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

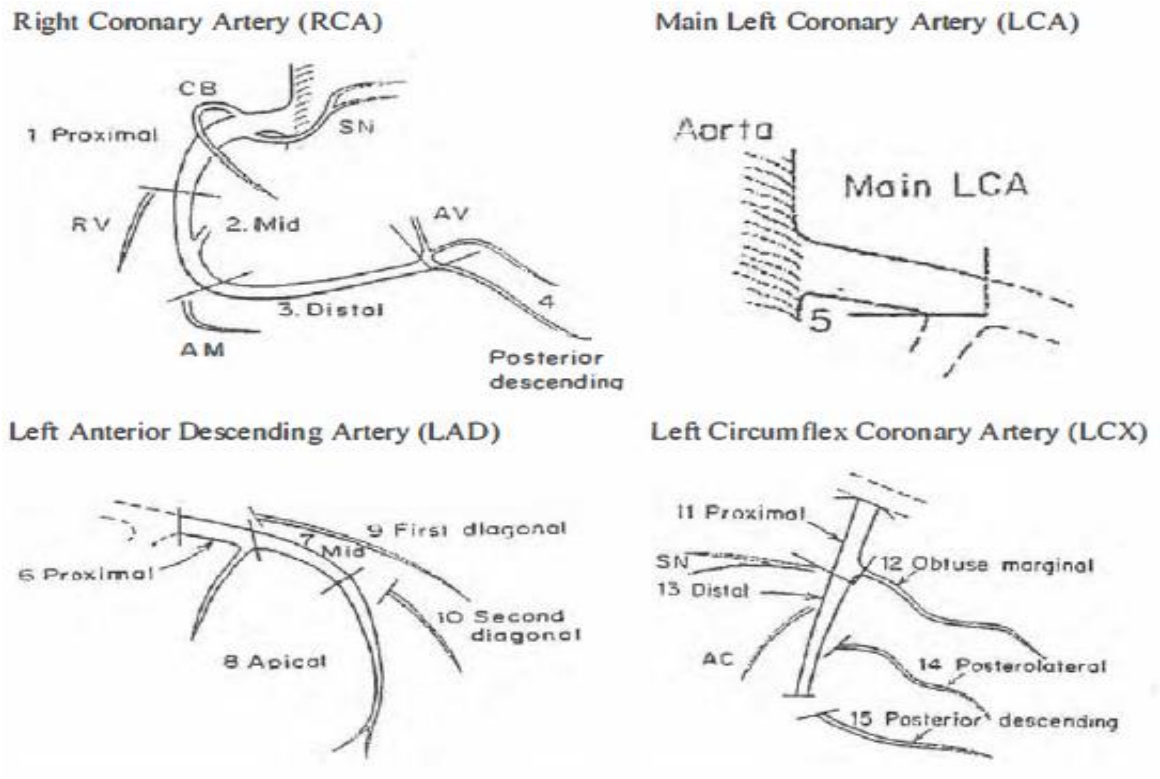
did not exceed the maximum volume specified in the product package insert.

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).

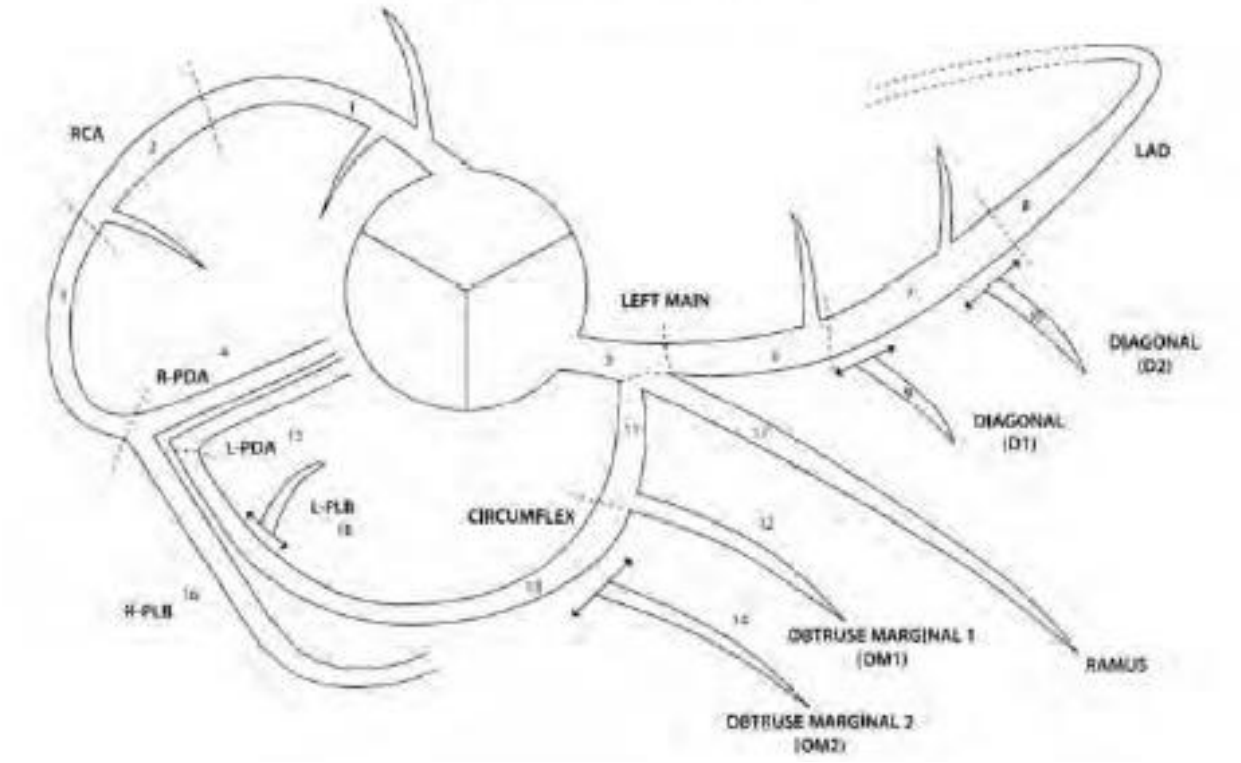
In the original read study, the CCTAs and ICAs were interpreted in terms of the degree of stenosis at each of 15 coronary artery segments (AHