to detect obstructive coronary stenosis compared to myocardial perfusion imaging (MPI) using QCA as a reference standard. The study involved patients with typical or atypical chest pain who were referred for evaluation with MPI and then underwent

CCTA as the study procedure. Patients with either positive MPI findings or abnormal CCTA findings were clinically referred for ICA.

Consensus reads were used for CCTA evaluation. The presence of significant stenosis was defined as both ≥50% and ≥70% luminal narrowing. Subject-level and vessel-level analyses were performed. CCTA, MPI, and QCA readers were blinded to the results of the other tests. A total of 230 subjects were enrolled, 48 of whom underwent ICA (182 did not undergo ICA).

The primary efficacy endpoint was the sensitivity of CCTA versus MPI for the diagnosis of CAD at the subject level when compared to QCA as the SOR. The results are shown in the following table.

Table 28 Sponsor's tabulation of diagnostic accuracy statistics from the PICTURE study, including only the study population that underwent ICA (48 of 230 total subjects)

	Sensitivity % (95% CI)	Specificity % (95% CI)	Positive Predictive Value (PV) % (95% CI)	Negative PV % (95% CI)
CT Angiography				
≥50%	92.0 (74.0,99.0)	78.3 (56.3,92.5)	82.1 (63.1,93.9)	90.0 (68.3,98.8)
≥70%	92.6 (73.8,99.0)	88.9 (70.8,97.7)	84.2 (60.4,96.6)	82.8 (64.2,94.2)
MPI				
≥50%	54.5 (34.9,75.6)	87.0 (66.4,97.2)	82.4 (56.6,96.2)	64.5 (45.4,80.8)
≥70%	59.3 (34.0,78.2)	81.5 (61.9,93.7)	70.6 (44.0,89.7)	71.0 (52.0,85.8)

The patient-level sensitivity for the ≥50% and ≥70% stenosis thresholds by QCA for CCTA was 92.0% and 92.6%, respectively, while the sensitivity of MPI was 54.5% and 59.3%, respectively. The sensitivity was thus considerably higher for CCTA than for MPI. The results suggest a clinical role for CCTA for the accurate identification of significant coronary stenoses in the population of outpatients with stable chest pain. The study results are limited by the small sample size (the sensitivity and specificity are based on the outcomes for 48 subjects), and by the consensus read methodology for the CCTA interpretation, which does not reflect how CCTA examinations are interpreted in clinical practice.

6.3.2. Literature Review of Major Recent Studies with Multiple Contrast Agents, Including Visipaque

The sponsor provides a summary of recent CCTA studies which included the use of multiple iodinated contrast agents, not exclusively or specifically Visipaque. Of these, the most significant is the PROMISE study, because of the large sample size and the robust study design. The PROMISE study is briefly reviewed.

PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) Trial

Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA. Outcomes of anatomical versus functional testing for coronary artery disease. New England Journal of Medicine. 2015 Apr 2;372(14):1291-300.

The aim of the large scale PROMISE trial was to determine the usefulness of CCTA in the assessment of patients with acute chest pain. The study was prospective, controlled and randomized, with a comparative effectiveness design, comparing anatomic imaging with CCTA to functional imaging. The study enrolled 10,003 symptomatic outpatients without known CAD who were referred for non-urgent, noninvasive cardiovascular testing for the evaluation of suspected CAD. Subjects were randomized to the strategy of initial anatomic testing with the use of CCTA or to initial functional testing (exercise ECG, nuclear stress testing, or stress echocardiography). The contrast used for CCTA was not specified. All CCTA procedures were done on ≥64-slice multidetector CT scanners. The tests were performed and interpreted by local physicians who made all subsequent clinical decisions. Follow-up was for a minimum of one year, with a mean follow-up period of 25 months. The study was conducted from 2010 – 2013, in 193 sites in the U.S., including both community and academic practices.

The primary endpoint was a composite of major cardiovascular events (death, MI, or hospitalization for unstable angina) over the follow-up period, or major complication of cardiovascular procedures or diagnostic testing (stroke, major bleeding, renal failure, and anaphylaxis) that occurred within 72 hours of testing. The secondary endpoints included the incidence of invasive cardiac catheterization showing no evidence of CAD (defined as an absence of any stenosis greater than or equal to 50%), as well as cumulative radiation exposure (within 90 days). A committee adjudicated all primary and secondary endpoint events in a blinded fashion.

The primary endpoint occurred in 164 (3.3%) of the patients in the coronary CTA group and in 151 (3.0%) of the patients in the functional testing group, indicating no significant outcome benefit for patients with initial evaluation with CCTA as compared to functional testing, in outpatients with suspected CAD. The overall primary event rate was 3.1%, significantly lower than the anticipated event rate of 8%. The authors suggest that the low event rate may be due to higher use of cardiovascular medications over the past decade. In order to demonstrate a difference in patient outcomes with different testing strategies given the low event rate for patients with new-onset stable chest pain, the study would have required either a large incremental test effect driving differences in downstream care or an extremely large study sample. Additionally, the follow-up period may be been insufficient to detect improved outcomes in either arm related to the implementation of preventive strategies secondary to the study test results, strategies that may have more obvious benefit over a longer time of observation.

The contrast-enhanced CCTA group was associated with fewer invasive angiograms (3.4%) showing no significant CAD as compared to the functional group (4.3%), but the result did not achieve statistical significance. It was notable that 72.1% of patients undergoing ICA after coronary CTA had significant coronary disease, compared to 47.5% of subjects in the functional test groups. This suggests improved diagnostic performance of CCTA over functional testing to identify significant disease, a finding that may be critical in the avoidance of unnecessary invasive angiography which is associated with significantly increased morbidity and cost as compared to CCTA.

A secondary endpoint was the comparative radiation exposures between the study arms. Patients in the coronary CTA cohort had an overall exposure (including follow-up testing) of 12.0 ± 8.5 mSv, which was significantly higher than in the cohort randomized to functional testing (10.1 ± 9.1 mSv). This result, however, is confounded by the 33% of subjects in the functional arm who had no radiation exposure at all (stress ECG or exercise ECG testing). Compared to patients who underwent nuclear stress testing as the initial evaluation, the cumulative radiation exposure was lower significantly in the CTA group (10.1 mSv) than in the functional-testing group (12.6 mSv)

SCOT-HEART (CT Coronary Angiography in Patients with Suspected Coronary Heart Disease) and SCOT-HEART Follow-up

The S. C. O. T. "CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial." The Lancet 385.9985 (2015): 2383-2391.

Williams MC, Hunter A, Shah AS, Assi V, Lewis S, Smith J, Berry C, Boon NA, Clark E, Flather M, Forbes J. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. Journal of the American College of Cardiology. 2016 Apr 19;67(15):1759-68.

The SCOT-HEART study and the subsequent post hoc analysis based on the electronic health records are briefly commented upon here, particularly in terms of how they complement the results from the PROMISE trial. Like the PROMISE trial, SCOT-HEART was a large scale effort prospectively evaluating the use of CCTA for the assessment of patients with suspected coronary disease. 4142 patients were suspected CAD were randomized to receive either only standard workup (in most cases, functional testing) or CCTA in addition to the standard workup. The contrast agents were not specified. CCTA scans were acquired using 64- or 320-detector row scanners.

In the initial analysis presented in the first publication above, the median follow-up period was 1.7 years. CCTA was associated with a non-significant 38% reduction in fatal and non-fatal MI.

The post hoc analysis demonstrated that the performance of CCTA was associated with markedly lower rates of normal coronary angiography (20 vs. 56; p<0.001) and higher rates of significant coronary artery disease (283 vs. 230, p=0.005) on subsequent invasive angiograms, as compared to the patients who underwent standard evaluation without CCTA.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The sponsor's two pivotal studies are fundamentally different in design, precluding an integrated presentation of efficacy data. Instead, this section includes a brief discussion of the totality of the efficacy data grouped according to the type of data (CCTA compared to ICA, CCTA compared to clinical outcomes) and according to the subject population (stable outpatients, acute ED patients).

Reviewer comment: Outpatients and ED patients are considered separately because they comprise two potentially distinct subtypes of the pathophysiology of coronary artery disease. Outpatients with stable chest pain due to CAD typically have reproducible chest pain secondary to insufficient coronary blood flow caused by stenosis from the presence of stable coronary artery plaque(s). Patients with acute chest pain due to CAD often have disease related to coronary thrombosis, as can occur acutely in the setting of plaque rupture. Both populations, however, can be indeterminate for CAD at presentation and can require imaging tests to evaluate for the presence or absence of significant CAD as the cause of their symptoms, potentially leading to the diagnosis of stable angina in the outpatient scenario, and acute coronary syndrome in the ED scenario.

Diagnostic Performance of CCTA compared to ICA – Stable Outpatient Population
The first GE study (GE-189-002 and re-read GE-012-101) evaluated the diagnostic performance of CCTA as compared to the gold standard of ICA in a population of stable outpatients with chest pain or other symptoms suggestive of coronary artery disease. The clinical and statistical review teams agreed that the best summary of the study results is the sensitivity and specificity of CCTA compared to ICA as considered at the vessel-level, using the threshold of ≥50% as the definition of significant stenosis. The vessel-level analysis allows for a consideration of the ability of CCTA to provide anatomic localization, an important feature of CT as an anatomic modality. The sensitivity and specificity ranges for the three readers at the vessel level were 76-89% and 84-89%, respectively. Consideration can also be given to the sensitivity and specificity results at the subject level. While these results do not include anatomic value, they are relevant for this particular test in the context of being used to "rule-out" significant disease at the patient level in clinical practice. The sensitivity and specificity ranges for the three readers at the subject level were 89-90% and 70-81%, respectively.

The sponsor refers to two literature reports that also consider CCTA compared to ICA in the outpatient population. The first, VCT001 (Budoff 2017a) is limited in particular by almost 20% missing data. The published sensitivity and specificity for CCTA at the ≥50% threshold for stenosis, and considered at the vessel-level, are 85% and 95%, respectively, slightly better results compared to GE-189/GE-012-101.

The PICTURE trial (Budoff 2017b) is the second study referenced in this category. The reported sensitivity and specificity at the subject-level with ≥50% threshold for stenosis was 92% and 78%, respectively. The study results are limited by a small sample size (the sensitivity and specific are based on the outcomes for 48 subjects), and by the consensus read methodology for the CCTA interpretation.

Diagnostic Performance of CCTA compared to ICA – Rule out ACS (ED) Population
No data provided.

Patient Outcomes Data for CCTA – Stable Outpatient Population
The second pivotal study provided by GE was a registry study (GE-012-096) designed to assess the prognostic value of CCTA in stable patients with suspected CAD, compared to subject outcomes over one year of follow-up. The results, provided in terms of the sensitivity and specificity of CCTA to detect downstream cardiac events, were 95% and 87%, respectively. In the clinical practice setting without a centrally prescribed CCTA technique, a negative CCTA carried excellent prognosis in terms of downstream cardiac events, with a NPV of over 99%. The results of the GE-sponsored registry study underscore the notion that Visipaque-enhanced CCTA is technically robust under conditions of locally varying clinical practice, without central pre-specification of a contrast administration and CT scanning protocol.

The PROMISE, SCOT-HEART and the SCOT-HEART follow-up analysis all fall into this category. The three trials used various contrast agents, and the percentage of Visipaque use, if any, is unknown. They are included because of the robust prospective, randomized controlled study design in large patient populations, and because of the assumption that high concentration iodinated contrast agents are generally interchangeable in terms of efficacy.

The PROMISE study demonstrated no significant improvement in clinical outcomes from the strategy of initial CCTA, as opposed to functional testing. The SCOT-HEART and the subsequent post hoc analysis demonstrated that the performance of CCTA was associated with a reduction of the incidence of MIs as compared to the group that did not undergo CCTA, but the result did not achieve significance. Results from all three studies suggested that initial evaluation with CCTA was associated with a decrease in the number of invasive angiograms showing no evidence of significant CAD, as compared to functional or standard evaluation.

Patient Outcomes Data for CCTA – Rule out ASC (ED) Population

The supportive evidence from the ROMICAT trial is especially useful because it is the only trial known to have evaluated outcomes in the acute ED population using Visipaque exclusively for the CCTA examinations. None of the sponsor submitted pivotal trials enrolled ED patients. The sensitivity and specificity of the finding of significant disease by the CCTA (≥50% stenosis, subject-level) for the outcome of ACS and MACE was 77% and 87%, respectively. The study also analyzed the value of the designation of "any plaque" on CCTA. The finding of no plaque had a 100% negative predictive value for ACS or MACE, suggesting that a negative CCTA test result can very effectively exclude the possibility of ACS or MACE. This was of particular significance because half of the study participants who had presented to the ED and were suspected of having ACS had no plaque, and thus an early CCTA could potentially have a significant impact on the management of this ED demographic, in terms of timely and safe discharge and the avoidance of more invasive testing.

The conclusions from the totality of the reviewed data from both the sponsor's CCTA trials and the literature, namely that CCTA is an effective diagnostic aid for the population of patients with suspected coronary disease, mirror the 2010 Appropriate Use Criteria for Cardiac CT, a collective guideline published by the American College of Cardiology Foundation in concert with the SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR.

Table 29 CCTA Appropriate Use Criteria (From ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR)

Detection of CAD in Symptomatic Patients Without Known Heart Disease*

Indication		Appropriate Use Score (1–9)		
Nonacute Symptoms Possibly Representing an Ischemic Equivalent				
Pretest Probability of CAD		**Low**	**Intermediate**	**High**
1.	• ECG interpretable AND • Able to exercise	U (5)	A (7)	I (3)
2.	• ECG uninterpretable OR • Unable to exercise	A (7)	A (8)	U (4)
Acute Symptoms With Suspicion of ACS (Urgent Presentation)				
3.	• Definite MI	I (1)		
4.	• Persistent ECG ST-segment elevation following exclusion of MI	U (6)		
5.	• Acute chest pain of uncertain cause (differential diagnosis includes pulmonary embolism, aortic dissection, and ACS ["triple rule out"])	U (6)		
Pretest Probability of CAD		**Low**	**Intermediate**	**High**
6.	• Normal ECG and cardiac biomarkers	A (7)	A (7)	U (4)
7.	• ECG uninterpretable	A (7)	A (7)	U (4)
8.	• Nondiagnostic ECG OR • Equivocal cardiac biomarkers	A (7)	A (7)	U (4)

*Note: All indications are for CTA unless otherwise noted.
A indicates appropriate; I, inappropriate; and U, uncertain.

Source: Taylor 2010

The table summarizes CCTA usage recommendations for the population of patients with

symptoms suggestive of CAD, but without known heart disease. The top half of the table indicates appropriateness criteria for stable outpatients, whereas the bottom half describes usage for acute ED patients. The letter "A" designates appropriateness of the test. CCTA is described as appropriate for both non-acute and acute populations with low and intermediate pretest probability of CAD. In general terms, high risk patients in both groups would be better served by ICA, allowing for concurrent intervention if appropriate, whereas for the lower risk patients, CCTA serves as a gatekeeper to ICA.

7.1.1. Dose and Dose-Response

No dose-response studies were conducted for this efficacy supplement. Several publications address the optimization of iodinated contrast dosing and injection rate for CCTA protocols. Specifically, the 2009 SCCT Guidelines for performance of CCTA recommend a total contrast volume of 50-120 mL of high iodine concentration agent, with injection rates of 4-7 mL/s (Abbara 2009).

The GE-189-002 study protocol called for a main dose of 70-80 mL of Visipaque, injected at 4-5 mL/s (not including the initial 20 mL Visipaque dose commonly given to calculate scan time delay in preparation for the study). The actual main dose administered was 50-106 mL. The mean administered dose in the registry study was 91 mL, with a range of 30 – 180 mL; no dose or injection rate was pre-specified in the registry study. The dosing guideline for the performance of CT on the VIsipaque label is 75-150 mL, a range which is inclusive of the mean administered dose for each study. There is no Visipaque CT injection rate currently specified on the label.

7.2. Integrated Assessment of Effectiveness

The results from the pivotal GE-sponsored CCTA trials, supported by additional evidence from published reports, provide adequate evidence in favor of the proposed indication statement: Visipaque-enhanced CCTA can assist in the diagnostic evaluation of patients with suspected coronary artery disease.

CCTA is technically complicated to perform. The effectiveness of the test depends on the skilled execution of the study by the responsible physicians and technologists. This review and the relevant associated labeling provide a general framework in terms of dosing and injection rate reflective of the parameters in the GE-189-002 study, which was conducted from 2006-2007 on a 64-detector row scanner. Continuous technologic evolution requires detailed optimization on a site specific basis in order to achieve ideal contrast concentration in the coronary arteries at the time of scanning. The administered contrast dose and injection rate need to be determined within the context of site specific scanner technology, reconstruction algorithms, and ECG gating applications, patient specific variables including size and heart rate, as well as other adjustable parameters including tube voltage, scan time delay, and dilution

phase. The effectiveness of CCTA in clinical practice is well demonstrated in the sponsor's CCTA registry study in which 857 patients underwent CCTA at 17 institutions with no instructions to the study sites other than that the examinations should be done according to local institutional practices. The effectiveness of CCTA across practice patterns is demonstrated by the sensitivity and specificity results of 95% and 87%, respectively, to predict downstream cardiac outcomes, in the context of reported Visipaque dosing ranging from 30-180 mL.

While CCTA in general and Visipaque CCTA specifically have clearly demonstrated clinical utility, the test has limitations, the most notable of which is the lack of functional information regarding the heart. Recent studies have suggested that the functional significance of stenoses should guide patient management. For example, stenotic lesions that do not induce ischemia may be optimally managed medically, as opposed to interventional revascularization (Tonino 2009). Functional assessment of stenoses by measuring the fractional flow reserve (FFR), a comparison of maximal blood flow in a stenotic artery to the normal maximal flow, are common components of ICA examinations, and are being increasingly applied to CCTA imaging (Koo 2011). No evaluation or comparison of the use of FFR is included with this application. In current practice, functional imaging remains largely the domain of MPI, which is often obtained in conjunction with CCTA.

While CCTA without concurrent functional assessment may not allow for an analysis of the significance or optimal treatment of detected disease, the sponsor's application clearly supports the clinical value of CCTA for the reliable determination of the absence of significant CAD, exemplified by low rates of false negative results across the studies. Perhaps most notable are the results from the ROMICAT study. The ROMICAT study not only assessed luminal narrowing in terms of greater than or less than 50% stenosis, the study also assessed outcomes (ACS, MACE) based on the presence or absence of any plaque. Not unexpectedly, none of the patients categorized as "no plaque" had ACS or MACE events. What was notable was that half of the study subjects (183 of 337), consisting of patients presenting to the ED with chest pain for rule out acute coronary syndrome, had no plaque, highlighting the significant benefit of CCTA in terms of rapid testing and early and safe discharge of a significant portion of ED patients.

8 Review of Safety

8.1. Safety Review Approach

Visipaque has been used for intra-arterial and intravenous applications in the US for over 20 years, with safety data collected since the initial approval of Visipaque in Europe in 1993. The safety review is focused on the question of whether the use of Visipaque for CCTA is associated with unique safety signals (including new adverse reactions, as well as increased rates of known

adverse reactions to Visipaque) as compared to the use of Visipaque for currently labeled applications.

Safety data regarding the use of Visipaque for CCTA include both the GE-sponsored pivotal CCTA trials submitted with this application, as well as a review of the GE Adverse Events Database (GAED) for all reactions reported in the context of cardiac imaging. The GE-sponsored studies were not conducted under IND and the safety data collected was limited. Specifically, the protocols for both studies limited the reporting period of adverse events to 48 hours after Visipaque administration, and the sites were instructed to report only serious and unexpected adverse events. Adverse events rates from the CCTA trials thus could not be pooled with the AE data for previous trials with Visipaque.

The available safety data is presented independently in the first three sections and then integrated contextually in the last section, with portions of the template omitted as non-applicable to this efficacy supplement:

- Section 8.2 Review of the Safety Database: a review of the safety data from the GE-sponsored pivotal CCTA studies submitted with this application
- Section 8.3 Submission Specific Safety Issue: Drug-drug interactions between Visipaque and beta blockers.
- Section 8.4 Safety in the Postmarketing Setting: a review of Visipaque post-marketing safety
- Section 8.5 Integrated Assessment of Safety: a consideration of the totality of the safety data, in the context of safety concerns specific to the use of Visipaque for CCTA.

8.2. Review of the Safety Database – GE-189-002 and GE-012-096

8.2.1. Overall Exposure

The pivotal GE-sponsored studies GE-189-002 and GE-012-096 included a total of 1106 subjects who received Visipaque and were thus included in the safety population. Each subject received one dose of the study drug. The ranges of the doses administered in GE-018-002 and GE-012-096 were 50-106 mL and 30-180 mL per patient, respectively, doses that can be considered in context of the currently labeled Visipaque dose for general CT applications, 70-150 mL.

Reviewer comment: The GE-012-101 study was a re-read of the original images in the GE-189-002 study and involved no additional safety data.

8.2.2. Deaths

GE-189-002

There were no deaths reported during the protocol-specified 48 hour follow-up period for reporting AEs after Visipaque injection in study GE-189-002. Up to six months of follow-up for patient outcomes was performed for 53 out of the 232 subjects, during which time four subject deaths were reported. One of the cases of death was later determined to represent a coding error since the subject had subsequently returned for follow-up, resulting in a total of three deaths in the follow-up interval. The following text represents the sponsor's details of the subject deaths, from page 7 of the Summary of Clinical Safety.

> Subject (b)(6) was a 52-year-old male who had the study CCTA procedure on (b)(6). At the month 6 follow-up check, medical records indicated that he died on (b)(6) The death was not cardiac related.
>
> Subject (b)(6) was a 67-year-old male who had the study CCTA procedure on (b)(6). At the month 1 follow-up he was reported as deceased. This subject had coronary artery bypass graft surgery and experienced cardio-pulmonary arrest at home 2 days after being discharged from the hospital which resulted in death.
>
> Subject (b)(6) was a 54-year-old female who had the study CCTA procedure on (b)(6). Death was reported at the month 6 follow-up: she was found dead in her bed on (b)(6) by her daughter. She appeared to have died in her sleep. No autopsy was performed per her family request, and etiology of death was unknown.

Reviewer comment: The three subject deaths were not counted as adverse events in the study because they because they did not occur during the pre-specified AE reporting period. Based on the case summaries, I agree that the deaths do not appear to be related to the administration of Visipaque.

GE-012-096
There were no deaths reported during the protocol-specified 48 hour follow-up period for reporting AEs after Visipaque injection in study GE-012-096. Subjects in this registry study were followed over one year for the occurrence of major adverse cardiac events, as well as all causes of death. There were a total of four subject deaths collected as MACE outcomes in the study.

8.2.3. Serious Adverse Events

Both study protocols included the recording of all serious adverse events that occurred up to 48 hours after the Visipaque-enhanced CCTA procedure, allowing for the pooling of the SAE data between the studies, and consideration of an incidence rate. Of the total safety population of 1106 subjects, serious adverse events were reported in 8 subjects, for an incidence rate of

0.7%. None of the serious adverse events reported were considered related to Visipaque administration.

GE-189-002
No SAEs were reported for the 232 patients in the safety population of the GE-189-002 study.

GE-012-096
In the GE-012-096 study, a total of 10 SAEs were reported in the 48 hour AE reporting period in 8 of 874 (1%) of subjects. Two SAEs were severe in intensity, seven were moderate, and one was mild. None of the SAEs were considered related to Visipaque administration, and none led to study discontinuation.

Table 30 Sponsor's summary of SAEs GE-012-096

	All Events (N=874)		Intensity	Causal Relationship to Visipaque	Outcomes
System Organ Class Preferred Team[a]	Number of Subjects n (%)	Number of Events	Number of Events	Number of Events	Number of Events
Subjects with at least one SAE	8 (1%)	10			
Cardiac disorders					
Angina pectoris	3 (<0.5%)	3	Moderate (1); Severe (2)	Not suspected (3)	Resolved (3)
Coronary artery disease	2 (<0.5%)	2	Moderate (2)	Not suspected (2)	Resolved (2)
Coronary artery stenosis	1 (<0.5%)	2	Moderate (2)	Not suspected (2)	Resolved (2)
General disorders and administration site conditions					
Non-cardiac chest pain	1 (<0.5%)	1	Mild	Not suspected	Resolved
Respiratory, thoracic and mediastinal disorders					
Pulmonary embolism	1 (<0.5%)	1	Moderate	Not suspected	Resolved
Vascular disorders					
Aortic aneurysm	1 (<0.5%)	1	Moderate	Not suspected	Resolved

Source: pg 8, Summary of Clinical Safety

Review of the case summaries for the eight subjects (with 10 SAEs) demonstrates that in seven of the cases the SAE represented findings on the CCTA study: coronary stenosis (5), pulmonary embolism (1), and aortic aneurysm (1). One patient had chest pain that was determined to be non-cardiac. All of the SAEs were reported as resolved following appropriate management.

Reviewer comment: I agree that the SAEs do not appear to represent reactions to Visipaque administration.

8.2.4. Treatment Emergent Adverse Events and Adverse Reactions

The sponsor coded adverse events terms using MedDRA version 11.0 for both studies. There

were significant differences in reporting practices between the two studies. Specifically, while both study protocols specified the reporting of only unexpected or SAE, in the GE-189-002 study, some sites mistakenly reported all AEs on the CRFs, and these were retained in the database. In study GE-012-096, on the other hand, expected AEs were not included in the CRFs from any sites. The disparity in the reporting of the non-serious AEs limits the usefulness of pooling TEAEs between the studies. More importantly, the widespread absence of reporting of expected TEAEs in both pivotal studies significantly limits the meaningfulness of the TEAE incidence rates.

Reviewer comment: The sponsor specified unexpected AEs as follows: "An unexpected AE was defined as an AE that had not been previously reported in the Visipaque product labeling or an AE that had been documented in the product labeling but occurred with unexpected severity or frequency."

GE-189-002

As noted above, the GE-189-002 study protocol called for the reporting of only unexpected or SAE, but some sites mistakenly reported all AEs on the CRFs. For the majority of the study sites and subjects, no events were reported. Table 31 summarizes all recorded TAEAs for the study.

Table 31 Sponsor's summary of TEAE in GE-189-002

System Organ Class Preferred Term	N=232 n (%)
Subjects with any TEAE	18 (7.8)
Cardiac Disorders	8 (3.4)
Chest discomfort	3 (1.3)
Chest pain	3 (1.3)
Dyspnea	2 (0.9)
Palpitations	1 (0.4)
General disorders and administration site conditions	3 (1.3)
Feeling hot	1 (0.4)
Hyperhidrosis	1 (0.4)
Injection site extravasation	1 (0.4)
Immune system disorders	2 (0.9)
Periorbital edema	1 (0.4)
Urticaria	1 (0.4)
Musculoskeletal and connective tissue disorders	1 (0.4)
Neck pain	1 (0.4)
Nervous system disorders	4 (1.7)
Dizziness	1 (0.4)
Headache	3 (1.3)
Respiratory, thoracic and mediastinal disorders	3 (1.3)
Dyspnea	1 (0.4)
Laryngospasm	2 (0.9)
Skin and subcutaneous tissue disorders	3 (1.3)
Dermatitis allergic	1 (0.4)
Rash	1 (0.4)
Urticaria	1 (0.4)

Source: pg 9 Summary of Clinical Safety

A total of 25 TEAEs occurred in 18 of the 232 (8%) subjects in the safety population. Eleven (4.7%) of the subjects had TEAEs that were considered at least possibly related to the CCTA procedure, including Visipaque administration and procedural medications, including: urticarial (2 events in 2 subjects), dermatitis allergic (1 event in 1 subject), chest discomfort (1 event in 1 subject), dyspnea (2 events in 2 subjects), laryngospasm (2 events in 2 subjects), feeling hot (1 event in 1 subject), and headache (2 event in 2 subjects).

Two unexpected AEs (laryngospasm) were reported, but in both cases they were later considered coding errors and re-coded as expected AEs. The first case involved a patient with a mild anaphytactoid reaction that was initially coded as laryngospasm. Since laryngospasm is not labelled, the reaction was classified as unexpected. The sponsor later concluded that the patient had experienced a mild anaphylatoid reaction, which is labelled. The second case involved a subject who had the sensation of having to cough, in conjunction with dyspnea. This was initially coded as laryngospasm (unlabeled) and dyspnea (labeled), and later re-coded as a single labelled event (probably angina or possible physiologic dyspnea due to breath-holding

required for the procedure). Thus there were no unexpected AEs in the study.

Reviewer comment: The incidence rates of the non-serious AEs recorded for study GE-189-002 are not considered meaningful because of the disparity in reporting the non-serious AEs between the sites. The adverse events related to study GE-189-002 could not be meaningfully compared the second GE pivotal study, or to the sponsor's overall safety database.

GE-012-096

In the GE-012-096 study, only unexpected and SAEs were recorded. Known AEs related to Visipaque administration were captured on the source documents but not entered into the CRFs.

A total of 27 TEAEs occurred in 17 of 874 subjects (2%) in the study. Ten TEAE in 5 of 874 subjects (1%) were considered related to Visipaque administration, including: hypersensitivity (7 events in 2 subjects), arthritis (1 event in 1 subject), diplopia (1 event in 1 subject), and hypertension (1 event in 1 subject).

The TEAEs are summarized in Table 32.

Table 32 Sponsor's summary of TAEAs by SOC, preferred term, and relationship to Visipaque

System Organ Class/ Preferred Term[a]	All Events (N=874)		Causal Relationship to VISIPAQUE	
	Number of Subjects n (%)	Number of Events	Number of Subjects n (%)	Number of Events
Subjects with at least 1 AE	17 (2%)	27	5 (1%)	10
Cardiac disorders				
Angina pectoris	4 (<0.5%)	4	0	0
Coronary artery disease	3 (<0.5%)	3	0	0
Coronary artery stenosis	2 (<0.5%)	3	0	0
Eye disorders				
Diplopia	1 (<0.5%)	1	1 (<0.5%)	1
Gastrointestinal disorders				
Abdominal pain	1 (<0.5%)	1	0	0
General disorders and administration site conditions				
Fatigue	1 (<0.5%)	1	0	0
Non-cardiac chest pain	1 (<0.5%)	1	0	0
Pyrexia	1 (<0.5%)	1	0	0
Immune system disorders				
Hypersensitivity	2 (<0.5%)	7	2 (<0.5%)	7
Investigations				
Catheterization cardiac	1 (<0.5%)	1	0	0
Musculoskeletal and connective tissue disorders				
Arthritis	1 (<0.5%)	1	1 (<0.5%)	1
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism	1 (<0.5%)	1	0	0
Vascular disorders				
Aortic aneurysm	1 (<0.5%)	1	0	0
Hypertension	1 (<0.5%)	1	1 (<0.5%)	1

Source: pg 45 ge012-096-study-report-body

Reviewer comment: A greater percentage of TEAEs are reported for GE-198-002 (8%) than for GE-012-096 (2%). This is not unexpected because expected AEs were variably reported by some sites in GE-198-002, whereas expected AEs were not included in the CRFs in GE-012-096.

8.2.5. Laboratory Findings

GE—189-002

Only blood urea nitrogen (BUN) and serum creatinine were monitored in the GE-189-002 study, at baseline and again at 48 hours post-injection. There was no evidence of deterioration of renal function after Visipaque administration. The results are summarized in Table 33.

Table 33 Sponsor's tabulation of renal function tests, GE-189-002

Parameter	Measurement time		N=232 Actual value	N=232 Change from baseline
Blood urea nitrogen (mg/dL)	Baseline	N	230	
		Mean ± SD	16.17 ± 5.00	
		Range (min to max)	4.0 to 35.0	
	48 hours	N	231	229
		Mean ± SD	16.17 ± 4.76	-0.03 ± 3.45
		Range (min to max)	5.0 to 32.0	-11.0 to 10.0
Serum creatinine (mg/dL)	Baseline	N	232	
		Mean ± SD	1.00 ± 0.19	
		Range (min to max)	0.5 to 1.6	
	48 hours	N	232	232
		Mean ± SD	1.00 ± 0.20	-0.00 ± 0.12
		Range (min to max)	0.5 to 1.7	-0.4 to 0.4

Source: pg 12 Summary of Clinical Safety

Significant changes in individual test results were flagged in accordance with the study protocol as follows:

- BUN changes of > 40%, and values ≥ 80% the span of the normal limits
- Serum creatinine changes from baseline of > 25%, changes > 0.5 mg/dL, and changes ≥1.0 mg/dL.

BUN-only changes were flagged in eight subjects (3.5%). Serum creatinine-only changes were flagged in six subjects (2.6%). One subject had both BUN and creatinine changes flagged. Many of the flagged values represented changes that remained within the reference range. No subjects had an increase in serum creatinine of >0.5 mg/dL. There was no evidence of deterioration in renal function during the 48 hour follow-up interval.

GE-012-096
No clinical laboratory evaluations were conducted in the GE-012-096 study.

8.2.6. Vital Signs

GE-189-002
In the GE-189-002 study, heart rate, blood pressure, and respiratory rate were measured at screening, baseline (initial and pre-nitroglycerin), and at 5-15 minutes, 30-60 minutes, and 48 hours after baseline. Vital signs values were flagged as follows:

- Systolic blood pressure values changed by >20 mmHg from baseline
- Diastolic blood pressure values changed by >10 mmHg from baseline
- Heart rate values changed by >10 beats per minute
- Respiratory rate values changed by >10 breaths per minute

No concerning vital signs changes were detected.

GE-012-096
No vital signs measurements were recorded in the GE-012-096 study.

8.3. Analysis of Submission-Specific Safety Issues

8.3.1. Drug-drug interaction with beta blockers

There is evidence that the use of beta blockers is a risk factor for anaphylactoid reactions to iodinated contrast media. Both the American College of Radiology Manual on Contrast Media (2016) and the European Society of Urogenital Radiology Guidelines on Contrast Media (2011) remark on the drug interaction. The ACR Manual cites two articles from Lang in the early 1990s, both case control studies, which showed that individuals receiving beta blockers were at increased risk for moderate and severe reactions to iodinated contrast agents, including hypotension and brochospasm (Lang 1991, Lang 1993). Beta blockers have additionally been associated with reduced responsiveness to treatment of anaphylactoid reactions with epinephrine (Javeed 1996).

The issue of a potential drug interaction between Visipaque and beta blockers is clearly a CCTA-specific safety issue in that the population of patients undergoing CCTA is many times more likely to be concurrently exposed to beta blocking medication than those receiving Visipaque for non-CCTA examinations. Cardiac patients are often prescribed beta blocking medications, and beta blockade for heart rate control is common practice for CCTA studies. Of the 1106 subjects in the safety population in the two GE-sponsored CCTA trials, 920 subjects (83%) had beta-blocking agents listed as prior and concomitant medications.

Notably, Lang suggests the use of low osmolality contrast media (LOCM) in high-risk patients, and Visipaque has the lowest osmolality of the LOCMs, considered to be isosmolar to plasma. Several studies report on the substantially lower reaction rates for lower osmolar agents as compared to hyperosmolar preparations (Lieberman 1999).

While the risk of a drug interaction with beta blockers may be less pronounced or less common with Visipaque, and indeed no specific reports are identified, there is evidence of a class-wide association. The following wording is recommended for inclusion in the label by GE, and is timely as practitioners of CCTA should be particularly mindful of the risks potentially posed by beta blockers:

> The use of beta-adrenergic blocking agents lowers the threshold for and increases the severity of contrast reactions, and reduces the responsiveness of treatment of anaphylactoid reactions with epinephrine.

Reviewer comment: Conventional invasive coronary angiography procedures do not generally use beta blockers as procedural medications because heart rate control is less important for ICA (Landau 1994). Thus while patients undergoing ICA may be on previously prescribed beta blockers, the administration of beta blockers immediately prior to the test is unique to the CCTA procedure.

8.4. Safety in the Postmarket Setting

8.4.1. Safety Concerns Identified Through Postmarket Experience

[In this section, two data sets from the sponsor representative of safety in the postmarket setting are reviewed:

- Pooled data on adverse events reporting for the last 10-year representative period (from 2007 up to the end of March 2016) from the GE Healthcare GAED
- ADRs reporting specifically for cardiac investigations.

Reviewer comment: The second dataset is provided in response to an IR to the sponsor, received 2/13/2017.

Since first approval and up to March 2016, a total of (b)(4) vials of Visipaque have been sold, with each vial representing one dose. Approximately (b)(4) of the vials were sold in the US and Canada. The sponsor reports an overall adverse reaction reporting rate of 6.1 per 100,000 patient exposures, and the reporting rate for serious case reports of 2.6 per 100,000 patient exposures.

Adverse drug reaction reports received in the past 10 years (from 2007 until March 31, 2016) included a total of 2,852 individual case safety reports containing 4,922 adverse drug reactions, and of those 1,220 were considered serious, with a total of 89 fatal outcomes.

The most common causes of fatality were cardiac adverse reactions (26%) and severe hypersensitivity (17%). In many cases, fatal cardiac or cardio-respiratory arrest was considered to be a consequence of severe immediate hypersensitivity. In other cases, underlying disease or an interventional procedure or a combination of both were considered to be factors in the fatal outcome. There were deaths reported from 4 cases of myocardial infarction, 2 cases of cardiopulmonary failure, and one each of ventricular fibrillation, cardiac failure, cardiogenic shock, and arrhythmia.

Of the non-fatal adverse reactions, 66% were allergic-type reactions. Much less common reactions included general disorders (chills, feeling hot, malaise), gastrointestinal (vomiting and nausea), and also dyspnea, dizziness, and headache. Renal and urinary disorders constituted 2% of the adverse reactions, most frequently acute renal failure. There were case reports

concerning neurotoxic reactions, termed contrast-induced encephalopathy. The sponsor reports one case of hypothyroidism following Visipaque administration in the database, in an adult patient. GE considers the causal relationship between Visipaque and hypothyroidism to be indeterminate at this time.

Three FDA Tracked Safety Issues (TSIs) were issued during the past 10 year reporting period: severe cutaneous adverse reactions, exacerbation of myasthenia gravis, and hypothyroidism in newborn and infants. Individual safety reviews of these TSIs are provided separately by the Deputy Director of Safety, Ira Krefting. Information regarding severe cutaneous adverse reactions and hypothyroidism are incorporated into the label with the concurrent PLR conversion. In addition, GE reports the addition of the following undesirable effects to their CCSI over the past ten years, all of which are also included in the concurrent PLR conversion: transient contrast induced encephalopathy, cardiac arrest and cardio-respiratory arrest, and myocardial infarction.

The overall 10 year post-marketing data safety analysis suggests that Visipaque is generally very well tolerated, with a relatively low number of adverse reactions reported given the total number of doses administered. Serious risks and known adverse reactions are appropriately included in the label. New information from the TSIs and the new association with transient contrast induced encephalopathy are concurrently incorporated into the PLR conversion.

Given the inability to compare overall AE rates between the CCTA and non-CCTA trials, an information request was sent to the sponsor requesting comparative post marketing data as reported for cardiac studies and all other studies. The sponsor provided counts of adverse drug reactions after use for cardiac indications and other indications as captured since 1996. There were 954 counts of ADR after use in cardiac indications and 11,160 counts of ADR after use in other indications. The cardiac indication studies were not further classified as intra-arterial angiography or intravenous CCTA. The rates are provided in terms of the number of events in a MedDRA SOC category, per total events for cardiac or non-cardiac studies.

Table 34 Sponsor provided counts and rates of ADRs after intravascular administration for cardiac and non-cardiac investigations by MedDRA SOC[1], reported since 1996

	Counts of ADRS (Rates of ADRs)		
MedDRA SOC	Other than cardiac investigations, n=11,160	Cardiac investigations, n=954	All investigations, n=12,114
Blood and lymphatic system disorders	22 (0.2%)	9 (0.9%)	31 (0.3%)
Cardiac disorders	208 (1.9%)	61 (6.4%)	269 (2.2%)
Ear and labyrinth disorders	10 (0.1%)	1 (0.1%)	11 (0.1%)
Endocrine disorders	5 (0.0%)	1 (0.1%)	6 (0.0%)
Eye disorders	168 (1.5%)	18 (1.9%)	186 (1.5%)

Gastrointestinal disorders	1031 (9.2%)	90 (9.4%)	1121 (9.3%)
General disorders and administration site conditions	810 (7.3%)	77 (8.3%)	887 (7.3%)
Hepatobiliary disorders	9 (0.1%)	2 (0.2%)	11 (0.1%)
Immune system disorders	4801 (43.0%)	356 (37.3%)	5157 (42.6%)
Infections and infestations	55 (0.5%)	7 (0.7%)	63 (0.5%)
Injury, poisoning and procedural complications	55 (0.5%)	8 (0.8%)	63 (0.5%)
Investigations	156 (1.4%)	16 (1.7%)	172 (1.4%)
Metabolism and nutrition disorders	16 (0.1%)	5 (0.5%)	21 (0.2%)
Musculoskeletal and connective tissue disorders	71 (0.6%)	17 (1.8%)	88 (0.7%)
Nervous system disorders	534 (4.8%)	38 (4.0%)	572 (4.7%)
Psychiatric disorders	85 (0.8%)	5 (0.5%)	90 (0.7%)
Renal and urinary disorders	211 (1.9%)	45 (4.7%)	256 (2.1%)
Respiratory, thoracic and mediastinal disorders	424 (3.8%)	28 (2.9%)	452 (3.7%)
Skin and subcutaneous tissue disorders	2209 (19.8%)	150 (15.7%)	2359 (19.5%)

[1]For clarity of presentation, I omitted SOC categories with no cardiac investigations (Neoplasms, Reproductive system, Social circumstances, and Surgical and medical procedures) from the table.
Source: IR response from sponsor received 2/13/2017

In general, adverse drug reaction reporting does not allow for reliable estimates of AE rates or for a definitive causal relationship to exposure, both because the reporting is voluntary and because the total population size is uncertain. The analysis here is further confounded by the category of "cardiac investigations" which does not differentiate between intra-arterial studies and CCTA. With these limitations in mind, some important information can be gleaned from the counts of the adverse drug reactions provided in the table.

First, taken collectively, immune system disorders and skin and subcutaneous tissue disorders account for over half of all of the reports in each category: non-cardiac (62.8%), cardiac (53%), and all investigations (62.1%). When considered alongside the sponsor's table of all counts from post marketing surveillance using preferred term names (source: pgs 8-34 sponsor's IR response dated 2/13/2017), the MedDRA SOC immune system disorders consists predominantly of allergic reactions (for example, anaphylactoid shock, contrast media allergy, drug hypersensitivity) and the MedDRA SOC skin and subcutaneous tissue disorders also includes predominantly reactions that are considered to be allergic (for example, erythema, pruritus, rash, urticaria). The frequency of reports of allergic-type reactions to Visipaque is not unexpected.

Second is a consideration of the rates of the MedDRA SOC cardiac disorders. Cardiac disorders represented 1.9% of the ADRs reported for non-cardiac studies, and 6.4% of the ADRs reported for cardiac studies. The MedDRA SOC cardiac disorders (again taken from the sponsor's table of

PTs for all counts of ADRs) includes most commonly: palpitations, tachycardia, coronary artery thrombosis, cardio-respiratory arrest, and coronary no-reflow phenomenon (in order of highest to lowest number of counts). As noted earlier, the cardiac studies are not further subdivided between intra-arterial angiography/angiocardiography and intravenous CCTA studies. One would reasonably assume that over the 20 year reporting period, there were more intra-arterial cardiac studies than intravenous CCTA studies, since intra-arterial cardiac studies have been a labeled indication since 1996. The ADRs reported for cardiac studies are in line with known AEs related to both Visipaque administration and to specific risks related to intra-arterial catheterization. Additionally, one would expect a higher rate of cardiac events in patients presenting with cardiac symptoms.

Renal and urinary disorders accounted for 1.9% of non-cardiac investigations, and 4.7% of cardiac investigations. The reason for the higher percentage of renal drug reactions of all drug reactions for cardiac investigations is not known. The finding can be considered in the context of the likelihood of greater percentage of comorbidities in the cardiac grouping, which probably represents predominantly ICA studies. Reassuringly, serum creatinine and BUN were measured in the GE-189-022 trial and there was no evidence of renal impairment in relation to the Visipaque-enhanced CCTA at 48 hours of follow-up.

Lastly is consideration the MedDRA PT thrombocytopenia, within the SOC blood and lymphatic system disorders. While not subcategorized in Table 14, the sponsor reports that there were 5 cases of thrombocytopenia within the category of cardiac investigations. Cross referencing with the sponsor's table of all ADRs from postmarketing surveillance (not included in this report), there were a total of 6 cases of thrombocytopenia (from all Visipaque studies) in the past 20 years, all of which were classified as serious, and none of which were fatal. There is thus evidence that thrombocytopenia is associated with cardiac studies, and not with other types of Visipaque studies. This is not unexpected as heparin-induced thrombocytopenia, an immune-mediated condition, has been reported to have occurred during percutaneous coronary interventions, which frequently use heparin (Brieger 1998). The low total number of cases may relate to a lower rate of the event overall in recent years, or to the knowledge that the thrombocytopenia is due to the heparin, and subsequently not reported as an ADR to Visipaque. There is no known association between thrombocytopenia and Visipaque-enhanced CCTA, and there were no cases of thrombocytopenia in the safety population of the CCTA trials.

8.5. Integrated Assessment of Safety

The critical question for the safety analysis of this efficacy supplement is the following: are there new risks or higher rates of known risks associated with the use of Visipaque for CCTA, as compared to the use of Visipaque for other indications? Regrettably, the study design of the pivotal CCTA trials precludes a direct comparison of AE rates data in the CCTA trials with AE data with the AE table from non-CCTA trials. The protocols for both GE-189-002 and GE-012-096 restricted the reporting of AEs to those which were serious or unexpected, and restricted

the period for AE reporting to within 48 hours after Visipaque administration. Thus most non-serious AEs already listed on the package insert were not reported in the trials. As expected, the overall AE rate (19.9%) reported on the Visipaque label AE table is significantly higher than that for the CCTA trials (8% for GE-189-002 and 2% for GE 012-096).

While no overall comparison of AE rates between the CCTA trials and non—CCTA trials was feasible, the CCTA trials did allow for a consideration of the incidence rates of SAEs and unexpected AEs. First, there were no deaths or serious AEs considered related to Visipaque administration reported in the combined safety population (1106 subjects) from the two CCTA trials. While expected AEs were variably reported, all SAEs occurring with 48 hours were reportable. There were a total of 8 SAEs reported, which were determined to be unrelated to Visipaque administration.

A reasonable question can be asked regarding the reliability of the rates of SAEs: did the 48 hour AE reporting period result in the under-reporting of SAEs that occurred more than 2 days after the Visipaque dose? Most contrast reactions occur immediately after contrast administration and well within the 48 hour reporting period. There is increasing awareness, however, of the category of delayed hypersensitivity reactions to iodinated contrast agents, as addressed in a recent TSI. Most delayed hypersensitivity reactions related to contrast consist of mild skin disorders such as hives or rash that develop in the days following the contrast administration. There are, however, severe delayed hypersensitivity reactions, which are largely cutaneous and referred to collectively as severe cutaneous adverse reactions (SCARs). The GAED database included 56 cases of these reactions, including: Stevens-Johnson syndrome (5), toxic epidermal necrolysis (5), drug reaction with eosinophilia and systemic symptoms (5), acute generalized exanthematous pustulosis (13), skin exfoliation (5), dermatitis exfoliation (10), toxic skin eruption (12), and vascular purpura (1). The TSI led to a class-wide labeling update to include a warning for delayed hypersensitivity reactions, which will occur concurrent with this CCTA supplement and the PLR conversion (see separate reviews by the Deputy Director for Safety, Ira Krefting, and the Associate Director of Labeling, Michele Fedowitz). The safety data from the CCTA trials provides no new information regarding the risk for delayed hypersensitivity reactions and by design would likely have not captured any such event. Both trials are noted to have taken place several years prior to the issuance of the TSI.

Other than delayed hypersensitivity reactions, SAEs are unlikely to occur more than 48 hours after Visipaque administration. The 48 hour SAE reporting period, while not ideal in terms of delayed hypersensitivity, should have captured most cases of serious reactions and the absence of SAEs attributed to Visipaque in the CCTA trials is reassuring in terms of the safety of Visipaque use for this diagnostic test.

Reviewer comment: (b)(4)

(b)(4)

The second conclusion from the CCTA trials relates to unexpected AES. Both CCTA trials specified the collection of unexpected AEs. Only two AEs related to Visipaque administration, both largospasm, were initially coded as unexpected. Upon further review of the cases, both were re-coded into hypersensitivity categories, which are considered expected. Thus there were no safety signals suggesting new AEs for the use of Visipaque for CCTA in the two clinical trials.

It might be reasonable to assume that the risks related to Visipaque for CCTA are the same as the risks related to Visipaque for intra-arterial coronary angiography, minus the risks related to the presence and manipulation of an intra-arterial catheter, as well as any intervention such as angioplasty or stenting undertaken during an ICA. There is, however, a key distinction between the two studies that might convey an increased risk for the use of Visipaque for CCTA, related to the use of beta blockers for CCTA. In the CCTA clinical trials, about 70% of the subjects were treated with a beta blocker for the CCTA examination, whereas beta blockers are not routinely administered for ICA procedures (Landau 1994). Additional discussion regarding the risk for interaction between Visipaque and beta blockers is in Section 8.5 Analysis of Submission-Specific Safety Issues. Appropriately, a warning for the potential drug interaction is recommended this application.

Finally, is a consideration of the radiation dose associated with CCTA. Visipaque-enhanced CCTA is proposed to evaluate patients with suspected coronary artery disease, and thus the radiation dose associated with the test can be compared to other methods of evaluating patients with suspected coronary disease, namely ICA and radionuclide myocardial perfusion imaging. If the use of CCTA for the proposed population is associated with a significantly higher radiation dose as compared to other available modalities, then radiation risks would have be considered in the risk-benefit calculation for this efficacy supplement.

The effective dose (expressed in units of milliSievert, mSv) is a radiation dose parameter that provides a broad estimate of the risk of harm from an exposure to ionizing radiation, and allows for comparisons between different types of radiological examinations. Published estimates of the effective dose related to CCTA vary and depend on scanner specifications and the use of dose reduction technologies. For example, a comparison between cardiac CT using different ECG gating techniques with over 50 subjects in each group demonstrated effective doses of 4.2 mSv ±1.5 for prospective gating and 18.1 mSv ±3.0 for retrospective gating (Shuman 2008). A more recent report in Radiology demonstrates the potential to achieve much lower doses using a 320-detector row CT in conjunction with techniques including faster gantry rotation, wide volume coverage, iterative reconstruction, automated exposure control, and larger power generator, achieving effect doses of less than 1 mSv, as demonstrated in Table 35 (Chen 2013). Conventional invasive coronary angiography without intervention is generally associated with doses in the range of 5 mSv (Coles 2005). Myocardial perfusion imaging is associated with a

range of effective doses depending on the specific modality and testing protocol, reported in the range of 8-30 mSv (Cerqueira 2010).

Table 35 Summary of radiation dose data from first and second generation 320-detector row scanners

Parameter	Second-Generation Unit ($n = 107$)	First-Generation Unit ($n = 100$)	*P* Value
Median $CTDI_{vol}$ (mGy)	6.0 (3.5–10.5)	14.4 (8.6–20.1)	<.0001
Median dose-length product (mGy · cm)	66.8 (41.1–124.9)	190.8 (120.1–285.6)	<.0001
Median estimated effective dose (mSv)	0.93 (0.58–1.74)	2.67 (1.68–4.00)	<.0001
Mean effective patient diameter (cm)	33.8 ± 4.7	34.4 ± 5.1	.42
Median SSDE (mGy)	6.0 (4.1–10.0)	13.2 (10.2–18.6)	<.0001

Source: Chen, Marcus Y., Sujata M. Shanbhag, and Andrew E. Arai. "Submillisievert median radiation dose for coronary angiography with a second-generation 320–detector row CT scanner in 107 consecutive patients." Radiology 267.1 (2013): 76-85.

Reviewer comment: Note the third row in the table, in which second-generation and first-generation 320-detector row scanners resulted in effective doses of 0.93 mSv and 2.67 mSv, respectively.

While the exposures related to the different testing modalities can be considered individually, a more robust analysis of the total cumulative radiation exposure of patients undergoing evaluation for suspected coronary disease is available in the PROMISE trial. The PROMISE trial was a large scale controlled study in which subjects were randomly assigned to evaluation with either CCTA or functional imaging (see Section 6.3.2). Differential cumulative radiation exposures, including exposures from additional downstream testing, between the CCTA arm and the function testing arm was a study endpoint.

The results demonstrated that patients in the coronary CTA cohort had a higher overall exposure (including follow-up testing) of 12.0 ± 8.5 mSv, compared to the functional testing group, 10.1 mSv ± 9.1 mSv. The result, however, is confounded by the 33% of the subjects in the functional arm who had no radiation exposure at all (stress ECG or exercise ECG testing). Among the patients who underwent nuclear stress testing within the functional arm, the cumulative radiation exposure was lower in the CTA group (10.1 mSv) than in the MPI group (12.6 mSv).

The CCTA radiation exposure is thus not greater when compared to MPI testing, but is currently considered greater when compared to ICA. Initial assessment of patients with suspected cardiac disease with CCTA is associated with a lower cumulative radiation exposure as

compared to initial assessment with MPI. Taken in context of higher rates of morbidity with ICA testing, as well as higher rates of additional diagnostic information with CCTA testing, the relatively small difference in radiation dose between CCTA and ICA does not negatively impact the risk-benefit analysis of the efficacy supplement.

In summary, while portions of the safety data are limited, the following conclusions can be drawn from the totality of safety data included with this application:

- There is no evidence that the use of Visipaque for CCTA is associated with higher rates of death and other serious adverse events within 48 hours after injection.
- The CCTA clinical trials data does not allow for an assessment of the incidence of delayed hypersensitivity, however, most delayed reactions are mild, and the rare subset of severe cutaneous adverse reactions are concurrently added to the label in the form of a warning for all Visipaque indications.
- In the post marketing data, cardiac examinations were associated with a higher percentage of reports concerning cardiac disorders, renal disorders, and thrombocytopenia as compared to the percentage of reports for non-cardiac examinations. A significant portion of these reports can be inferred to be in the context of invasive intra-arterial coronary procedures, for which these risk associations are well known, and which are usually performed in patients with additional comorbidities. Physiologically, both types of coronary imaging involve the presence of Visipaque in the coronary arteries. The absence of coronary catheterization for the CCTA studies could be hypothesized to result in lower cardiac events as compared to ICA.
- The use of Visipaque for CCTA is uniquely associated with the risk of drug drug interactions between iodinated contrast agents and beta blockers, given that most patients undergoing CCTA are either already routinely taking beta blockers, or will be given beta blockers as a procedure medication for heart rate control. This drug interaction is appropriately incorporated into the Visipaque label with the concurrent PLR conversion
- Typically reported effective radiation doses from CCTA are higher than those reported from ICA, and similar to reports for MPI. Recent literature suggests that CCTA doses could be significantly diminished with state of the art equipment. CCTA has significant added value over ICA in the form of reduced morbidity and enhanced visualization of regional anatomy and pathology, rendering the added radiation exposure reasonable. The PROMISE trial provides reassuring data regarding lower cumulative radiation doses for patients initially evaluated with CCTA, as compared to patients initially evaluated with MPI.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was convened.

10 Labeling Recommendations

10.1. Prescribing Information

The labeling changes associated with this efficacy supplement include a concurrent PLR conversion of the product label, including both the 270 mgI/mL concentration and the 320 mgI/mL concentration of Visipaque. A full review of the conversion is submitted separately by the Associate Director of Labeling, Michele Fedowitz.

With respect to the CCTA portion of the label, substantial changes were recommended relative to the sponsor's proposed labeling in sections 2.3 Intravenous Dosage and Administration, 7.1 Drug-Drug Interactions, and 14.2 Intravenous Administration Studies. Additional commentary is provided on notable PLR conversion changes from the clinical perspective. The section is summarized below:

- 2.3 Intravenous Dosage and Administration:
  - Pediatric dosing: CCTA dosing recommendation for pediatric patients over 12 years of age (1-2 mL/kg).
  - Contrast dilution: Inclusion of guidance for variations in the dosing scheme related to the use of dilute contrast administration.
  - Main bolus Visipaque dose: adjusted to reflect the prescribed protocol dose in study GE-189-002, 70-80 mL.
- 7.1 Drug-Drug Interactions: Inclusion of beta-adrenergic blocking agents.
- 14.2 Intravenous Administration Studies: CCTA portion rewritten to reflect most robust analysis of results from the CCTA clinical trials.
- Notable PLR conversion changes, from the clinical perspective
  - SCARs TSI

Pediatric inclusion
The sponsor requested a full waiver from the performance of pediatric studies for the CCTA indication because obstructive coronary artery stenosis is due to atherosclerotic disease, which is largely a disease of adults. The inclusion of pediatric patients over 12 years of age for the CCTA indication was subsequently recommended by the Pediatric Review Committee (PeRC) on 3/1/2017. The committee stated that no additional studies would be required on the part of the sponsor, noting that reference could be made to literature reports in support of the

effectiveness of CCTA in adolescents, and that the safety of Visipaque in the pediatric population has been previously established.

The recommendation of the Pediatric Review Committee was based on the known use of CCTA for the population of pediatric patients with Kawasaki disease, the leading cause of acquired coronary disease in children. Kawasaki disease occurs primarily in infants and young children, and about 20% of the patients develop coronary artery aneurysms. Echocardiography is the mainstay of cardiac imaging during the acute phase of the disease for the detection and characterization of aneurysms. Older children and young adults with a history of coronary artery aneurysms from Kawasaki disease are at risk for the development of progressive coronary artery stenosis and subsequent myocardial ischemia; these patients require life-long imaging surveillance for CAD. Thickening of the chest wall with age renders echocardiography progressively less reliable for the evaluation of the coronary arteries, thus imaging options for the older Kawasaki disease follow-up population include CCTA, cardiac MRI, conventional angiography, and stress testing (Newburger 2016).

While there are no large clinical trials evaluating the use of CCTA for patients with Kawasaki disease, and no known published reports regarding the specific use of Visipaque in this population, there are several small scale reports on imaging protocols and efficacy results for the use of CCTA in the older pediatric population with a history of Kawasaki disease.

One published study reported the successful performance of CCTA in adolescents and young adults with Kawasaki disease in a study involving 16 patients, 8 of whom were less than 18 years of age (age range of 13-17). CCTA was performed using a 4-detector row CT scanner, and the images were compared to the patients' previous conventional angiography studies. The authors concluded that adequate images were obtained for 96% of major coronary segments, and that the sensitivity and specificity of CCTA to detect significant stenosis was 88% and 93%, respectively, as compared to ICA (Kanamaru 2005). A second study involving the performance of CCTA in 32 pediatric patients with Kawasaki disease (mean age 12.9) demonstrated the ability of CCTA to detect coronary stenoses that were not visualized by other noninvasive imaging tests (Han, 2014). Notably, the youngest subject enrolled in the GE CCTA clinical trials was 19 years of age.

Reviewer recommendation: I agree with the PeRC recommendation to add children over 12 years of age to the CCTA indication. It is reasonable to expect that CCTA in older children would have similar efficacy as compared to adults, and this is supported by evidence in the literature.

Pediatric dosing

The contrast administration protocol in the Kanamaru study cited above included a test bolus of 15 mL of 300 mgI/mL contrast agent, followed by a main bolus of the remainder of a 1.7 mg/kg dose, with a maximum dose of 85 mL, injected at 3.3 mL/s (Kanamaru 2005). The second study

reported mean dosing of 1.47 mL/kg, (mean dose administered: 64 mL, range 35 – 84 mL) of an unspecified iodinated contrast agent (Han, 2014).

The pediatric dosing information for CCTA in the literature closely mirrors the current dosing on the Visipaque label for general CT applications in children <12 years of age (1-2 mL/kg) and is similar to the proposed CCTA dosing for adults (70-80 mL), but is notably lower than the current general CT dosing for children over 12 years of age (75 – 150 mL).

Reviewer recommendation:
The current CT dose recommendation for children over 12 years of age (75-150 mL) may be more than is needed for CCTA. To avoid unnecessarily high doses of contrast, I recommend weight based dosing of 1-2 mL/kg for CCTA for pediatric subjects greater than 12 years of age, reflecting practice standards in the literature reports.

Contrast dilution
It is common clinical practice to divide the main contrast dose for CCTA into an initial full concentration contrast dose, followed by a dilute contrast dose (diluted with saline). The addition of dilute contrast in the second half of the injection reduces artifacts that can result when there is a high concentration of contrast in the right heart at the time of optimal coronary artery opacification. The CCTA trial GE-189-002 included the following contrast dilution protocol as one of two Visipaque dosing options:

> Main bolus: 50-60 mL Visipaque followed by 50 mL contrast-saline dilution (20/30), followed by 20 mL saline flush.

Reviewer recommendation:
I recommend the inclusion of a dilute contrast injection protocol into the CCTA dosing table, in line with the protocol used for the trial.

Main bolus Visipaque dose
The dosing protocol in study GE-189-002 specified a main bolus volume of 80 mL in the Cardiac CT Imaging Manual and specified a main bolus volume of 70-80 mL in the Study Design and Procedures (see Section 6.1.1 Study Design, in this review). The mean recorded main bolus administration for the study subjects was 73 mL Visipaque. In the registry study GE-096-101, the Visipaque dosing was not specified, and varied widely by site (mean 91 mL, range 30-180 mL). It is possible that some of the study sites in the registry study may have included the test bolus dose (typically 20 mL) into the reporting of the volume of the main dose.

The proposed CCTA dosing table specifies a main bolus volume of (b)(4) mL Visipaque. It is probable that the proposed dosing incorporates the 20 mL of Visipaque that is often administered prior to the scan in order to establish optimum scan time delay, but the table is

unclear since the dose is included under (b)(4)."

Reviewer recommendation:
I recommend changing the main bolus volume from (b)(4) mL to 70-80 mL in order to reflect the dosing in the CCTA clinical trial GE-189-002 and to avoid unnecessarily high doses of Visipaque. The optional use of 20 mL dose of Visipaque to determine scan time delay should be listed separately to avoid confusion.

Beta-adrenergic blocking agents
There have been reports of beta blockers both lowering the threshold for severe contrast reactions, and reducing the responsiveness of treatment of hypersensitivity reactions with epinephrine (see section 8.3 in this review). The ADL has proposed the inclusion of this information in the Drug Interactions section of the label.

Reviewer recommendation:
I agree with the ADL regarding the inclusion of information about the reports of interaction between Visipaque and beta blockers, which is particularly relevant given the common practice of beta blocker administration prior to CCTA for heart rate control.

Intravenous administration studies
Section 14.2 in Clinical Trials was substantially rewritten to reflect the most statistically robust analysis of the results from GE-189-002/GE-012-096, as calculated by the statistical review team (see separate review by Satish Misra). Specifically, the vessel-level analysis was considered most relevant given the anatomic expectations of CCTA and the head to head comparison to ICA. The interpretations of the original read study were reanalyzed using the statistical plan from the re-read study in order to avoid bias and to apply more conservative statistical rules.

Severe cutaneous adverse events
This supplement coincides with the class wide safety labeling change issued for severe cutaneous adverse events, of which the GAED database included 56 cases (see Section 8.5 Integrated Assessment of Safety), including cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis. Most of these reactions manifest from hours to several days after the Visipaque exposure, and are considered to represent a type of delayed hypersensitivity reactions.

Reviewer comment: The CCTA trials submitted for this supplement did not include safety follow-up beyond 48 hours of Visipaque administration and thus no data was collected regarding the incidence of these significant delayed reactions.

11 Risk Evaluation and Mitigation Strategies (REMS)

No REMS is recommended with respect to this application.

12 Postmarketing Requirements and Commitments

No post-marketing commitment is requested from the sponsor.

13 Appendices

13.1. References

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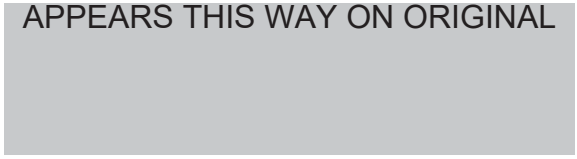
13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): GE-189-002/GE-012-101 and GE-012-096

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 43		
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): 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: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	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)



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/s/

KAREN B BLEICH
03/10/2017

ANTHONY F FOTENOS
03/13/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 020351 **Applicant: GE** **Stamp Date:**

Drug Name: Visipaque **NDA/BLA Type: efficacy supplement**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/LawsActsandRules/ucm084159 htm	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	As discussed in type B meeting 7/13/16
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			No specific document, but adequate discussion provided.
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505b(1)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Treatment Arms: Location in submission:			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 GE 189-002 Indication: CCTA vs ICA Pivotal Study #2 GE 012-096 Indication: CCTA vs outcomes	X			
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?			X	
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
25.	Has the applicant submitted the coding dictionary[2] used for	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	mapping investigator verbatim terms to preferred terms?				
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			*see notes below
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None

*Notes regarding the PSP:

The PSP was initially not included with the sNDA application.

A review of the minutes from the 8/27/2009 end of phase 2 meeting, the 11/10/15 Type C meeting, and the 7/13/2016 Type B meeting, all held between GE and DMIP revealed no discussion regarding pediatric studies or the iPSP requirement.

Notably, at the 7/13/16 meeting, GE described the data package and their proposed indication statement for a supplemental CCTA indication. The data package proposed by GE included three GE sponsored trials, three published trials using Visipaque-only, and four supportive publications including the use of various contrast agents. None of the studies in the proposed data package included pediatric subjects. DMIP noted at the meeting that GE's "proposed indication, "to assist in the diagnostic evaluation of patients with suspected coronary artery disease, " appears sufficiently supported for sNDA filing review." DMIP did not ask GE to submit as iPSP at that time, nor did GE discuss the regulatory requirements regarding iPSP.

Based on the minutes of the discussions, it seems that the issue of iPSP was overlooked both by the sponsor and by DMIP, likely because the disease process involved, atherosclerosis, is uncommon among the pediatric population. At the request of the FDA, a pediatric study plan amendment to the supplement was submitted by GE, dated 11/10/2016.

Karen Bleich, MD 11/22/2016
Reviewing Medical Officer Date

Anthony Fotenos, MD

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Clinical Team Leader Date

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/s/

KAREN B BLEICH
11/23/2016
The filing checklist is complete and the application is fileable from the clinical perspective.

ANTHONY F FOTENOS
11/23/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020351/S-044
020808/S-025

PRODUCT QUALITY REVIEW(S)

Review of Chemistry, Manufacturing, and Controls

Clinical Review Division: HFD-160 • Division of Medical Imaging Products

NDA #: 20–351 (lead) **Chem. Review #:** 1 **Review Date:** 3/30/2017

NDA #s	SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
20–351	SE–044 (PA)	10/5/2016	10/5/2016	10/20/16
20–808	SE–025 (PA)	10/5/2016	10/5/2016	10/20/16

NAME & ADDRESS OF APPLICANT: GE Healthcare, 101 Carnegie Center
Princeton, NJ 08540–6231 USA
Phone (609) 514–6427

DRUG PRODUCT NAME

Proprietary:	Visipaque® Injection
Nonproprietary/USAN:	Iodixanol
Code Name#:	NA
Other Names:	NA
Chem.Type/Ther.Class:	1S

Patent Status: NA

PHARMACOLOGICAL CATEGORY/INDICATION(s): Radiographic Contrast Agent

DOSAGE FORM: Sterile solution

STRENGTHS: 270 and 320 mg I/mL

ROUTE OF ADMINISTRATION: Intrathecal, intravascular, or oral/body cavity use

DISPENSED: Rx

PACKAGE SIZES: Multiple presentations

SPECIAL PRODUCTS: ☐ Yes ☒ No (If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

NANOTECHNOLOGY PRODUCTS: Not Applicable

CHEMICAL NAME: 1,3-Benzenedicarboxamide, 5,5'-[(2- hydroxy-1,3-propenediyl)bis(acetylimino)]-bis[N,N,-bis(2,3-dihydroxypropyl)-2,4,6-triiodo

SUPPORTING DOCUMENTS: NA

CONSULTS: NA

REMARKS/COMMENTS: The submission proposes to add a new indication for Visipaque 320: "*Visipaque Injection (320 mgI/mL) is indicated for use in coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease.*

CONCLUSIONS & RECOMMENDATIONS: The supplements are recommended for approval from a CMC standpoint.

***Note**: Signature Block is appended at the end of this document.*

REVIEW NOTES

Verbatim citations from the NDA submission are presented in Sans Serif typeface.
Summaries are presented in Roman type.
Reviewer commentary, deficiencies, and suggestions are presented in Italics.

DRUG SUBSTANCE – The drug substance remains unchanged.

Satisfactory. There are no changes to the drug substance.

DRUG PRODUCT – The efficacy supplement provides for a new indication to be added for coronary computed tomography angiography (CCTA) for Visipaque 320. CMC reviewable items are Environmental Assessment and Labeling.

Environmental Assessment – The drug substance does not qualify for a categorical exclusion, since the Aquatic EIC has been estimated at (b)(4) ppb, exceeding the 1.0 ppb threshold. Note that the calculation is presented for all iodixanol in Visipaque expected to be released into the environment including the slight additional iodixanol expected to be used and released due to the new indication for CCTA.

(b)(4)

Since a categorical exclusion is not possible, iodixanol was subjected to three standard living organism tests (Tier 2), as summarized below. No toxicity was found in the vertebrate and invertebrate organisms, and no effect was observed in algal growth.

Summary of aquatic toxicity tests

Tests	Results
Fish. Acute Toxicity Test	Fish (b)(4)
Daphnia sp. Acute Immobilisation Test	Daphnia (b)(4)
Alga. Growth Inhibition Test	Algal (b)(4)

The final calculation in Tier 2 is the ratio of the drug substance concentration to the EIC. If this calculation exceeds the threshold value of 100, it reflects low toxicity, and no further testing is required.

Fish toxicity: (b)(4)

Daphnia toxicity: (b)(4)

Algal toxicity: (b)(4)

Satisfactory. The toxicity assessments show that no remediation is necessary when disposing of iodixanol in the waste water stream and aquatic environment.

Labeling – There are no labeling changes related to CMC (such as Description or How Supplied) in the Package Insert. Immediate container labels and cartons are also unchanged.

Satisfactory.

DRAFT SUPPLEMENT LETTER

There are no CMC comments to convey to the sponsor.

cc: Orig. NDA 20–351 SE–044, NDA 20–808 SE–025

David A. Place -S

Digitally signed by David A. Place -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=David A. Place -S, 0.9.2342.19200300.100.1.1=1300070739
Date: 2017.03.30 10:38:41 -04'00'

Review Chemist

Branch Chief

filename: N20351SE044PlusBundleAP.pdf

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/s/

KIM E ROBINSON
04/21/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020351/S-044
020808/S-025

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation
Clinical Studies

NDA/BLA	NDA 20351 s44
Drug Name:	**Visipaque (Iohexol)**
Proposed Indication(s):	Visipaque Injection (320 mgI/mL) is indicated for coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease
Applicant:	GE Healthcare Inc.
Date(s):	NDA Submission: October 5, 2016 PDUFA Date: April 5, 2017
Review Priority:	Priority
Biometrics Division:	
Statistical Reviewer:	Satish C. Misra, Ph. D.
Concurring Reviewers:	Jyoti Zalkikar, Ph. D., Secondary Statistical Reviewer Peiling Yang, Ph. D., Tertiary Statistical Reviewer Division of Biostatistics I
Medical Division:	Division of Medical Imaging Products (DMIP)
Clinical Team:	Karen Bleich, M.D. Clinical TL: Anthony Fotenos, M.D.
Project Manager:	Frank Lutterodt/ Kyong Kang (TL)

Keywords: Sensitivity, Specificity, Efficacy, Safety, Confidence Interval

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1. EXECUTIVE SUMMARY

The sponsor's interaction with the FDA on this NDA started in 2009. After numerous meetings and exchange of information, this NDA s44 was submitted based on guidance given by the FDA Division of Medical Imaging Products (DMIP) to the Sponsor.

GE Healthcare proposes to add a CCTA indication for Visipaque 320 mgI/mL based on evidence from GE-sponsored clinical studies, and supporting evidence of safety and efficacy evidence in the published literature (including studies performed only with Visipaque).

- **Visipaque Injection (320 mgI/mL) is indicated for use in coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease.**

In support of the indication, the sponsor submitted the efficacy results of the following pivotal GE sponsored studies:

(1) GE-189-002 (also known as VCT002); an open-label, prospective, multi-center study to evaluate diagnostic performance of Visipaque-enhanced CCTA using the GE LightSpeed VCT scanner for detection of coronary artery obstruction in typical or atypical chest pain patients. There were 245 patients enrolled in this study with 232 safety patients and 230 efficacy patients. A re-read of this study (study GE-012-101) was performed to evaluate the diagnostic performance Visipaque enhanced CCTA in terms of sensitivity and specificity.

(2) GE-012-096; a registry study to assess, prospectively, the value of CCTA examination findings in predicting the occurrence of downstream adverse cardiac events in patients with symptomatic chest pain syndrome who are undergoing Visipaque-enhanced CCTA.

The statistical review team presented the results for Study 1 at the subject-level, at the vessel-level, and at the segment-level to the clinical review team and that team decided that, clinically, the vessel-level analysis reflected the most useful data, in terms of providing localization of disease.

Therefore the results for Study 1 (GE-189-002 also known as VCT002) at vessel-level are summarized below:

Vessel Level Analysis - Original and reread data - By Reader Analysis

Table 1 provides VISIPAQUE™-enhanced CCTA Visual Assessments Compared to CATH as Standard of Truth by Reader with Segments Unevaluable or <2mm by CATH Excluded (Summation of All Vessels) (Stenosis ≥ 50%) (Efficacy Population). This table provides sensitivity and specificity for summation of all vessels by readers and by majority read for both original read data and reread data.

This table showed moderate sensitivity ranging from 76% to 89 % for the original data and 57% to 80% for reread data. It also showed specificity ranging from 84% to 89% for the original data and 91% to 97% for reread data

Table 1: Summation of All Vessels (Stenosis ≥ 50%) by reader for original and reread data

Vessel-level Analysis (Summation of all vessels) (Stenosis ≥ 50%)								
	GE-189-002 (Original Data)				GE-012-101(Reread Data)			
Readers	Reader 1	Reader 2	Reader 3	Majority	Reader A	Reader B	Reader C	Majority
Sens. (%) 95% CI**	76.0 (63.1, 85.5)	89.3 (78.8, 95.0)	77.3 (64.8, 86.3)	83.6% (70.2, 91.7	57.0 (46.5, 66.9)	63.2 (52.5, 72.7)	79.8 (70.8, 86.6)	68.4 (58.4, 77.0)
Spec (%) 95% CI**	85.2 (81.1, 88.5)	84.1 (80.6, 87.1)	89.1 (86.1, 91.4)	89.4% (86.3, 91.8)	96.5 (94.6, 97.8)	94.9 (93.0, 96.2)	91.2 (88.5, 93.4)	95.4 (93.4, 96.8)

** logit transform and cluster sampling variance was used for all segments pooled analysis and all vessels pooled analysis to adjust for intra-subject correlation (sponsor provided)

Study # 2 - Registry (GE 012-096):

The diagnostic accuracy of Visipaque-enhanced CCTA results (positive finding of ≥50% stenosis) on predicting downstream cardiovascular events at each follow-up period when compared to the actual occurrence of events are summarized in Table 2. The sensitivity of Visipaque-enhanced CCTA for detection of downstream cardiac events was 96.1%, 95.8%, and 94.7% at the 1-, 6-, and 12-month follow-up time points, respectively, and the specificity was 84.5%, 86.6%, and 87.0%.

Table 2: Diagnostic Efficacy of CCTA for Prediction of Cardiac Events

Follow-up Period	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
1 month	49/51=96.1% (86.5, 99.5)	681/806=84.5% (81.8, 86.9)	49/174=28.2% (21.6, 35.5)	681/683=99.7% (98.9, 100.0)
6 month	68/71=95.8% (88.1, 99.1)	677/782=86.6% (84.0, 88.9)	68/173=39.3% (32.0, 47.0)	677/680=99.6% (98.7, 99.9)
12 month	72/76=94.7% (87.1, 98.5)	667/767=87.0% (84.4, 89.3)	72/172=41.9% (34.4, 49.6)	667/671=99.4% (98.5, 99.8)

CI = Confidence interval (Exact Binomial); NPV = Negative predictive value; PPV = Positive predictive value
Registry – disease prevalence predicted to be 25% in this population

Inferences:

- The clinical and statistical review teams have concluded that the presence of an (unintentional) verification bias in the re-read data, based on the knowing the data from the original read study, could not be excluded. Therefore the statistical review team did post-hoc re-analyses of the data from the original read study, applying the more conservative statistical rules from the Statistical Analysis Plan of the re-read study. The results are as follows:

- Vessel-level analysis of VISIPAQUE™-enhanced CCTA vs. ICA for a stenosis threshold of ≥50% and with segments <2 mm by ICA excluded showed moderate sensitivity ranging from 76% to 89 % for the original data. It also showed specificity ranging from 84% to 89% for the original data.

  Summary of most relevant results of Visipaque-enhanced CCTA, compared to ICA, at the vessel-level, with ≥ 50% stenosis threshold, and with segments < 2 mm by ICA excluded are given in the following Table 3

Table 3: Summary of Visipaque-enhanced CCTA at the vessel-level

Vessel-level (summation of all vessels)	Sensitivity % (95% CI)	Specificity % (95% CI)
Reader 1	76.0 (63.1, 85.5)	85.2 (81.1, 88.5)
Reader 2	89.3 (78.8, 95.0)	84.1 (80.6, 87.1)
Reader 3	77.3 (64.8, 86.3)	89.1 (86.1, 91.4)

- Registry study GE-012-096 demonstrates that symptomatic patients with intermediate pretest probability of CAD or an uninterpretable/equivocal stress test and no significant coronary artery stenosis by Visipaque-enhanced CCTA have a low likelihood of experiencing adverse cardiac outcomes in the following 12 months.

2. INTRODUCTION

GE Healthcare proposes to add a CCTA indication for Visipaque 320 mgI/mL based on evidence from GE-sponsored clinical studies, and supporting evidence of safety and efficacy evidence in the published literature (including studies performed only with Visipaque). The sponsor stated that evidence from both sources supports the diagnostic value of Visipaque-enhanced CCTA in the evaluation and management of patients with suspected coronary artery disease (CAD).

2.1 Overview

Visipaque (iodixanol) Injection is a dimeric, isosmolar, nonionic, water-soluble, radiographic X-ray contrast medium with a molecular weight of 1550.20 (iodine content 49.1%). It is administered by intravascular injection.

Visipaque (iodixanol) Injection has been approved by the United States Food and Drug Administration (US FDA) for the following indications:

- VISIPAQUE Injection (270 mgI/mL) is indicated for intra-arterial digital subtraction angiography.
- VISIPAQUE Injection (320 mgI/mL) is indicated for angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography.
- VISIPAQUE Injection (270 mgI/mL) is indicated for CECT imaging of the head and body, excretory urography, and peripheral venography.
- VISIPAQUE Injection (320 mgI/mL) is indicated for CECT imaging of the head and body, and excretory urography
- VISIPAQUE Injection (320 mgI/mL) is indicated for CECT imaging of the head and body, and excretory urography.

GE submitted this New Drug Application to the FDA, seeking to add an intravenous indication for Visipaque, to perform coronary CT angiography and proposes the following indications:

- *VISIPAQUE Injection (320 mgI/mL) is indicated for coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease.*

2.1.1 Regulatory History

Sponsor stated that "worldwide, particularly in Europe, IV coronary computed tomography angiography (CCTA) is considered an approved indication under the assumption that examination of the coronary artery system is covered under the computed tomography (CT) body indication; however, CCTA is considered off-label use in the US. Currently, no iodinated X-ray contrast agent has received FDA approval for this indication."

A brief regulatory history is as follows:

- End of phase 2 meeting on 27 August 2009

  - GE Healthcare pursued a potential CCTA indication for Visipaque 320 mgI/mL in 2009 [redacted] based on published literature and data from GE Healthcare-sponsored studies supporting its diagnostic value in management of patients with suspected CAD.

  - Given the inadequacy of the reviewed study data to form the basis of an approvable NDA submission, FDA recommended additional pivotal studies are needed.

- Type C Meeting on November 10, 2015

  - To discuss GE's proposed Phase 3 study for proposed indication "[redacted]

  - FDA suggested a pre sNDA meeting to evaluate the studies and literature that have already been done, new prospective study that the sponsor had proposed might not be necessary.

- Type B Meeting on July 13, 2016

  - CCTA indication "to assist in the diagnostic evaluation of patients with suspected CAD".

  - FDA agreed that the currently proposed indication, "to assist in the diagnostic evaluation of patients with suspected coronary artery disease," appeared sufficiently supported for sNDA filing review.

2.2 Data Sources

Data and definition files were provided by the sponsor.

The NDA in eCTD and SAS export files of these data are located at:
EDR Location: : \\CDSESUB1\evsprod\NDA020351\0000 Submission 0000

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and analysis provided by the sponsor were adequate.

3.2 Evaluation of Efficacy

3.2.1 Study Design

There were two studies evaluating the efficacy and safety.

The first study [GE-189-002 (VCT002)] was an open-label, prospective, multi-center, non-randomized study of outpatients with typical or atypical Chest Pain (CP) suspected of CAD. Visipaque dose was: Test bolus: 20 mL at 4-5 mL/s Main injection: 70-80 mL at 3.5-5 mL/s.

A re-read of this study (study GE-012-101) was performed to evaluate the diagnostic performance Visipaque enhanced CCTA in terms of sensitivity and specificity using the state-of-the-art, 64 detector row. The applicant states that "the purpose of the re-read was to assess the Visipaque-enhanced CCTA images in accordance with current published guidelines and clinical practice, and to address various aspects of the original image reading and assessment methodology that were judged to be suboptimal by the FDA."

We review these two studies simultaneously because they are based on two different reads of one set of test imaging and Standard of Truth (SoT) data from one clinical trial. The differences between the studies are that they used different anatomical models and that the re-read study included a comprehensive statistical analysis plan (please see Table 4). The re-read study was not conducted under the IND for Visipaque and therefore there was no input or guidance provided from DMIP/OB Statistics team for the re-read study.

The second study GE-012-096 was an open-label, prospective, multi-center, registry study of outpatients with chest pain syndrome scheduled to undergo CCTA. Visipaque dose was at the discretion of the prescribing physician. Mean dose: 91.5 mL Range: 30-180 mL The objective of this study was to assess prognostic value (sensitivity, specificity, PPV and NPV) of CCTA compared to subsequent ICA findings (if performed) or subject outcomes (MACE, death, revascularization). After eligibility confirmation/informed consent CCTA procedure was performed. Follow-up clinical outcome was assessed at 1, 6, and 12 month follow-up. This study evaluated prognostic value of CCTA.

3.2.2 Objective and number of subjects

Table 4 provides an overview of the pivotal GE-sponsored clinical efficacy studies. Table 5 provides evaluation methods and number of subjects in pivotal GE-sponsored clinical efficacy studies.

Table 4: Overview of the Pivotal GE-sponsored Clinical Efficacy Studies (Sponsor)

-	Study		
	Study1a: GE-189-002 (also known as VCT002)	**Study1b: GE-189-002 Re-read (GE-012-101)**	**Study2: GE-012-096**
Design	Open-label, prospective, multi-center, non-randomized	Open-label, prospective, multi-center, non-randomized re-read	Prospective, multi-center, registry
Study Phase	Phase 3	Phase 3	Phase 4
Number of Centers	17 centers in the United States (16 centers included subjects)	17 centers in the United States (16 centers included subjects)	17 centers in the United States and Canada
Population	Subjects with typical or atypical chest pain suspected of having CAD	Data from subjects previously dosed with iodinated contrast agent and imaged in GE-189-002 were analyzed.	Subjects with chest pain syndrome scheduled to undergo a Visipaque-enhanced CCTA examination
CT Scanner	GE LightSpeed™ VCT (64 slices)	GE LightSpeed™ VCT (64 slices)	Scanner types were not pre-specified or recorded.
Visipaque Dose	Test Bolus: 20 mL at 4 to 5 mL/sec. Main injection: 70-80 mL at 3.5 to 5 mL/sec	Re-read of data from GE-189-002 – dosing not applicable	IV administration at the discretion of the prescribing physician based upon institutional requirements for the CCTA procedure. Mean dose of 91.5 mL and range of 30-180 mL
Primary Endpoint	To evaluate the diagnostic performance of contrast-enhanced CCTA using the state-of- the-art, 64-detector-row LightSpeed VCT scanner for detection of presence or absence of coronary artery obstruction in typical or atypical subjects with chest pain when compared against CATH (QCA), the SoT	To evaluate the diagnostic performance of Visipaque™-enhanced CCTA in terms of sensitivity and specificity using the state-of-the-art, 64-detector-row LightSpeed VCT scanner for detection of presence or absence of coronary artery obstruction in typical or atypical subjects with chest pain when compared against QCA as the SoT.	To assess prognostic value in terms of sensitivity, specificity, PPV and NPV of CCTA compared to a SoT, i.e., subsequent ICA findings (if performed) or binary subject outcomes (occurrence of death, MACE, revascularization) during each follow-up period.
Standard of Truth	Quantitative assessment of elective ICA	Quantitative assessment of elective ICA	ICA findings (if performed after CCTA) or the binary subject outcomes (occurrence of death, MACE, revascularization) as assessed at each follow-up visit.

Table 5: Evaluation Methods and Subjects - Efficacy Studies (Sponsor)

	Study		
	Study1a: GE-189-002 (also known as VCT002)	**Study1b: GE-189-002 Re-read (GE-012-101)**	**Study2: GE-012-096**
Main Evaluation	Blinded image evaluation using AHA 15 coronary segmental model; segments <2mm by QCA excluded*	Blinded image evaluation using SCCT 18 coronary segment model; segments <2mm by QCA excluded*	CCTA images were evaluated on-site. Clinical outcomes at 1, 6, and 12 months were determined by an independent adjudicator based on review of clinical data collected by the sites.
Safety Evaluation	SAEs and unexpected AEs; tests of renal function (blood urea nitrogen, creatinine), vital signs	No new safety evaluation.	Frequency of unexpected AEs or SAEs up to 48 hours post-Visipaque administration
Number of Subjects Enrolled	245	232	885
Number of Subjects Dosed	232	NA	874
Age, Mean (Range)	57.1 (31-82)	57.1 (31-82)	58.8 (19-89)
Gender, % Male/Female	59.1/40.9	59.1/40.9	51/49
Race, %White/Black/Other	87.8/5.7/6.5	87.8/5.7/6.5	78/10/12
Number of Subjects Evaluable for Efficacy	230	230	857

Notes: AE = Adverse event; AHA = American Heart Association; **CAD** = Coronary artery disease; **CCTA =** Coronary computed tomography angiography; **CP** = Chest Pain; **ICA =** Invasive cardiac angiography; IV = Intravenous; MACE = Major adverse cardiac events; NA = Not applicable; NPV = Negative predictive value; PPV = Positive predictive value; **QCA =** Quantitative coronary analysis; SAE = Serious adverse event; SCCT = Society of Cardiovascular Computed Tomography; SoT = Standard of truth.
*Segments <2 mm by QCA excluded from the analysis because they cannot be treated by percutaneous intervention and as such are not clinically relevant in terms of estimating sensitivity and specificity of one test versus another one.

3.2.3 Demographic and Baseline Characteristics

Subject demographics were similar across the pivotal studies. In both the GE-189-002 and GE-012-096 studies, a slightly higher proportion of males (59% and 51% in GE-189-002 and GE-012-096 respectively) than females were enrolled. The mean age of subjects was also similar across the 2 studies (57.1 and 58.8 years). However, the age range of subjects included in the GE-189-002 study (31 to 82 years) was narrower than in the GE-012-096 study (19 to 89 years).

The demographic characteristics for the efficacy populations in the pivotal studies are presented in Table 6.

Table 6: Subject Demographics and Baseline Characteristics (Pivotal Studies)

Variable		First GE study – original and reread N=230	Second GE study - registry N=874
Age (years)	Mean ± SD	57.1 ± 9.9	58.8 ± 11.96
	Range (min-max)	31 - 82	19 - 89
Gender	Male	136 (59%)	443 (51%)
	Female	94 (41%)	431 (49%)
Race	Caucasian	202 (88%)	684 (78%)
	African American	13 (6%)	86 (10%)
	Other	15 (6%)	104 (12%)
Weight (kg)	Mean ± SD	92.5 ± 21.1	86.0 ± 20.41
	Range (min-max)	49 - 174	45 - 177
BMI (kg/m2)	Mean ± SD	31.4 ± 6.2	29.7 ± 6.39
	Range (min-max)	16.8 - 50.5	15.2 – 71.0
CAC score*	Mean +- SD	284.0 ± 538.2	216.4 ± 527.01
	Range (min-max)	0.0 - 3859.0	0 - 5077

Notes: Registry – Asian 38 (4%), American Indian or Alaska native 5 (1%), Other 61 (7%)
*Coronary Artery Calcium (CAC) Score is total sum of calcium scores from the 4 main vessels
BMI = Body Mass Index

3.3 Results and Conclusions

3.3.1 Pivotal Studies

There were two GE sponsored pivotal studies.

Study 1– (a) original and Study 1-(b) reread (2006-2007)

First GE study1 GE-189-002 (also known as VCT002) was an open-label, prospective, multi-center, non-randomized study of outpatients with typical or atypical CP suspected of CAD. The re-read of the original was study GE-012-101.

The objective was to evaluate the diagnostic performance (sensitivity, specificity, PPV and NPV) of CCTA for the detection or presence or absence of coronary artery obstruction when compared against ICA

Second GE study 2 – registry (2008-2010)

The second GE study GE-012-096 was an open-label, prospective, multi-center, registry study of outpatients with chest pain syndrome scheduled to undergo CCTA.

The objective was to assess prognostic value (sensitivity, specificity, PPV and NPV) of CCTA compared to subsequent ICA findings (if performed) or subject outcomes (MACE, death, revascularization).

The results of each of these two studies are discussed below.

3.3.2 GE Study # 1 (a) Original Read and Study 1 (b) Re-read

Primary objective for both original read and re-read studies was to evaluate the diagnostic performance (sensitivity, specificity, PPV and NPV) of CCTA for the detection or presence or absence of coronary artery obstruction when compared against ICA (performed 2-21 days later than CCTA procedure. Both had blinded image evaluation to determine the co-primary efficacy endpoints, sensitivity and specificity.

The original read study and its re-read evaluated the diagnostic performance of CCTA and involved 3 central readers.

For both the original study and for the reread, each segment was graded. Each segment was first determined to be evaluable or not evaluable (reasons for not-evaluable: vessel motion, banding artifact, calcification, not seen, other).

For each segment, the diameter was designated as less than 2 mm or as greater than or equal to 2 mm

For each segment, a quantitative degree of stenosis was estimated (0-100), and a degree of qualitative stenosis was categorized.

There were three CCTA readers for the study. Each reader independently read each CCTA blindly.

All of the CCTAs and all of the ICAs were read in the original study and were reread in the reread study. The ICA images were interpreted by a single independent blinded reader using quantitative coronary analysis (QCA) software. For the original read study (GE-189-002), the QCA reader performed the automated QCA assessment on each coronary segment that was deemed to be >30% in stenosis by visual inspection. For the re-read study, the QCA reader performed the QCA assessment on every coronary segment. As with the CCTA interpretations, the AHA 15 segmental model was used for the original study, and the SCCT 18 segmental model was used for the re-read study. The QCA reader for the original study and the QCA reader for the reread study were two different physicians, trained in interpretation of ICA.

3.3.3 GE Study # 1 – Data Analysis – (a) Original Read and (b) Re-read

- Based on the data collected from the CCTA and ICA interpretations, the diagnostic performance was evaluated as follows:

  - Subject, vessel, or segment level analyses
    - Compare segment read to segment read
    - Compare vessel read to vessel read
    - Compare subject read to subject read
  - Definition of significant stenosis
    - ≥ 50% stenosis
    - ≥ 70% stenosis
  - Any segment unevaluable by ICA was excluded
  - Inclusion or exclusion of segments < 2mm by ICA
    - Inclusion of segments < 2 mm diameter
    - Exclusion of segments < 2 mm diameter
  - Inclusion or exclusion of segments < 2 mm by CCTA
    - Inclusion of segments < 2 mm diameter
    - Exclusion of segments < 2 mm diameter

3.3.4 Statistical Analyses

The co-primary endpoints of the GE-012-101 study were sensitivity and specificity of Visipaque-enhanced CCTA vs. QCA for a stenosis threshold of ≥50% and with segments <2 mm by QCA excluded.

The primary analysis was the determination of the point estimates and exact 95% binomial CIs for the co-primary endpoints of sensitivity and specificity of the blinded visual assessment of

the Visipaque-enhanced CCTA images at the subject level, vessel-level and segment-level with segments <2 mm by QCA excluded. The blinded visual image assessments were performed by 3 independent, blinded readers trained and experienced in the interpretation of CCTA images. The primary analysis was conducted independently for each reader and for the majority read.

For a subject-level analysis, a subject would be categorized as positive if there is a significant (≥50% or 70%) stenosis in any segment of any vessel by SoT. At the vessel-level positive (abnormal) vessels had significant coronary artery stenosis (≥50%) in at least 1 segment within the vessel by the SoT and negative (normal) vessels had 0 segments within the vessel with significant coronary artery stenosis (≥50% or 70%) by SoT. In a segment level analysis, a segment is categorized as positive if there is significant (≥50% or 70%) stenosis by SoT.

Exact binomial confidence interval was used for individual segment analysis, individual vessel analysis, and subject level analysis; logit transform and cluster sampling variance was used for all segments pooled analysis and all vessels pooled analysis. Exact binomial confidence limits were used for 0/N or N/N.

For vessel-level and segment-level analyses, the 95% confidence interval was adjusted for intra-subject correlation, using SAS PROC SURVEYMEANS to compute the adjusted standard error, and the accuracy was improved through using a logit transform (Edwardes MD – "The evaluation of confidence sets, with application to binomial confidence intervals", Statistica Sinica 1998;8: 393-409.) Specifically, with SE = adjusted standard error, and P = the estimate (of sensitivity, specificity), the 95% confidence limits are

$$1 - 1/[1+P\times\exp(\pm 1.96\times SE/(P(1-P))/(1-P)].$$

Where P = 0 or 1, exact binomial confidence limits were used for 0/N or N/N, with N being the number of subjects, because P = 0 or 1 implies perfect intra-subject correlation.

The pre-specified co-primary endpoints for the original read study were the sensitivity and specificity of CCTA at the subject level; for the re-read study, the pre-specified co-primary endpoints were the sensitivity and specificity at the vessel level.

Both subject level and vessel level analyses are valuable. A vessel level analysis is valuable in terms of evaluating the disease localization of Visipaque-enhanced CCTA, which is a reasonable expectation of a CT-based test. In subject-level analysis, there is clinical benefit in terms of the ability of Visipaque to reliably "rule-out" any significant coronary stenosis at the subject level.

3.3.5 Sample Size:

Subject Level Analysis:

245 subjects enrolled
- 13 had no CCTA
- 232 underwent CCTA
-2 excluded

230 subjects (efficacy population) had both CCTA and CATH images available for blind read.

Vessel Level Analysis

Summation of all vessels included 906 vessels (4 vessels per subject).

- Right coronary artery (RCA)= 221,
- Left coronary artery (LCA) = 229,
- Left anterior descending coronary artery (LAD)=227,
- Left circumflex coronary artery (LCX)=229,
- 7 were discordance (one reader rated diseased, one not diseased, and one unevaluable)

Segment Level Analysis

Efficacy populations - summation of all segments included 2023 segments with 16 discordance for 50% stenosis threshold with with Segments Unevaluable or <2mm by CATH Excluded. The distribution of these segments is given below in Table 7:

Table 7: Efficacy Populations - Reader Discordance

50% Stenosis Threshold	Total (N)	Discordance (n, %)
Summation of all	2023	25 (1.2)
Segment 01: pRCA	219	0 (0)
Segment 02: mRCA	189	3 (1.6)
Segment 03: dRCA	177	2 (1.1)
Segment 04: PDA	82	1 (1.2)
Segment 05: LM	229	2 (0.9)
Segment 06: pLAD	227	4 (1.8)
Segment 07: mLAD	198	2 (1.0)
Segment 08: aLAD	33	0 (0)
Segment 09: D1	82	2 (2.4)
Segment 10: D2	26	0 (0.0)
Segment 11: pLCX	228	2 (0.9)
Segment 12: OM1	156	1 (0.6)
Segment 13: dLCX	149	4 (2.7)
Segment 14: PL	24	2 (8.3)
Segment 15: PD	4	0 (0)

3.3.6 GE Study # 1a - Original Read (GE 189-002, aka VCT 002):

Subject level analysis was pre-specified. Standard of Truth **was q**uantitative assessment of elective ICA.

Original read study "Subject level sensitivity was defined as the proportion of subjects with at least 1 diseased segment by ICA who also had at least 1 diseased segment by CCTA for at least 2 readers.

Original read study "Subject level specificity was defined as the proportion of subjects with no diseased segments by ICA who had none of the same segments diseased by CCTA for at least 2 readers"

3.3.7 GE Study # 1a - Original Read Results:

The original read results for study1a at subject level are given in the following table 8.

Table 8: Study GE-189-002 Subject Level Analysis (Majority Read)

	Primary endpoint (≥ 50%) excluding segments < 2mm by QCA			Additional endpoint (≥ 50%) including segments < 2mm by QCA		
	ICA +	ICA -	Total	ICA +	ICA -	Total
CCTA +	45	38	83	52	30	82
CCTA -	2	142	144	3	142	145
Total	47	180	227	55	172	227
Sensitivity (%) 95% CI	95.7 (85.5, 99.5)			94.6 (84.9, 98.9)		
Specificity (%) 95% CI	78.9 (72.2, 84.6)			82.6 (76.1. 87.9)		
NPV	98.6%			97.9%		

Comment: 3 discordant subjects were excluded, 2 with disease by CATH (ICA), 1 without
Additional endpoint includes segments < 2mm by QCA
CI = 95% exact binomial confidence interval.

3.3.7 GE Study # 1b - Reasons for doing reread study **(GE 102-101):**

- Data analysis
  - "All analyses were to be performed for each reader separately according to the protocol.
  - SAP was changed so that the analyses were performed based on "reader consensus" rather than for each reader separately
- Original study failed to reject the hypothesis that specificity is ≤80% which was a pre-specified :
  - For subject-level sensitivity and specificity, null and alternative hypotheses were tested:
  - H_0: Sensitivity ≤ 0.80 versus H_a: Sensitivity > 0.80, and
  - H_0: Specificity ≤ 0.80 versus H_a: Specificity > 0.80
- FDA feedback on GE-189-002 (Type B Meeting 8-27-2009)

- Study is not adequate as confirmatory or pivotal study forming (in part or in isolation) the basis of an approvable NDA submission

- Lower limit of the CI on both Sensitivity and specificity not greater than 80% Image assessment procedure

- Lack of clarity regarding characterization of non-evaluable segments

3.3.8 Major differences in First read and Re-read analyses:

Major differences in First read and Re-read analysis are given in the following Table 9

Table 9: Original and Reread Analysis Differences

	GE-189-002 original	GE-012-101 Reread
Coronary artery model	AHA 15 segment	SCCT 18 segment (2009)
CCTA read		
3 independent blinded readers		
Consensus	Agreement of 2/3	Agreement of 2/3
Discordant results	Excluded	Counted as FN or FP, depending on SoT
By reader analysis	Not done	Done
Unevaluable segments	Given same result as most adjacent segment	Counted as FN or FP, depending on the SoT
Hypotheses Testing	Done; Failed to reject null for specificity	Not formulated
Intra-reader reliability	Not done	Done for 10% of subjects
ICA read	QCA by one blinded reader	QCA by single reader
Intra-reader reliability	Not done	Done for QCA

3.3.9 Post-hoc Subject Level Per Reader Analysis - original read data:

230 subjects had both CCTA and CATH (ICA) images available for blind read. (59.1% male, 57±10 years). The mean inter-test interval between CCTA and CATH (ICA) was 5.9±4.3 days. On a subject-based model, the sensitivity and specificity to detect ≥50% stenosis and 95% confidence interval based on exact binomial test are provided in Table 10.

Table 10: GE-102-101 (original data) per Subject Level Analysis

	Readers – Original Read Data								
	Reader 1			Reader 2			Reader 3		
	ICA +	ICA -	Total	ICA +	ICA -	Total	ICA +	ICA -	Total
CCTA +	44	33	77	48	54	102	44	33	77
CCTA -	2	137	139	1	126	127	4	147	151
Unevaluable	3	11	14	0	1	1	1	1	2
All Total	49	181	230	49	181	230	49	181	230
Sensitivity (%) 95% CI	44/49 = 89.8 (77.8, 96.6)			48/49 = 98.0 (89.2, 100.0)			44/49 = 89.8 (77.8, 96.6)		
Specificity (%) 95% CI	137/181 = 75.7 (68.8, 81.8)			126/181 = 69.6 (62.4. 76.2)			147/181 = 81.2 (74.8, 86.6)		

Notes: 1> For sensitivity unevaluable were treated as FN and for specificity unevaluable were treated as FP per defined algorithm. (conservative assignment)
2> 95% Confidence Intervals are based on Exact Binomial Test

Sponsor stated that "None of the readers achieved statistical significance for either sensitivity or specificity at the ≥70% stenosis threshold. There were only 28 patients who were diseased by CATH at the ≥70% stenosis threshold.

3.3.10 Subject Level, Per Reader Analysis – re-read data:

230 subjects had both CCTA and CATH (ICA) images available for blind reread. (59.1% male, 57±10 years). The mean inter-test interval between CCTA and CATH (ICA) was 5.9±4.3 days. On a subject-based model, the sensitivity and specificity to detect ≥50% stenosis and 95% confidence interval based on exact binomial test are provided in Table 11.

Table 11: Study 012-101 (reread Data) per Patient Level

	Readers – Reread data GE-012-101								
	Reader A			Reader B			Reader C		
	ICA +	ICA -	Total	ICA +	ICA -	Total	ICA +	ICA -	Total
CCTA +	48	6	54	56	17	73	63	20	83
CCTA -	23	152	175	15	151	156	8	138	146
Total	71	158	229	71	158	229	71	158	229
Sensitivity %) 95% CI	67.6 (55.5, 78.2)			78.9 (67.6, 87.7)			88.7 (79.0, 95.0)		
Specificity (%) 95% CI	96.2 (91.9, 98.6)			89.2 (83.3, 93.6)			87.3 (81.1, 92.1)		

3.3.11 Post-hoc Vessel Level Analysis - Original read data - by reader analysis:

Table 12 provides VISIPAQUE™-enhanced CCTA Visual Assessments Compared to CATH (ICA) as Standard of Truth by Reader with Segments Unevaluable or <2mm by CATH (ICA) Excluded (Summation of All Vessels Assuming Independent Vessels) (Stenosis ≥ 50%) (Efficacy Population). The Sensitivity estimates for readers 1, 2 and 3 are 76% , 89% and 77% respectively and the Specificity estimates for readers 1, 2 and 3 are 85% , 84% and 89% respectively

Table 12: Summation of All Vessels (Stenosis ≥ 50%) by reader for original data

	Readers – Original Read Data (Stenosis ≥ 50%)								
	Reader 1			Reader 2			Reader 3		
	CATH +	CATH -	Total	CATH +	CATH -	Total	CATH +	CATH -	Total
CCTA +	57	68	125	67	126	193	58	74	132
CCTA -	14	708	722	8	699	707	14	740	754
Unevaluable	4	55	59	0	6	6	3	17	20
All Total	75	831	906	75	831	906	75	831	906
Sensitivity (%) **95% CI*** **95% CI****	57/75 = 76.0 (64.8, 85.1) (63.1, 85.5)			67/75 = 89.3 (80.1, 95.3) (78.8, 95.0)			58/75 =77.3 (66.2, 86.2) (64.8, 86.3)		
Specificity (%) **95% CI*** **95% CI****	708/831 = 85.2 (82.6, 87.5) (81.1, 88.5)			699/831 = 84.1 (81.5, 86.5) (80.6, 87.1)			740/831 = 89.1 (86.7, 91.1) (86.1, 91.4)		

*based on exact binomial confidence interval assuming independent vessels

** logit transform and cluster sampling variance was used for all segments pooled analysis and all vessels pooled analysis to adjust for intra-subject correlation (sponsor provided)

Notes: 1> For sensitivity unevaluable were treated as FN and for specificity unevaluable were treated as FP per defined algorithm. (a conservative assignment)

2> A vessel was categorized as diseased if there was at least 1 diseased segment by CATH (ICA) within the vessel and not diseased if there were no diseased segments within the vessel.

Table 13 provides VISIPAQUE™-enhanced CCTA Visual Assessments Compared to CATH (ICA) as Standard of Truth by Reader with Segments Unevaluable or <2mm by CATH (ICA) Excluded (Summation of All Vessels Assuming Independent Vessels) (Stenosis ≥ 70%) (Efficacy Population). The Sensitivity estimates for readers 1, 2 and 3 are 76% , 88% and 88% respectively and the Specificity estimates for readers 1, 2 and 3 are 89% , 87% and 90% respectively

Table 13: Summation of All Vessels (Stenosis ≥ 70%) by reader for original data

	Readers Original Read Data (Stenosis ≥ 70%)								
	Reader 1			Reader 2			Reader 3		
	CATH +	CATH -	Total	CATH +	CATH -	Total	CATH +	CATH -	Total
CCTA +	25	34	59	29	105	133	29	66	95
CCTA -	7	781	788	4	762	766	3	788	791
Unevaluable	1	58	59	0	6	6	1	19	20
All Total	33	873	906	33	873	906	33	873	906
Sensitivity %)	25/33 = 75.8			29/33 = 87.9			29/33 = 87.9		
95% CI*	(57.7, 59.1)			(71.8, 96.6)			(71.8, 96.6)		
95% CI**	(56.9, 88.1)			(70.9, 95.6)			(71.6, 95.4)		
Specificity (%)	781/873 = 89.5			762/873 = 87.3			788/873 = 90.3		
95% CI*	(87.2, 91.4)			(84.9, 89.4)			(88.1, 92.2)		
95% CI**	(85.5, 92.4)			(84.1, 89.9)			(87.4, 92.6)		

*based on exact binomial confidence interval assuming independent vessels

** logit transform and cluster sampling variance was used for all segments pooled analysis and all vessels pooled analysis to adjust for intra-subject correlation (sponsor provided)

Notes: 1> For sensitivity unevaluable were treated as FN and for specificity unevaluable were treated as FP per defined algorithm. (a conservative assignment)

2> A vessel was categorized as diseased if there was at least 1 diseased segment by CATH (ICA) within the vessel and not diseased if there were no diseased segments within the vessel.

95% Confidence Interval are based on sponsor's analysis

Comparing side-by-side 50% Stenosis vs. 70% Stenosis, sensitivity & specificity are similar.

3.3.12 Post-hoc Vessel Level Analysis - read and reread data summary by reader:

Table 14 provides VISIPAQUE™-enhanced CCTA Visual Assessments Compared to CATH as Standard of Truth by Reader with Segments Unevaluable or <2mm by CATH Excluded (Summation of All Vessels) (Stenosis ≥ 50%) (Efficacy Population). This table provides sensitivity and specificity for summation of all vessels by readers and by majority read for both original read data and reread data.

This table showed moderate sensitivity ranging from 76% to 89 % for the original data and 57% to 80% for reread data. It also showed specificity ranging from 84% to 89% for the original data and 91% to 97% for reread data

Table 14: Summation of All Vessels (Stenosis ≥ 50%) by reader for original and reread data

Vessel-level Analysis (Summation of all vessels) (Stenosis ≥ 50%)								
	GE-189-002 (Original Data)				GE-012-101(Reread Data)			
Readers	Reader 1	Reader 2	Reader 3	Majority	Reader A	Reader B	Reader C	Majority
Sens. (%) 95% CI**	76.0 (63.1, 85.5)	89.3 (78.8, 95.0)	77.3 (64.8, 86.3)	83.6% (70.2, 91.7	57.0 (46.5, 66.9)	63.2 (52.5, 72.7)	79.8 (70.8, 86.6)	68.4 (58.4, 77.0)
Spec (%) 95% CI**	85.2 (81.1, 88.5)	84.1 (80.6, 87.1)	89.1 (86.1, 91.4)	89.4% (86.3, 91.8)	96.5 (94.6, 97.8)	94.9 (93.0, 96.2)	91.2 (88.5, 93.4)	95.4 (93.4, 96.8)

** logit transform and cluster sampling variance was used for all segments pooled analysis and all vessels pooled analysis to adjust for intra-subject correlation (sponsor provided)

3.3.13 Post-hoc Segment Level Analysis - Original and reread data summary by reader:

Table 15 provides VISIPAQUE™-enhanced CCTA Visual Assessments Compared to CATH (ICA) as Standard of Truth by Reader with Segments Unevaluable or <2mm by CATH (ICA) Excluded (Summation of All Segments) (Stenosis ≥ 50%) (Efficacy Population). This table provides sensitivity and specificity for summation of all segments by readers and by majority read for both original read data and reread data.

This table shows showed moderate sensitivity ranging from 55% to 77 % for the original data and 40% to 60% for reread data. It also showed specificity ranging from 88% to 91% for the original data and 94% to 96% for reread data.

Table 15: Post-hoc Summation of All Segments for original and reread data

Segment-level Analysis (Summation of all segments)(Stenosis ≥ 50%)								
	GE-189-002 (Read)				GE-012-101 (Reread)			
Readers	Reader 1	Reader 2	Reader 3	Majority	Reader A	Reader B	Reader C	Majority
Sens. (%) 95% CI**	62.1 (50.5, 72.4)	77.0 (66.9, 84.7)	55.2 (43.8, 66.0)	64.7 (52.6, 75.2)	40.0 (31.4, 49.3)	47.4 (37.7, 57.4)	60.0 (50.9, 68.4)	47.4 (38.0, 57.0)
Spec (%) 95% CI**	87.6 (83.6, 90.7)	89.4 (87.0, 91.4)	91.4 (89.3, 93.1)	92.9 (90.8, 94.6)	95.5 (94.1, 96.5)	95.6 (94.5, 96.5)	93.8 (92.1, 95.2)	96.2 (95.0, 97.1)

** logit transform and cluster sampling variance was used for all segments pooled analysis and all vessels pooled analysis to adjust for intra-subject correlation (sponsor provided)

The clinical and statistical review teams concluded that the presence of an (unintentional) verification bias in the re-read data, based on the knowing the data from the original read study, could not be excluded. Therefore the statistical review team did post-hoc re-analyses of the data from the original read study, applying the more conservative statistical rules from the Statistical Analysis Plan of the re-read study. The results were the same as the applicant's post-hoc analysis results of the original read data, as provided above.

The statistical review team presented the results at the subject-level, at the vessel-level, and at the segment-level to the clinical review team and that team decided that, clinically, the vessel-level analysis reflected the most useful data, in terms of providing localization of disease.

3.3.14 Study # 2 - Registry (GE 012-096):

Design: GE-012-096 was an open-label, prospective, multi-center registry study of outpatients with chest pain syndromes scheduled to undergo CCTA.

The purpose of the Visipaque-enhanced CCTA registry study was to evaluate the usefulness of CCTA findings in predicting patient outcome in routine clinical practice. The study was conducted between September 2008 and September 2010 with 885 patients enrolled at 17 centers. 11 had no CCTA, 874 underwent CCT and 17 were excluded. This resulted in the efficacy population of 857 subjects and 850 subjects completed the study.

The Primary endpoint was to assess prognostic value (sensitivity, specificity, PPV and NPV) of CCTA compared to subsequent ICA findings (if performed) or subject outcomes (MACE, death, revascularization). After eligibility confirmation/informed consent CCTA procedure was performed. Follow-up clinical outcome was assessed at 1, 6, and 12 month follow-up. This study evaluated prognostic value of CCTA. The clinical outcome for the follow-up period is given in the following table 16:

Table 16: Clinical Outcomes Follow-up Period

Clinical Outcome	Follow-up Period		
	1 month	6 month	12 month
	N = 857	N = 853	N = 843
Positive	51 (6%)	71 (8%)	76 (9%)
Negative	806 (94%)	782 (92%)	767 (91%)

The diagnostic accuracy of Visipaque-enhanced CCTA results (positive finding of ≥50% stenosis) on predicting downstream cardiovascular events at each follow-up period when compared to the actual occurrence of events are summarized in Table 17. The sensitivity of Visipaque-enhanced CCTA for detection of downstream cardiac events was 96.1%, 95.8%, and 94.7% at the 1-, 6-, and 12-month follow-up time points, respectively, and the specificity was 84.5%, 86.6%, and 87.0%.

Table 17: Diagnostic Efficacy of CCTA for Prediction of Cardiac Events

Follow-up Period	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
1 month	49/51=96.1% (86.5, 99.5)	681/806=84.5% (81.8, 86.9)	49/174=28.2% (21.6, 35.5)	681/683=99.7% (98.9, 100.0)
6 month	68/71=95.8% (88.1, 99.1)	677/782=86.6% (84.0, 88.9)	68/173=39.3% (32.0, 47.0)	677/680=99.6% (98.7, 99.9)
12 month	72/76=94.7% (87.1, 98.5)	667/767=87.0% (84.4, 89.3)	72/172=41.9% (34.4, 49.6)	667/671=99.4% (98.5, 99.8)

CI = Confidence interval(Exact Binomial); NPV = Negative predictive value; PPV = Positive predictive value
Registry – disease prevalence predicted to be 25% in this population

3.3.15 Pediatric Subjects:

There are no GE-sponsored studies in the pediatric population for this indication. The sponsor refers to the current Visipaque Injection package insert for information to pediatric subjects.

3.4 Evaluation of Safety

Study 1: In the GE-189-002 study, the VISIPAQUE™- enhanced CCTA procedure was well tolerated. There were no reported deaths nor any serious, significant or severe in intensity AEs. Of the 232 subjects in the safety population of the GE-189-002 study, 24 subjects experienced a total of 34 AEs: 25 were mild in intensity and 9 were moderate. Eleven subjects experienced AEs classified as cardiac disorders: 7 subjects experienced a mild cardiac disorder, and 4 subjects experienced a moderate cardiac disorder.

Study 2: Of the 874 subjects included in the Safety population, 17 (2%) subjects experienced 1 or more TEAEs and 5/874 (1%) subjects had TEAEs that were considered related to VISIPAQUE administration. There were 10 SAEs reported for 8 (1%) subjects. None of the SAEs were considered related to VISIPAQUE administration. A total of 27 TEAEs occurred in 17 of 874 subjects (2%) in this registry study. The most commonly reported TEAEs were hypersensitivity, followed by angina pectoris, CAD and coronary artery stenosis. There were no TEAEs leading to death or discontinuation during the study. Results are summarized in Table 18.

Table 18: Overall Summary of TEAEs (Safety Population) Study 2

	All Event	Causal Relations
Subjects with at Least 1 AE, n (%)	17 (2%)	5
Number of AEs, n	27	10
Subjects with Related AEs, n (%)	5	5
Number of Related AEs, n	10	10
Subjects with SAEs, n (%)	8	0
Number of SAEs, n	10	0
Subjects with AEs Leading to Discontinuation from	0	0
Deaths, n (%)	0	0

N = number of subjects in the safety population; n = number in category; % = n/N*100%. Adverse events (AEs) summarized in this table are treatment-emergent unexpected AEs or serious adverse events (SAEs) occurring within 48 hours following administration of VISIPAQUE.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant stated that no comparison of results in sub-populations has been performed. Patients included in the pivotal studies discussed here were from similar populations. As such, comparison of results in sub-populations is not applicable. There were no special groups identified by the clinical team.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor's interaction with the FDA on this NDA started in 2009. After numerous meetings and exchange of information, this NDA s44 was submitted based on guidance given by the FDA Division of Medical Imaging Products (DMIP) to the Sponsor.

GE Healthcare proposes to add a CCTA indication for Visipaque 320 mgI/mL based on evidence from GE-sponsored clinical studies, and supporting evidence of safety and efficacy evidence in the published literature (including studies performed only with Visipaque).

- **Visipaque Injection (320 mgI/mL) is indicated for use in coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease.**

In support of the indication, the sponsor submitted the efficacy results of the following pivotal GE sponsored studies:

(a) GE-189-002 (also known as VCT002); an open-label, prospective, multi-center study to evaluate diagnostic performance of Visipaque-enhanced CCTA using the GE LightSpeed VCT scanner for detection of coronary artery obstruction in typical or atypical chest pain patients. There were 245 patients enrolled in this study with 232 safety patients and 230 efficacy patients. A re-read of this study (study GE-012-101) was performed to evaluate the diagnostic performance Visipaque enhanced CCTA in terms of sensitivity and specificity.

(b) GE-012-096; a registry study to assess, prospectively, the value of CCTA examination findings in predicting the occurrence of downstream adverse cardiac events in patients with symptomatic chest pain syndrome who are undergoing Visipaque-enhanced CCTA.

The statistical review team presented the results for Study 1 at the subject-level, at the vessel-level, and at the segment-level to the clinical review team and that team decided that, clinically, the vessel-level analysis reflected the most useful data, in terms of providing localization of disease.

Therefore the results for Study 1 (GE-189-002 also known as VCT002) at vessel-level are summarized below:

Vessel Level Analysis - Original and reread data - By Reader Analysis

Table 19 provides VISIPAQUE™-enhanced CCTA Visual Assessments Compared to CATH as Standard of Truth by Reader with Segments Unevaluable or <2mm by CATH Excluded (Summation of All Vessels) (Stenosis ≥ 50%) (Efficacy Population). This table provides sensitivity and specificity for summation of all vessels by readers and by majority read for both original read data and reread data.

This table showed moderate sensitivity ranging from 76% to 89 % for the original data and 57% to 80% for reread data. It also showed specificity ranging from 84% to 89% for the original data and 91% to 97% for reread data

Table 19: Summation of All Vessels (Stenosis ≥ 50%) by reader for original and reread data

Vessel-level Analysis (Summation of all vessels) (Stenosis ≥ 50%)								
	GE-189-002 (Original Data)				GE-012-101(Reread Data)			
Readers	Reader 1	Reader 2	Reader 3	Majority	Reader A	Reader B	Reader C	Majority
Sens. (%) 95% CI**	76.0 (63.1, 85.5)	89.3 (78.8, 95.0)	77.3 (64.8, 86.3)	83.6% (70.2, 91.7	57.0 (46.5, 66.9)	63.2 (52.5, 72.7)	79.8 (70.8, 86.6)	68.4 (58.4, 77.0)
Spec (%) 95% CI**	85.2 (81.1, 88.5)	84.1 (80.6, 87.1)	89.1 (86.1, 91.4)	89.4% (86.3, 91.8)	96.5 (94.6, 97.8)	94.9 (93.0, 96.2)	91.2 (88.5, 93.4)	95.4 (93.4, 96.8)

** logit transform and cluster sampling variance was used for all segments pooled analysis and all vessels pooled analysis to adjust for intra-subject correlation (sponsor provided)

Study # 2 - Registry (GE 012-096):

The diagnostic accuracy of Visipaque-enhanced CCTA results (positive finding of ≥50% stenosis) on predicting downstream cardiovascular events at each follow-up period when compared to the actual occurrence of events are summarized in Table 20. The sensitivity of Visipaque-enhanced CCTA for detection of downstream cardiac events was 96.1%, 95.8%, and 94.7% at the 1-, 6-, and 12-month follow-up time points, respectively, and the specificity was 84.5%, 86.6%, and 87.0%.

Table 20: Diagnostic Efficacy of CCTA for Prediction of Cardiac Events

Follow-up Period	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
1 month	49/51=96.1% (86.5, 99.5)	681/806=84.5% (81.8, 86.9)	49/174=28.2% (21.6, 35.5)	681/683=99.7% (98.9, 100.0)
6 month	68/71=95.8% (88.1, 99.1)	677/782=86.6% (84.0, 88.9)	68/173=39.3% (32.0, 47.0)	677/680=99.6% (98.7, 99.9)
12 month	72/76=94.7% (87.1, 98.5)	667/767=87.0% (84.4, 89.3)	72/172=41.9% (34.4, 49.6)	667/671=99.4% (98.5, 99.8)

CI = Confidence interval (Exact Binomial); NPV = Negative predictive value; PPV = Positive predictive value
Registry – disease prevalence predicted to be 25% in this population

Inferences:

- The clinical and statistical review teams have concluded that the presence of an (unintentional) verification bias in the re-read data, based on the knowing the data from the original read study, could not be excluded. Therefore the statistical review team did post-hoc re-analyses of the data from the original read study, applying the more conservative statistical rules from the Statistical Analysis Plan of the re-read study. The results are as follows:

- Vessel-level analysis of VISIPAQUE™-enhanced CCTA vs. ICA for a stenosis threshold of ≥50% and with segments <2 mm by ICA excluded showed moderate sensitivity ranging from 76% to 89 % for the original data. It also showed specificity ranging from 84% to 89% for the original data.

  Summary of most relevant results of Visipaque-enhanced CCTA, compared to ICA, at the vessel-level, with ≥ 50% stenosis threshold, and with segments < 2 mm by ICA excluded are given in the following Table 21

Table 21: Summary of Visipaque-enhanced CCTA at the vessel-level

Vessel-level (summation of all vessels)	Sensitivity % (95% CI)	Specificity % (95% CI)
Reader 1	76.0 (63.1, 85.5)	85.2 (81.1, 88.5)
Reader 2	89.3 (78.8, 95.0)	84.1 (80.6, 87.1)
Reader 3	77.3 (64.8, 86.3)	89.1 (86.1, 91.4)

- Registry study GE-012-096 demonstrates that symptomatic patients with intermediate pretest probability of CAD or an uninterpretable/equivocal stress test and no significant coronary artery stenosis by Visipaque-enhanced CCTA have a low likelihood of experiencing adverse cardiac outcomes in the following 12 months.

SIGNATURES/DISTRIBUTION LIST

Signatures:

Primary Statistical Reviewer:	Satish Misra, Ph. D.
Secondary Statistical Reviewer:	Jyoti Zalkikar, Ph. D.
Tertiary Statistical Reviewer:	Peiling Yang, Ph. D. Division of Biostatistics I

Distribution List:

Project Manager:	Frank Lutterodt/ Kyong Kang (TL)
Medical Officer:	Karen Bleich, M.D.
Medical Team Leader:	Anthony Fotenos, M.D.
Division Director:	Libero Marzella, M. D., DMIP
Primary Statistical Reviewer:	Satish Misra, Ph. D., DBI
Secondary Statistical Reviewer	Jyoti Zalkikar, Ph. D., DBI
Tertiary Statistical Reviewer	Peiling Yang, Ph. D., DB1
Biometrics Division Director:	Hsien Ming J. Hung, Ph. D., DBI
Biometrics Division (Files)	Lillian Patrician, DBV

File: C:\CDER\2017 IND NDA\NDA 20351 Stat Review 12 March 2017

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/s/

SATISH C MISRA
03/17/2017

JYOTI ZALKIKAR
03/17/2017
This primary review for the medical imaging drug Visipaque is satisfactory. I concur with its findings.

PEILING YANG
03/18/2017
Signed for Dr. H.M. James Hung.

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA 020351
Supplement #:	S-0044
Product Name:	Visipaque
Indication(s):	CCTA to assist in diagnostic evaluation of Patients with suspected coronary artery disease.
Applicant:	GE Healthcare
Dates:	Submission: 10/05/16 ; PDUFA Date 4/05/17
Review Priority:	Priority
Biometrics Division:	Division 1
Statistical Reviewer:	A G Mucci, PH. D.
Concurring Reviewers:	Jyoti Zalkikar PH. D.
Medical Division:	Division of Medical Imaging
Clinical Team:	Reviewer: Karen Bleich M.D. ; Team Leader: Anthony Fotenos M.D.
Project Manager:	Frank Lutterodt

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings
GE-189-002	MC Crossover	Visipaque	Primary: Sensitivity/Specificity	
GE -012 096	Re-Read of GE-189-002	Visipaque	Primary: Sensitivity/Specificity	

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled

2. Assessment of Protocols and Study Reports

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	**Y**
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**Y**
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	**Y**
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	**Y**
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	**Y**

3. Electronic Data Assessment

[*Note to Reviewer: The following section is meant to document the details as they pertain to the electronic data submitted in the application.*]

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA020351\020351.enx
Were analysis datasets provided?	Y
Dataset structure (e.g., SDTM or ADaM)	ADaM
Are the define files sufficiently detailed?	Y
List the dataset(s) that contains the primary endpoint(s)	ADEF.xpt
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Y
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that	Y

Content Parameter	Response/Comments
you request to be inspected and the rationale.	
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Y

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

[*Note to Reviewer: This information is needed or essential to be able to review the application.*]

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc..	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.).			**x**	
Safety and efficacy were investigated for gender, racial, and geriatric subgroups.	x			
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	x			
Application appears to be free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements.	x			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE? Yes / No

5. Comments to be Conveyed to the Applicant

[*Note to Reviewer: In this section provide all comments that should be conveyed to the sponsor. Section 5.1 "Refuse-to-File Information Requests" should be based upon deficiencies identified in Section 4 of the Filing Review. Section 5.2 "Information Requests/Review Issues" should be used to request any additional information that would facilitate the review or to note any review issues identified by the time of filing that are meant to be conveyed to the sponsor. All comments in this section should be written in such a way that they can be copied by the project management staff.*]

5.1. Refuse-to-File Issues

5.2. Information Requests/Review Issues

APPEARS THIS WAY ON ORIGINAL

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/s/

ANTHONY G MUCCI
11/10/2016

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020351/S-044
020808/S-025

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	020351
Link to EDR	\\CDSESUB1\evsprod\NDA020351\020351.enx
Submission Date	October 5, 2016; SDN 303
Submission Type	Efficacy Supplement; PLR conversion
Brand Name	Visipaque™
Generic Name	Iodixanol
Dosage Form and Strength	Injectable solution. The current efficacy supplement is exclusively for the 320 mg I concentration.
Route of Administration	Intravenous (for proposed indication)
Dosing Regimen	70-80 mL main bolus volume at a flow rate of (b)(4) mL/s, followed by 20 mL saline flush
Indication (s)	**Approved Indications:** **INTRA-ARTERIAL** VISIPAQUE Injection (270 mgI/mL) is indicated for intra-arterial digital subtraction angiography. VISIPAQUE Injection (320 mgI/mL) is indicated for angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography. **INTRAVENOUS** VISIPAQUE Injection (270 mgI/mL) is indicated for CECT imaging of the head and body, excretory urography, and peripheral venography. VISIPAQUE Injection (320 mgI/mL) is indicated for CECT imaging of the head and body, and excretory urography. **Proposed New Indication (in red):** Visipaque Injection (320 mgI/mL) is indicated for use in coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease.
Applicant	GE Healthcare
Associated IND/NDA	IND 34,585 and NDA 20-808
OCP Review Team	Christy S John, Ph.D., Gene Williams, Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

Visipaque is approved for intra-arterial administration for angiography and angiocardiography, and for intravenous administration for CT of the head and body, excretory urography and peripheral venography. GE Healthcare proposes to add a new indication for the use of Visipaque Injection (320 mgI/mL) for use in coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease. CCTA is a procedure in which images are acquired during the arterial phase of contrast enhancement in order to visualize the coronary arteries. The current efficacy supplement is exclusively for the 320 mg I concentration.

There are no pharmacokinetics or drug interaction data in the submission.

To support the new indication the applicant has conducted two clinical studies: GE-189-002/GE012-101 and GE012-096. The standard of truth (SoT) for GE-012-101 was invasive coronary angiography for many patients, whereas Study GE-012-096 used clinical outcomes as a SoT. The sensitivity for the two studies were 90, 90, 98% for three different readers for Study GE012-101 and 90% Study GE-012-096. The specificity for Study GE-012-101 was 70, 76, 81% for three different readers and 87% for Study GE-012-096. This data suggested that Visipaque CCTA can assist in the diagnostic evaluation of patients with suspected coronary artery disease.

No dose finding data was acquired to support the CCTA indication. The recommended dosing is based on clinical studies conducted by applicant, published literature on CCTA, and guidelines from The Society of Cardiovascular Computed Tomography (SCCT) and The American College of Radiology (ACR).

1.1 Recommendations

From the clinical pharmacology perspective this supplemental NDA is approvable provided an agreement can be reached on labeling.

1.2 Post-Marketing Requirements and Commitments

From the Clinical Pharmacology perspective no post-marketing requirements or commitments are indicated.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

There are no pharmacokinetics or drug interaction data in the submission.

Visipaque™ (iodixanol) is a dimeric, isosmolar, nonionic, water-soluble, radiographic contrast medium with a molecular weight of 1550 Dalton (iodine content 49%). It is available as a ready-to-use sterile solution for IV injection in two concentrations (270 mgI/mL and 320 mgI/mL). Intravascular injection of iodixanol opacifies those vessels in the path of flow of the contrast agent, permitting radiographic visualization of the internal structures until significant dilution and elimination occurs.

The following is excerpted from the approved package insert, "The degree of enhancement, following administration of Visipaque Injection, is directly related to the iodine content in an administered dose with peak iodine plasma levels occurring immediately following intravascular injection. Iodine plasma levels fall rapidly within 5 to 10 minutes. Contrast enhancement with Visipaque Injection is greatest immediately after bolus injections (15 seconds to 120 seconds). Thus, greatest enhancement may be detected by a series of consecutive 2- to 3-second scans performed within 30 to 90 seconds after injection (i.e., dynamic computed tomographic imaging).

In an *in vitro* human plasma study, iodixanol did not bind to protein. The volume of distribution was 0.26 L/kg body weight (b.w.), consistent with distribution to extracellular space. Iodixanol metabolites have not been demonstrated. Measurements of plasma and urine levels suggest that body clearance of iodixanol is primarily due to renal clearance. In adults, approximately 97% of the injected dose of iodixanol is excreted unchanged in urine within 24 hours, with less than 2% excreted in feces within 5 days post-injection. ″

2.2 Dosing and Therapeutic Individualization

The applicant has proposed dosing of Visipaque for the CCTA indication be based on their clinical experience, published literature [Bae K.T. Radiology Vol 256, 33-51, 2010], and the recommendations of professional organizations such as The Society of Cardiovascular Computed Tomography (SCCT) guidelines for performance of coronary computed tomographic angiography [Abbara et al. Journal of Cardiovascular Computed Tomography, Vol 3, 190-204, 2009] and The American College of Radiology (ACR). **Table 1.** summarizes these sources.

Table 1. Comparison of CCTA Contrast Dosing and Injection Parameters

Recommendation	GE-189-002	GE-012-096	[Bae 2010]	SCCT [Abbara et al. 2009]	ACR [ACR 2014]
Concentration mgI/mL	320	320	320-370	High	>300
Rate in seconds	4-5 mL	According to facility guidelines	4-5 mL	4-7 mL	>3-5 mL
Volume	70-80 mL	30-180 mL (mean 91.5 mL)	75-100 mL	Typically 50-120 mL	None
Criteria for the selection of contrast volume	Selected by the investigator	According to facility guidelines	Injection rate and scan duration	Injection rate and scan duration	Weight
Biphasic, Multiphasic or both?	Both	According to facility guidelines	Both	Both	Biphasic preferred
Recommended Iodine delivery rate (g I/s)	1.28-1.6	According to facility guidelines	1.28-1.6	None	None
Optimal attenuation in coronaries	Not measured	Not measured	300-350 HU	>250	None
Test bolus, bolus tracking or both?	Test bolus	According to facility guidelines	Both	Both	Both

No individualization of dose has been studied. The applicant recommends a dose of 1 ml/kg, not to exceed 150 mL, for patients >80 kg/mL. Both weight-based and fixed volume dosing have been used in published studies of CCTA [Nakaura et al. Investigative Radiology, 43, 512-519, 2008; Komatsu et al. Journal of Cardiology, 61, 155-161, 2013]. Nakaura et al. studied software-tailored contrast injections based on patient weight and compared them to a fixed-volume control group using 75 mL at 7.2 mL per second with no adjustments made for weight. Comparable image noise and quality were found between both groups. Nakaura et al. also compared patient weight-adjusted and fixed iodine protocols. Patients in both groups received contrast at a concentration of 370 mgI/mL. The fixed dose group received 80 mL at 4 mL/second (i.e., a constant injection duration of 20 seconds) while the weight-adjusted group received 1.0 mL/kg with injection rate adjusted to achieve an injection duration of 15 seconds. This study showed that, using qualitative scoring, beam hardening artifacts were higher in the fixed volume dose group but the level of enhancement in the coronaries was similar for both groups.

Clinical pharmacology agrees the applicant's proposed dosing recommendations, with the exception that we recommend that an option for weight-based dosing – for all patients, not only patients of large body weight – be added to the package insert dosing table.

2.3 Outstanding Issues

There are no outstanding issues.

2.4 Summary of Labeling Recommendations

There are no pharmacokinetics or drug interaction data in the submission. Regarding the new indication for CCTA, clinical pharmacology recommends edits to the dosing table that the applicant proposes for the package insert, including the addition of an option for weight-based

dosing. As part of the review of the new PLR format, edits to sections 7, 8 and 12 are also recommended. These recommendations were incorporated during internal meetings with the clinical division (the Division of Medical Imaging Products: DMIP). The revised package insert has yet to be conveyed to the applicant for negotiation. The applicant's annotated proposed package insert (from the initial submission), and FDA's currently proposed version, are attached to this review as appendices (**Appendix 1** and **Appendix 2**, respectively).

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Visipaque 320 mgI/mL was first approved for intra-arterial (IA) use in February 1993 and for intravenous use in 1994. Visipaque is approved in the United States for IA administration for angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography and for IV administration for contrast-enhanced CT imaging of the head and body, and excretory urography.

The regulatory guidance from the FDA regarding the coronary CTA indication began in 2009 and continued through 2016, as summarized in **Table 2.**

Table 2. Regulatory History

Date	Application	Description
8/27/2009	IND 034585	Meeting minutes (3/22/2009) from face-to-face meeting regarding sponsor's submitted clinical trial results. FDA concluded "given the inadequacy of the reviewed study data to form the basis for an approvable NDA submission, FDA recommends that additional pivotal studies are needed to support the use of Visipaque as an imaging agent in CCTA for diagnosis and exclusion of CAD."
6/16/2015	IND 034585	Sponsor submitted correspondence requesting a meeting to discuss Phase 3 study design and clinical program to support a coronary CTA indication for Visipaque
11/10/2015	IND 034585	Face-to-face meeting for re-positioning of sponsor's request based on newly available information and guidelines. The sponsor-proposed Phase 3 study was deemed unnecessary by FDA. FDA suggested a future pre sNDA meeting for presentation of the relevant studies and publications.
5/13/2016	IND 034585	Pre-sNDA meeting requested by sponsor to discuss the studies

3.2 General Pharmacology and Pharmacokinetic Characteristics

The following information is adapted from the approved package insert.

Iodixanol is a dimeric, isosmolar, nonionic, water soluble, iodinated x-ray contrast agent for intravascular administration. Intravascular injection of iodixanol opacifies those vessels in the path of flow of the contrast agent, permitting radiographic visualization of the internal structures until significant dilution and elimination occurs.

Pharmacokinetics

Distribution
In an *in vitro* human plasma study, iodixanol did not bind to protein. The volume of distribution was 0.26 L/kg body weight, consistent with distribution to extracellular space.

Elimination
Plasma and urine levels suggest that body clearance of iodixanol is primarily due to renal clearance. In adults, approximately 97% of the injected dose of iodixanol is excreted unchanged in urine within 24 hours, with less than 2% excreted in feces within five days post-injection. In 40 healthy, young male volunteers receiving a single intravenous administration of VISIPAQUE Injection in doses of 0.3 to 1.2 gI/k body weight, the elimination half-life was 2.1 h (± 0.1); and renal clearance was 110 mL/min (±14), equivalent to glomerular filtration (108 mL/min). These values were independent of the dose administered.

Metabolism
Iodixanol metabolites have not been demonstrated.

Pharmacokinetics in Special Populations
Renal Impairment:
In patients with significantly impaired renal function, the total clearance of iodixanol is reduced and the half-life in plasma phase is prolonged. In a study of 16 adult patients who were scheduled for renal transplant, the elimination of iodixanol 320 mgI/mL was studied. The patients' baseline mean creatinine levels were 6.3 mg/dL (±1.5) and mean creatinine clearances were 13.61 mL/min (±4.67). In these patients, the plasma half-life was increased to 23 hours (normal t1/2 = 2 hours). In these patients, levels of iodixanol were detected 5 days after dosing. Contrast enhancement time in kidneys increased from 6 hours to at least 24 hours.

Pediatric:
Comparing to adult half-life which is approximately 2 h, the half-life in children <12 years of age range from 2.3 to 4 h, being longer in newborn and children <2 months). Pharmacodynamic dose adjustments to account for differences in elimination half-life in pediatric patients <6 months of age have not been studied.

Pharmacodynamics

As with other iodinated contrast agents, following administration of Visipaque injection, the degree of enhancement is directly related to the iodine content in an administered dose. The peak iodine plasma levels occur immediately following rapid intravascular injection. Iodine plasma levels fall rapidly within 5 to 10 minutes.

The greatest enhancement may be detected by a series of consecutive two-to-three second scans performed within 30 to 90 seconds after injection (i.e., dynamic computed tomographic imaging). Iodinated contrast agents may be visualized in the renal parenchyma within 30-60 seconds following rapid intravenous injection. Opacification of the calyces and pelves in patients with normal renal function becomes apparent within 1-3 minutes, with optimum contrast occurring within 5-15 minutes. In normal brain with an intact blood-brain barrier, contrast enhancement is generally due to the presence of iodinated contrast agent within the intravascular space.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

There are no pharmacokinetics or dose-response data in CCTA patients to support the CCTA indication.

To support the new indication the applicant has conducted two clinical studies: GE-189-002/GE012-101 and GE012-096. The standard of truth (SoT) for GE-012-101 was invasive coronary angiography for many patients, whereas Study GE-012-096 used clinical outcomes as a SoT. The sensitivity for the two studies were 90, 90, 98% for three different readers for Study GE012-101 and 90% Study GE-012-096. The specificity for Study GE-012-101 was 70, 76, 81% for three different readers and 87% for Study GE-012-096. This data suggested that Visipaque CCTA can assist in the diagnostic evaluation of patients with suspected coronary artery disease.

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

The applicant has proposed dosing of Visipaque for the CCTA indication be based on their clinical experience, published literature [Bae K.T. Radiology Vol 256, 33-51, 2010], and the recommendations of professional organizations such as The Society of Cardiovascular Computed Tomography (SCCT) guidelines for performance of coronary computed tomographic angiography [Abbara et al. Journal of Cardiovascular Computed Tomography, Vol 3, 190-204, 2009] and The American College of Radiology (ACR). **Table 3.** summarizes these sources.

Table 3. Comparison of CCTA Contrast Dosing and Injection Parameters

Recommendation	GE-189-002	GE-012-096	[Bae 2010]	SCCT [Abbara et al. 2009]	ACR [ACR 2014]
Concentration mgI/mL	320	320	320-370	High	>300
Rate in seconds	4-5 mL	According to facility guidelines	4-5 mL	4-7 mL	>3-5 mL
Volume	70-80 mL	30-180 mL (mean 91.5 mL)	75-100 mL	Typically 50-120 mL	None
Criteria for the selection of contrast volume	Selected by the investigator	According to facility guidelines	Injection rate and scan duration	Injection rate and scan duration	Weight
Biphasic, Multiphasic or both?	Both	According to facility guidelines	Both	Both	Biphasic preferred
Recommended Iodine delivery rate (g I/s)	1.28-1.6	According to facility guidelines	1.28-1.6	None	None
Optimal attenuation in coronaries	Not measured	Not measured	300-350 HU	>250	None
Test bolus, bolus tracking or both?	Test bolus	According to facility guidelines	Both	Both	Both

No individualization of dose has been studied. The applicant recommends a dose of 1 ml/kg, not to exceed 150 mL, for patients >80 kg/mL. Both weight-based and fixed volume dosing have been used in published studies of CCTA [Nakaura et al. Investigative Radiology, 43, 512-519, 2008; Komatsu et al. Journal of Cardiology, 61, 155-161, 2013]. Nakaura et al. studied software-tailored contrast injections based on patient weight and compared them to a fixed-volume control group using 75 mL at 7.2 mL per second with no adjustments made for weight. Comparable image noise and quality were found between both groups. Nakaura et al. also compared patient weight-adjusted and fixed iodine protocols. Patients in both groups received contrast at a concentration of 370 mgI/mL. The fixed dose group received 80 mL at 4 mL/second (i.e., a constant injection duration of 20 seconds) while the weight-adjusted group received 1.0 mL/kg with injection rate adjusted to achieve an injection duration of 15 seconds. This study showed that, using qualitative scoring, beam hardening artifacts were higher in the fixed volume dose group but the level of enhancement in the coronaries was similar for both groups.

Reviewer's Dosing Recommendation

Both weight-based and fixed volume dosing have been used in published studies of CCTA. Nakaura et al. studied software-tailored contrast injections based on patient weight and compared them to a fixed-volume control group using 75 mL at 7.2 mL per second with no adjustments made for weight. Comparable image noise and quality were found between both groups. Nakaura et al. also compared patient weight-adjusted and fixed iodine protocols. Patients in both groups received contrast at a concentration of 370 mgI/mL. The fixed dose group received 80 mL at 4 mL/second (i.e., a constant injection duration of 20 seconds) while the weight-adjusted group received 1.0 mL/kg with injection rate adjusted to achieve an injection duration of 15 seconds. This study showed that, using qualitative scoring, beam hardening artifacts were higher in the fixed volume dose group but the level of enhancement in the coronaries was similar for both groups.

Bae advocates adjusting contrast dose (using iodine delivery rate) according to patient weight (as a surrogate for blood volume) with a trend towards a total recommended volume of iodinated contrast between 75 and 100 mL to achieve recommended opacification with fast multi-detector CT in an average sized adult. The Bae paper suggests, for modern fast CT scanners, this is best accomplished by increasing the iodine delivery rate with weight (either by increasing the iodine concentration at a fixed delivery volume and rate or by increasing the injection rate and total contrast volume) in order to maintain the same injection duration. Simply increasing the volume of contrast by patient weight above 70 kg at fixed concentration and injection rate would only serve to increase injection duration, which would be of no benefit to patients scanned on modern 64-slice CT scanners with CCTA acquisition times of 10 seconds or less.

The SCCT guidelines [Abbara et al. 2009] do not recommend adjustment of total contrast volume based on patient weight but only as a function of the injection rate and the injection duration to achieve a high intra-arterial opacification of more than 250 HU with an injection rate of 4-7 mL per second.

Based on these sources taken together, we agree with the applicant's proposed dosing recommendations, with the exception that we recommend that an option for weight-based dosing – for all patients, not only patients of large body weight – be added to the applicant's dosing table. The dosing table of the current FDA proposed package insert is reproduced, below (**Table 4**).

Table 4. Recommended Dosing for CCTA

ADULTS and PEDIATRIC PATIENTS[1] 12 YEARS OF AGE AND OLDER **VISIPAQUE (320 mg Iodine/mL) DOSING RECOMMENDATIONS FOR CCTA**						
Procedure	**Main VISIPAQUE Volume[2]**	**VISIPAQUE /saline Dilution Volume**	**Saline Flush**	**Injection Rate**	**Minimum VISIPAQUE Volume**	**Maximum VISIPAQUE Volume**
Without Dilution	70-80 mL[3,4]		40-50 mL	4-7 mL/sec	50 mL	150 mL
With Dilution	50-60 mL[4]	50 mL diluted VISIPAQUE (20 mL VISIPAQUE plus 30 mL saline)	20 mL	4-7 mL/sec	80 mL	225 mL

[1]For pediatric patients aged 12-17, recommended dose is 1-2 mL/kg.
[2]The main VISIPAQUE volume may be preceded by a test bolus consisting of 20 mL VISIPAQUE, immediately followed by a 20 mL saline flush, both injected at rate of 4-7 mL/sec.
[3]Alternatively, a dose of 1 mL/kg may be used to calculate total VISIPAQUE dose (excluding any test bolus).
[4]For CCTA acquired at < 120 kVp, the dose of VISIPAQUE may be reduced by up to 15% in patients < 85 kg and BMI < 30 kg/m^2. For CCTA acquired on a scanner with more than 64 detector rows, the dose of VISIPAQUE may be reduced in proportion to the scan duration.

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

For routine CCTA procedures (i.e. patients weighing ≤80 kg with scans acquired at 120 kVp on 64-slice scanners) using Visipaque 320 mgI/ mL, is the applicant proposes (b)(4)

When performing CCTA in patients >80kg, image noise levels typically are higher. Increasing arterial opacification levels can maintain an adequate contrast-to-noise ratio to allow for adequate coronary lumen visualization. Therefore, the dose for patients > 80 kg should be 1 mL/kg up to a maximum of 150 mL, including any test bolus.

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

Visipaque Injection is administered intravenously– food-drug interactions are not expected. No drug-interaction studies were conducted to support the new indication. This is acceptable, as the new indication does not introduce any new concern regarding drug interactions.

4. APPENDICIES

4.1 Appendix 1: Applicant's annotated proposed package insert

4.2 Appendix 2: FDA's currently recommended package insert version

28 pages of draft labeling have been withheld in full as (b)(4) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY S JOHN
03/15/2017

GENE M WILLIAMS
03/15/2017
I concur with the recommendations

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	20-351	**SDN**	303
Applicant	GE Healthcare	**Submission Date**	October 5, 2016
Generic Name	Iodixanol	**Brand Name**	Visipaque™
Drug Class	Imaging		
Indication	**Approved indications:** **INTRA-ARTERIAL** VISIPAQUE Injection (270 mgI/mL) is indicated for intra-arterial digital subtraction angiography. VISIPAQUE Injection (320 mgI/mL) is indicated for angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography. **INTRAVENOUS** VISIPAQUE Injection (270 mgI/mL) is indicated for CECT imaging of the head and body, excretory urography, and peripheral venography. VISIPAQUE Injection (320 mgI/mL) is indicated for CECT imaging of the head and body, and excretory urography. **Proposed new indication:** **Visipaque Injection (320 mgI/mL) is indicated for use in coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease**. Reviewer's Note: The new indication will be listed last in a separate paragraph under intravenous.		
Dosage Regimen	**Approved:** **INTRA-ARTERIAL** • 270 mgI/mL for intra-arterial digital subtraction angiography. • 320 mgI/mL for angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography. **INTRAVENOUS** • 270 and 320 mgI/mL for CECT imaging head and body and excretory urography. • 320 mgI/mL for CECT imaging peripheral venography. **Proposed new:** • **320 mgI/mL for CCTA to assist diagnostic evaluation of patients with suspected coronary artery disease.**		

	Dosage and Administration (Approved): • Individualize the combination of volume and concentration of VISIPAQUE Injection considering age, body weight, size of the vessel, rate of blood flow within the vessel, and other applicable factors. • For the adult population, the maximum recommended total dose of iodine is 80 grams. The maximum has not been established in the pediatric population. • Patients should be adequately hydrated prior to and following the intravascular administration of iodinated contrast agents		
Dosage Form	Injectable solution: In concentrations of 270 and 320 mg of organically bound iodine per mL (550 mg and 642 ml of Iodixanol per mL).	**Route of Administration**	Intravenous (for current indication)
OCP Division	Division of Clinical Pharmacology V	**OND Division**	Division of Medical Imaging Products

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Sam Habet, R.Ph., Ph.D.	Gene M. Williams, Ph.D.
Pharmacometrics	N/A	N/A
Genomics	N/A	

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	11/2/2016	**74-Day Letter Date**	12/18/2016
Review Due Date	3/1/2017	**PDUFA Goal Date**	4/5/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☐ Yes ☑ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	**Count**	**Comment(s)**
In Vitro Studies		
☐ Metabolism Characterization		

☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		.
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☐ Multiple Dose		
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics		Pediatric waiver was submitted	
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies	**In Vitro**		**In Vivo**	3
Total Number of Studies to be Reviewed				3

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**

1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☐Yes ☐No ☑N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☐Yes ☐No ☑N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☐Yes ☐No ☑N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☐Yes ☐No ☑N/A	It is not clear that dose discovery for this new indication was performed, but there are literature efficacy and safety data with the proposed dose
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes ☐No ☑N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☐Yes ☐No ☑N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		

Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☐Yes ☐No ☑N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☐Yes ☐No ☑N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	It is not clear that dose discovery for this new indication was performed, but there are literature efficacy and safety data with the proposed dose
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☐Yes ☐No ☑N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SAM HABET
11/28/2016

GENE M WILLIAMS
11/29/2016
I concur with the recommendations

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020351/S-044
020808/S-025

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From:	Erica Radden, M.D., Medical Officer Division of Pediatric and Maternal Health (DPMH), Office of New Drugs (OND)
Through:	Tamara Johnson, M.D., M.S., Maternal Health Team Leader Mona Khurana, M.D., Acting Pediatric Team Leader Lynne Yao, M.D., Director DPMH, OND
To:	Division of Medical Imaging Products (DMIP)
Drug:	Visipaque (iodixanol)
Application number:	Visipaque (iodixanol) Injection (NDA 020351) Visipaque Pharmacy Bulk Package (NDA 020808)
=	
Applicant:	GE Healthcare, Inc.
Approved indications:	For intra-arterial and intravenous applications to image vessels and organs during angiography or computed tomography scanning in adults and pediatric patients (see below)
Approved Dosage Form:	270 mg iodine/mL and 320 mg iodine/mL solutions
Route of Administration:	Intra-arterial and intravenous injection
Proposed indication:	Coronary computed tomography angiography (CCTA) to assist diagnostic evaluation of patients with suspected

coronary artery disease (for the 320 mg iodine/mL concentration).

Consult Request: DMIP consulted DPMH on January 13, 2017 requesting assistance with labeling for pediatric use, pregnancy, and lactation.

Materials Reviewed:

- Current Visipaque (iodixanol) labeling (dated July 6, 2015 in DARRTS)
- Applicant's proposed labeling (submitted October 5, 2016)
- DPMH Consult request (January 13, 2017)
  Pediatric Review Committee meeting minutes for March 1, 2017 (dated March 22, 2017 in DARRTS)

Background:

Visipaque (iodixanol) is an isosmolar, non-ionic, water-soluble iodinated radiographic contrast agent approved in two strengths (270 and 320 mg iodine/mL) as a single-dose injection (NDA 20351) on March 22, 1996 and as a pharmacy bulk package (NDA 20808) on August 29, 1997 for multiple intra-arterial and intravenous imaging indications in adults and pediatric patients as outlined below:

Intra-Arterial Procedures

Adults and pediatric patients 12 years of age and over:

- Intra-arterial digital subtraction angiography (270 and 320 mg iodine/mL).
- Angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography (320 mg iodine/mL).

Pediatric patients 1 year to 12 years of age:

- Angiocardiography, cerebral arteriography, and visceral arteriography (320 mg iodine/mL).

Intravenous Procedures

Adults and pediatric patients 12 years of age and over:

- Computed tomography (CT) imaging head and body and excretory urography (270 and 320 mg iodine/mL).
- CT imaging peripheral venography (270 mg iodine/mL).

Pediatric patients 1 year to 12 years of age:

- CT imaging of the head and body and excretory urography (270 mg iodine/mL).

On October 5, 2016, GE Healthcare, Inc. submitted an efficacy supplement seeking approval for a new indication for coronary computed tomography angiography (CCTA) to assist diagnostic evaluation of patients with suspected coronary artery disease with the

320 mg iodine/mL formulation. The current labeling is not in Physician Labeling Rule format. Therefore, the applicant has also submitted updated labeling in PLR format.

DMIP consulted DPMH to provide input on the applicant's proposed labeling related to pediatrics, pregnancy, and lactation.

Pediatric Assessment:

The applicant proposes a full waiver of the requirement to provide a pediatric assessment for this new CCTA indication, citing that necessary studies are impossible or highly impracticable because significant obstructive coronary artery disease is extremely rare in small children and adolescents and this indication would have extremely limited applicability to pediatric patients because the pathophysiology or disease occurs for the most part in adult populations.

DPMH agreed with the proposed full waiver. However, the proposal was reviewed by the Pediatric Review Committee (PeRC) on March 1, 2017. The PeRC proposed that sufficient information about use of the product for other indications may allow for a partial assessment in adolescent patients 12 to18 years of age who might require coronary artery visualization (e.g., due to stenosis related to Kawasaki disease). DMIP agreed to review the existing data to support the approval of this indication in adolescents. DMIP concluded that use of CCTA in adolescents is noted in literature at doses of 1-2 ml/kg, consistent with dosing recommendations for other currently approved intravenous procedures in this population. Additionally, the division agrees that the pathophysiology of the disease and mechanism of action of the drug are sufficiently similar to allow extrapolation of efficacy from the adult studies. Furthermore, extrapolation of efficacy is supported by the pediatric safety and PK studies that supported the approval of other intravascular imaging indications in this subpopulation. Therefore, the division has decided to grant the CCTA indication in adolescents as well as adults.

Review of Labeling:

The DPMH labeling review will focus on edits to section 6.3 (Pediatric Adverse Reactions), 8.1 (Pregnancy), 8.2 (Lactation) and 8.4 (Pediatric Use).

Pregnancy and Lactation Labeling
On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*," also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format is required

for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

Pediatric Use Labeling:
The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. When substantial evidence does not exist to support a pediatric indication, all relevant pediatric information related to the unapproved use should be restricted to the Pediatric Use subsection only, to avoid an inference of an approved pediatric indication as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. The guidance also states that any negative or inconclusive pediatric studies must be described in the Pediatric Use subsection, and the basis for the determination of safety and effectiveness in the pediatric population should also be provided (e.g., providing an explanation for why the available evidence does not support pediatric approval). (Also see draft Guidance for Industry and Review Staff Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, February, 2013.)

See Appendix 1 for proposed applicant labeling for Visipaque (iodixanol) dated October 5, 2016.

The applicant's proposed labeling simply reorganized the pregnancy, lactation and pediatric use information in the current labeling into PLR format without any substantive changes. The proposed labeling also provides the current regulatory language recommended by PLLR.

Discussion on Labeling Recommendations:

Reviewer comment: DPMH [previously the Pediatric and Maternal Health Staff (PMHS)] has provided three reviews on the use of the class of ICM agents in pregnancy, lactation and pediatric patients, and a focused labeling review for Oraltag (iohexol), another ICM.[1,2,3,4] The labeling recommendations provided in these reviews are consistent with the ones provided here. See additional discussion under PEDIATRIC USE.

PREGNANCY
Nonclinical Experience

[1] PMHS Memo Nursing Mothers labeling dated November, 28, 2012, primary author Jeanine Best, M.S.N., R.N., under Omnipaque (iohexol), NDA 18956
[2] PMHS Pediatric Labeling Review dated November 30, 2012, primary author Donna L. Snyder, M.D., under Omnipaque (iohexol), NDA 18956
[3] Pediatric and Maternal Health Team Follow-up Review dated October 1, 2013, primary author Donna L. Snyder, M.D. under Omnipaque (iohexol), NDA 18956

Developmental toxicity studies conducted in rats and rabbits with iodixanol at doses up to 2 g iodine/kg daily [0.24 (rat) or 0.48 (rabbit) times the maximum recommended human intravenous dose] revealed no evidence of harm to the fetus due to iodixanol.

Review of Literature

DPMH conducted a review of literature regarding use in pregnancy for iodixanol in TERIS, REPROTOX, and PubMed. No studies of prenatal exposure to iodixanol were identified. However, the American College of Radiology (ACR) has reviewed the effects of prenatal exposure to intravenously administered iodinated contrast media (ICM). Because the iodine in ICMs may cross the placenta, a risk for neonatal hypothyroidism following ICM exposure exists, and there have been rare reports of hypothyroidism in neonates following prenatal exposure to ICMs. However, this occurred only following amniofetography using a fat-soluble ICM. The ACR further notes the following:

> *Intravenous administration of iodinated contrast media does not affect short-term neonatal thyroid stimulating hormone (TSH), likely because the overall amount of excess iodide in the fetal circulation is small and transient. However, the long-term effects are unknown. To date, there has been no documented case of neonatal hypothyroidism from the maternal intravascular injection of water-soluble iodinated contrast agents. Given the current available data and routine evaluation of all newborns for congenital hypothyroidism by measurement of TSH levels at the time of their birth, no extra attention is felt to be necessary.*[5]

Additionally, the American College of Obstetricians and Gynecologists concur that the risk for adverse effects of free iodide on the fetal thyroid gland have not been borne out in human studies, but recommends that contrast only be used if absolutely required to obtain additional diagnostic information that will affect the care of the fetus or woman during the pregnancy.

Summary

There are no data with iodixanol use in pregnant women to inform any drug-associated risks. There may be a risk of thyroid dysfunction in neonates following prenatal exposure to iodixanol; however, neonatal screening for congenital hypothyroidism will likely identify an infant who may develop thyroid dysfunction because of prenatal exposure to an ICM, including iodixanol. Additionally, animal reproduction studies performed in rats and rabbits with intravenous administration of iodixanol at doses up to 2 g iodine/kg daily [0.24 (rat) or 0.48 (rabbit) times the maximum recommended human intravenous dose] from implantation of the embryo (gestation day 7 in rat; 6 in rabbit) through closure of the hard palate (gestation day 17 in rats; 18 in rabbits) demonstrated no evidence of adverse developmental effects. DPMH also provided labeling

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[4] DPMH Pregnancy and Lactation Labeling Review dated March 16, 2015, primary author Carol Kasten, M.D., under Oraltag (iohexol), NDA 205383

[5] American College of Radiology Committee on Drugs and Contrast Media. Administration of contrast media to pregnant or potentially pregnant patients. In, ACR manual on contrast media. 2016;Version 10.2:97.

recommendations that revised the applicant's proposed labeling with current regulatory language.

LACTATION

Nonclinical Experience

No nonclinical data was provided to inform lactation.

Review of Literature

DPMH conducted a review of literature regarding lactation for iodixanol using LactMed and PubMed which revealed no available studies. However, LactMed notes that

> *Intravenous iodinated contrast media are poorly excreted into breastmilk and poorly absorbed orally so they are not likely to reach the bloodstream of the infant or cause any adverse effects in breastfed infants. Guidelines developed by several professional organizations state that breastfeeding need not be disrupted after a nursing mother receives a iodine-containing contrast medium.*[6,7,8,9] *However, because there is no published experience with iodixanol during breastfeeding, other agents may be preferred, especially while nursing a newborn or preterm infant.*

Furthermore, a breastfeeding mother may reduce the risk of iodixanol exposure to her infant by pumping and discarding her breast milk for 10 hours (5 times the half-life of 2.1 hours) following iodixanol administration.

Summary

The risk of iodixanol exposure via breastfeeding appears to be low and any exposure can be minimized by discarding any breast milk produced for 10 hours following iodixanol exposure. Therefore, as required under PLLR, DPMH recommends this information be included under the Clinical Considerations subheading.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

No information is available to inform the reproductive potential of females and males. Therefore, according to PLLR, section 8.3 can be omitted.

PEDIATRIC USE

As noted above, all of the approved indications are indicated for pediatric patients 12 years of age and older. However, of those, only the following indications are approved for pediatric patients 1-12 years of age:

- Angiocardiography, cerebral arteriography, and visceral arteriography (320 mg iodine/mL).

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[6] American College of Radiology Committee on Drugs and Contrast Media. Administration of contrast media to breast-feeding mothers. In, ACR manual on contrast media. 2016;Version 10.2:101.
[7] Webb JA, Thomsen HS, Morcos SK et al. The use of iodinated and gadolinium contrast media during pregnancy and lactation. Eur Radiol. 2005;15:1234-40.
[8] Chen MM, Coakley FV, Kaimal A, Laros RK Jr. Guidelines for computed tomography and magnetic resonance imaging use during pregnancy and lactation. Obstet Gynecol. 2008;112:333-40.
[9] American College of Obstetricians and Gynecologists Committee on Obstetric Practice. Committee Opinion No. 656: Guidelines for Diagnostic Imaging During Pregnancy and Lactation. Obstet Gynecol. 2016;127:e75-e80.

- CT imaging of the head and body and excretory urography (270 mg iodine/mL).

Use in these populations was established based on adequate and well controlled studies in adults, in addition to PK and safety information in 459 pediatric patients. Additionally, labeling notes that safety and effectiveness have only been established in pediatric patients age 1 year and older; and, while pediatric PK and safety studies included patients less than 1 year of age, "the relative safety of the volumes injected, the optimal concentrations, and the potential need for dose adjustment because of prolonged elimination half-lives have not been systematically studied."

DMIP conducted a review of published literature to assess use of ICMs, including iodixanol in patients less than 1 year of age. The review confirmed ICM use in patients less than 1 year of age for the indications noted above that are currently limited to patients 1 to 12 years of age. Furthermore, the doses administered to patients less than 1 year of age were consistent with the currently labeled dosing recommendations of 1-2 ml/kg (maximum 4 ml/kg) for patients 1 to 12 years of age (see the review by Dr. Michele Fedowitz).[10] Additionally, DMIP agrees with DPMH that the pathophysiology of the diseases for which this product is used and the mechanism of action are sufficiently similar in adults and pediatric patients to allow for full extrapolation of efficacy. Furthermore, labeling currently provides dosing and safety information for patients down to birth. Therefore, given the published evidence of ICM use in pediatric patients down to birth, the applicant was sent and Information Request (IR) to provide post-marketing data regarding effectiveness, safety, dosing and use in patients less than 1 year of age to potentially support extending the indications that are currently approved in patients 1 year to less than 12 years of age down to birth.

The applicant provided data from their pharmacovigilance database which identified 9 adverse events, 5 of which were classified as adverse reactions (see Appendix 2: Post-marketing experience in patients < 1 year of age). These few identified events were consistent with either hypersensitivity reactions or other currently labeled adverse events associated with this product. The applicant proposed the following additional labeling language to describe these events in this subpopulation under the (b)(4)

(b)(4):

(b)(4)

However, the additional language proposed by the applicant is (b)(4)

This response by the sponsor only provided safety data in patients less than 1 year of age; therefore, DMIP issued an another IR to the applicant requesting data regarding

[10] Michele Fedowitz, M.D.-- Primary Clinical Review, NDA 20808, dated March 24, 2017 in DARRTS

effectiveness and dosing in patients less than 1 year of age. The applicant noted that a literature review did not identify any use data specific to this age group; the applicant's findings are inconsistent with the data retrieved from the literature review conducted by DMIP. However, the applicant also provided results from a phase 3 randomized, blinded comparison of Visipaque (iodixanol) 320 mg iodine/mL and Omnipaque 350 (iohexol) in 58 pediatric patients requiring angiocardiography. The patients were stratified according to the following age groups: ≤ 1 year (30 patients) and age >1 year (28 patients). The results showed the following:

- The mean dose/body weight was 1.96 grams iodine per kilogram (g iodine/kg) for patients ≤1 year of age and 1.71 g iodine/kg for patients >1 year of age.
- The mean volume/weight was 5.60 mL/kg for patients ≤1 year of age and 4.88 mL/kg for patients >1 year of age.
- Efficacy results showed good or excellent overall quality of visualization in 100% of the patients (58/58) in the VIS-320 group including all patients ≤1 year of age.

Therefore, weight-based dosing and administration volumes were similar in patients 1 year of age or less and patients older than 1 year of age. These additional data further support efficacy and dosing for patients less than 1 year of age. Thus, DPMH agrees that indications that have been approved down to 1 year of age could reasonably be extended down to birth. Additionally, as noted above DPMH agrees that the CCTA indication should also be approved for patients 12 years and older.

Because the proposed and approved indications include pediatric patients, information regarding pediatric use in these populations should be placed throughout labeling according to 21 CFR 201.57(c)(9)(iv). Specifically, the indication statement in the INDICATIONS AND USAGE section should include the pediatric populations for which the product approved. The PEDIATRIC USE subsection (8.4) should describe the data used to establish safety and effectiveness. Additionally, this subsection should include information highlighting any differences in efficacy or safety in the pediatric population versus the adult population. Therefore, the information currently proposed for subsection (b)(4) .

Subsection (b)(4) the applicant's proposed labeling describes pediatric adverse events, noting that the (b)(4) (b)(4) should be moved to the Pediatric Adverse Reactions subsection (which will now be subsection 6.3), and a brief summary of the adverse events should be included in subsection 8.4 with a cross-reference to subsection 6.3. Additionally, (b)(4) Of note,

the applicant's proposed labeling states that the noted pediatric adverse events were (b)(4). In order to further understand this trend, the applicant was asked to provide an explanation for this observed trend in addition to an analysis of the routes of administration by age cohort (< 29 days, >29 days - < 6 months, > 6 months – 12 months). As anticipated, increased intra-arterial procedures, which are associated with higher doses of contrast and increased adverse events, were found to be directly proportional to decreasing age. Additionally, a review of the cases found that the youngest patients had more severe underlying diseases prompting the imaging study. Therefore, to provide additional context to this trend, we recommend including a description of the increasing percentages of intra-arterial procedures by decreasing age cohort in subsection 6.3.

The applicant's proposed labeling in the CLINICAL PHARMACOLOGY section includes data showing that elimination is prolonged with decreasing age. However, there do not appear to be any safety signals identified that are specific to patients less than 1 year of age that would preclude approval in this subpopulation. Nevertheless, a statement describing this information should be included in subsection 8.4.

Of note, a review by the Division of Pharmacovigilance (DPV) in September 2012 described 17 cases of new-onset hyperthyroidism and 11 cases of new-onset hypothyroidism following exposure to ICM. Of the 11 cases of hypothyroidism, 10 involved infants less than 4 months of age, including 4 premature infants. DPV recommended including labeling regarding the risk of hypothyroidism in pediatric patients, specifically infants less than 1 year with an emphasis on premature and very young infants. DMIP consulted DPMH to assist with labeling recommendations for ICM products. DPMH completed reviews and provided recommended changes to labeling.[11] However, DMIP has elected to collect more information from sponsors of ICM products and plans to make class labeling changes addressing this concern. An interim safety labeling change was issued to all the ICM products on July 6, 2015 to include language in the ADVERSE REACTIONS, Postmarketing Experience subsection conveying this noted safety concern. This approved safety language should also be included in subsection 8.4 because it describes adverse events specifically related to pediatric patients.

Conclusion:

DPMH reviewed the applicant's draft labeling, and participated in the team and labeling meetings held between January and March 2017. DPMH revised subsections 8.1 and 8.2 in Visipaque labeling for compliance with the PLLR (see below). DPMH also edited subsection 8.4 and recommended labeling for the pediatric population is provided below per 21 CFR 201.57(c)(9)(iv). The following recommendations are based on labeling discussions between DMIP and DPMH. DPMH's input will be reflected in the final

[11] Previous DPMH consult reviews by Dr. Donna Snyder for Iodinated contrast media for medical procedures, DARRTS Reference ID: 3229688 (December 12, 2012) and DARRTS Reference ID: 3382408 (October 2, 2013).

labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

DPMH Recommended Labeling for Visipaque (iodixanol):

6 ADVERSE REACTIONS

6.3 Pediatric Adverse Reactions

The overall character, quality, and severity of adverse reactions in pediatric patients is similar to that reported in adult patients from post marketing surveillance and other information.

Additional safety data was obtained in studies of VISIPAQUE in 459 pediatric patients. A total of 26 patients ranged in age from birth to <29 days, 148 ranged from 29 days to 2 years, 263 from 2 to <12 years, and 22 from 12 to 18 years. A total of 252 (55%) of the patients were male. The racial distribution was: Caucasian-81%, Black-14%, Oriental-2%, and other or unknown-4% The proportion of patients undergoing an intra-arterial procedure by age was: 92 % (<29 days), 55% (29 days – 6 months), and 29 % (>6 months). In these studies, adverse events were numerically higher in pediatric patients less than one year of age compared to older pediatric patients.

In pediatric patients who received intravenous injections of VISIPAQUE for computerized tomography or excretory urography, a concentration of 270 mg iodine/mL was used in 144 patients, and a concentration of 320 mg iodine/mL in 154 patients. All patients received one intravenous injection of 1-2 mL/kg.

In pediatric patients who received intra-arterial and intracardiac studies, a concentration of 320 mg iodine/mL was used in 161 patients. Twenty-two patients were < 29 days of age; 78 were 29 days to 2 years of age; and 61 were over 2 years. Most of these pediatric patients received initial volumes of 1-2 mL/kg and most patients received a maximum of 3 injections.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with iodixanol use in pregnant women to inform any drug-associated risks. In animal reproduction studies, no developmental toxicity occurred with intravenous iodixanol administration to rats and rabbits at doses up to 0.24 (rat) or 0.48 (rabbit) times the maximum recommended human intravenous dose (*see Data*).

All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Reproduction studies were performed in rats and rabbits with intravenous administration of iodixanol at doses up to 2 g iodine/kg, daily, from implantation of the embryo (gestation day 7 in rat; 6 in rabbit) through closure of the hard palate (gestation day 17 in rats; 18 in rabbits). No maternal toxicity occurred, and no adverse effects occurred on fetal survival, embryo-fetal development, or the ability of dams to rear a litter.

8.2 Lactation

Risk Summary

There are no data on the presence of iodixanol in human milk, the effects on the breastfed infant or the effects on milk production. Iodinated contrast agents are poorly excreted into human milk and are poorly absorbed by the gastrointestinal tract of a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VISIPAQUE and any potential adverse effects on the breastfed infant from VISIPAQUE or from the underlying maternal condition.

Clinical Considerations

Interruption of breastfeeding after exposure to iodinated contrast agents is not necessary because the potential exposure of the breastfed infant to iodine is small. However, a lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk for 10 hours (approximately 5 elimination half-lives) after VISIPAQUE administration in order to minimize drug exposure to a breast fed infant.

8.4 Pediatric Use

The safety and efficacy of VISIPAQUE have been established in pediatric patients down to birth for angiocardiography, cerebral arteriography, visceral arteriography, CT imaging of the head and body, and excretory urography. The safety and efficacy of VISIPAQUE have also been established in pediatric patients 12 years and older for intra-arterial digital subtraction angiography, peripheral arteriography, CT imaging peripheral venography and CCTA. Use of VISIPAQUE is supported by evidence from adequate and well controlled studies of VISIPAQUE in adults and additional safety data obtained in 459 pediatric patients. In general, the types of adverse reactions reported are similar to those of adults. A higher number of adverse events in patients less than 1 year of age compared to older patients was observed in a study of VISIPAQUE *[see Adverse Events (6.3)]*. The elimination of VISIPAQUE is slower in this age group *[see Clinical Pharmacology (12.3)]*. The safety and efficacy of VISIPAQUE have not been established in pediatric patients less than 12 years of age for intra-arterial digital subtraction angiography, peripheral arteriography, CT imaging peripheral venography and CCTA.

Thyroid function tests indicative of hypothyroidism or transient thyroid suppression have been uncommonly reported following iodinated contrast media administration to pediatric patients, including infants. Some patients were treated for hypothyroidism *[See Adverse Reactions (6.3)]*.

Pediatric patients at higher risk of experiencing an adverse reaction during and after administration of any contrast agent may include those with asthma, hypersensitivity to other medication and/or allergens, cyanotic and acyanotic heart disease, congestive heart failure, or a serum creatinine greater than 1.5 mg/dL. Pediatric patients with immature renal function or dehydration may be at increased risk for adverse events due to slower elimination of iodinated contrast agents *[see Clinical Pharmacology (12.3)]*.

Appendix 2: Post-marketing experience in patients < 1 year of age[12]

ID*	Source	Country	Indication	Route of administration/ Diagnostic procedure	Patient gender/age	AE/ADR	Seriousness/ Outcome	Dose injected/ Concentration	Case assessment
Patients < 29 days									
(b)(6)	Health authority	Denmark	Unknown	Intravenous/ Unknown	Female /1 hour	Hypersensitivity - Urticaria - Local swelling - Ear swelling	Not Serious/ Not recovered	Unknown/ 270 mgI/mL	(b)(4)
(b)(6)	Health authority	Sweden	Unknown	Via ostomy and rectally/ Loopogram	Male /14 days	- Cholestasis - Liver function test increased - Dehydration - Diarrhoea	Serious/ Recovered	50 mL (40 ml (dilution 10-20 mL) in ostomy + 10 mL (dilution 5-15 mL) in rectum)/ Unknown	

[12] From applicant's information request response (dated February 13, 2017 in DARRTS)

ID*	Source	Country	Indication	Route of administration/ Diagnostic procedure	Patient gender/age	AE/ADR	Seriousness/ Outcome	Dose injected/ Concentration	Case assessment
(b)(6) (b)(6)	Health authority	France	Lymphatic cyst	Body cavity	Male /15 days	- Diffuse alveolar damage - Lactic acidosis - Disseminated intravascular coagulation - Acute pulmonary oedema Cardiogenic shock	Serious/ Fatal	20 mL/ 320 mgI/mL	(b)(4)

ID*	Source	Country	Indication	Route of administration/ Diagnostic procedure	Patient gender/age	AE/ADR	Seriousness/ Outcome	Dose injected/ Concentration	Case assessment
>29 days – 6 months									
(b)(6)	Physician	France	Unknown	Intravenous/ Unknown	Female /4 months	- Injection site extravasation - No adverse event	Not Serious/ Recovered	15 mL/ 270 mgI/mL	(b)(4)
(b)(6)	HCP	Italy	Unknown	Intravenous	Female /5 months	Hypersensitivity - Rash erythematous	Not Serious/ Recovered	20 mL/ 320 mgI/mL	
(b)(6)	HCP	China	Investigation of the thoracic	Intravenous	Male /5 months	- Cyanosis - Cardio-respiratory arrest	Serious/ Recovered	11 mL/ 270 mgI/mL	
(b)(6)	Health authority	UK	Unknown	Unknown	Female /Some months	Hypersensitivity - Rash	Serious/ Not recovered	100 mL/ Unknown	

ID*	Source	Country	Indication	Route of administration/ Diagnostic procedure	Patient gender/age	AE/ADR	Seriousness/ Outcome	Dose injected/ Concentration	Case assessment
> 6 months - 12 months									
(b)(6)	HCP	Taiwan	Unknown	Unknown/ Cardiac CT	Unknown /8 months	Found dead	Serious/ Fatal	Unknown/ 320 mgI/mL	(b)(4)
(b)(6)	Literature	India	Unknown	Unknown/ Scan of brain	Unknown/ 9 months	Cardiac arrest	Serious/ Fatal	Unknown/ Unknown	

* No QA investigation was initiated for any of these cases

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/s/

ERICA D RADDEN
04/05/2017

TAMARA N JOHNSON
04/05/2017

MONA K KHURANA
04/05/2017

LYNNE P YAO
04/05/2017

Label and Labeling Review

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	January 17, 2016
Requesting Office or Division:	Division of Medical Imaging Products
Application Type and Number:	NDA 20351/S-044, NDA 20808/S-025
Product Name and Strength:	Visipaque (idodixanol) injection 270 mgI/mL Visipaque (idodixanol) injection 320 mgI/mL
Product Type:	Single Ingredient
Rx or OTC:	RX
Applicant/Sponsor Name:	GE Healthcare
Submission Date:	October 5, 2016
OSE RCM #:	2016-2692
DMEPA Primary Reviewer:	Idalia E. Rychlik, PharmD.
DMEPA Team Leader:	Hina Mehta, PharmD.

REASON FOR REVIEW

The Division of Medical Imaging Products (DMIP) has requested DMEPA to review the labeling for NDA 20351/S-044 Visipaque (idodixanol) injection 270 mgI/mL and NDA 20808/S-025 Visipaque (idodixanol) injection 320 mgI/mL submitted by GE Healthcare. The applicant submitted an efficacy supplement to pursue a coronary computed tomography angiography (CCTA) indication for the Visipaque and Visipaque Bulk Package. There are no other changes to dosage form, strength or administration within the submission. We have reviewed the proposed prescribing information (PI) for areas of vulnerability that could lead to medication errors.

MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant submitted an efficacy supplement to pursue a coronary computed tomography angiography indication for Visipaque and Visipaque Pharmacy Bulk. DMEPA evaluated the proposed prescribing information (pi) for areas of vulnerability in regards to medication error. We identified use of symbols, listed in ISMP's list of error prone abbreviation, symbols and dose designations. These symbols decrease readability and may interfere with the safe use of the product. Therefore, we conclude that the revised prescribing information can be improved to increase clarity and prominence of important information to promote safe use of the product.

CONCLUSION & RECOMMENDATIONS

The DMEPA identified areas in the labeling that can be improved to increase readability and promote the safe use of the product. We provide our recommendation in Section 4.1 for the PI.

1.1 RECOMMENDATIONS FOR THE DIVISION

i. Dangerous abbreviations, symbols, and dose designations that are included in Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols and Dose Designations[a] appear throughout the Prescribing Information. As part of a national campaign to avoid the use of dangerous dose designations, FDA agreed not to approve such error dose designations in the approved labeling of products. Thus, replace the symbols "<" and "≥" with their intended meanings to prevent misinterpretation and confusion throughout the prescribing information.

[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 April 2]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Visipaque that GE Healthcare submitted on October 5, 2016.

Table 2. Relevant Product Information for Visipaque		
Product Name	**Visipaque** NDA 20351	**Visipaque (Pharmacy Bulk Package)** NDA 20808
Initial Approval Date	03/22/1996	08/29/1997
Active Ingredient	iodixanol	
Indication	INTRA-ARTERIAL • 270 mgI/mL for intra-arterial digital subtraction angiography. • 320 mgI/mL for angiocardiography (left ventriculography and selective coronary arteriography), peripheral arteriography, visceral arteriography, and cerebral arteriography. INTRAVENOUS • 270 and 320 mgI/mL for CECT imaging head and body and excretory urography. • 320 mgI/mL for CECT imaging peripheral venography.	
Route of Administration	Intravenous, Intra-arterial	
Dosage Form	Solution for Injection	
Strength	In concentrations of 270 and 320 mg of organically bound iodine per mL (550 mg and 642 ml of Iodixanol per mL).	
Dose and Frequency	Individualize the combination of volume and concentration of VISIPAQUE Injection considering age, body weight, size of the vessel, rate of blood flow within the vessel, and other applicable factors. For the adult population, the maximum recommended total dose of iodine is 80 grams.	
How Supplied	50 mL, 100 mL, 150 mL, 200 mL vial, box of 10 50 mL, 100 mL, 150 mL, 200 mL glass bottle, boxes of 10 50 mL, 100 mL, 150 mL, 200 mL in +*PLUS*PAK™ (polymer bottle), boxes of 10	
Storage	20°C-25°C (68°F-77°F); excursions to 15°C-30°C (59°F-86°F)	

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On December 22, 2016, we searched the L:drive and AIMS using the terms, Visipaque to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 0 previous reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Visipaque (iodixanol) labels and labeling submitted by GE Healthcare on October 5, 2016.

- Prescribing Information (PI)

G.2 Label


Visipaque PI

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

IDALIA E RYCHLIK
01/17/2017

HINA S MEHTA
01/17/2017

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

020351/S-044
020808/S-025

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA #**20351 & 20808** SUPPL # **44 & 25** HFD # **160**

Trade Name **Visipaque Injection**

Generic Name **Iodixanol**

Applicant Name **GE Healthcare Inc.**

Approval Date, If Known **Apri1 5, 2017**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

d) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the

NDA #(s).

NDA# NDA20351 & Visipaque (Iodixanol) injection
NDA20808
NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets

"clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

(d)

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Main Evaluation	No. of patients enrolled
			GE-Sponsored Studies		
Study 1 GE-189-002 (VCT002)	Open-label, prospective, multi-center, non-randomized	Test bolus: 20 mL at 4-5 mL/s Main injection: 70-80 mL Visipaque at 3.5-5 mL/s	Diagnostic performance of CCTA using LightSpeed VCT scanner for detection of presence or absence of coronary artery obstruction in subjects with chest pain when compared against ICA as SOR	Blinded CCTA image evaluation using AHA 15 coronary segmental model	245
Study 2 GE-012-096	Prospective, multi-center, registry	Not pre-specified, mean dose of 91.5 mL Visipaque, range of 30-180 mL	Prognostic value in terms of sensitivity, specificity, PPV, and NPV of CCTA compared to subsequent ICA findings or binary subject outcomes	CCTA compared to clinical outcomes or ICA up to 12 months	885

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation

been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

both investigations were essential.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☒
		! Explain: **The studies were not conducted under IND because at the time of the study, the primary goal of the applicant was to evaluate the scanner, not subjects.**
Investigation #2		!
		!
IND #	YES ☐	! NO ☒
		! Explain: **The studies were not conducted under IND because at the time of the study, the primary goal of the applicant was to evaluate the scanner, not subjects.**

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☒
Explain:	! Explain: **Not Applicable**
Investigation #2	!
	!
YES ☐	! NO ☒
Explain:	! Explain: **Not Applicable**

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that

the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: **Frank Lutterodt**
Title: **Senior Regulatory Project Manager**
Date: **4/5/17**

Name of Division Director signing form: **Libero Marzella., M.D., Ph.D.**
Title: Director, DMIP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

FRANK A LUTTERODT
04/11/2017

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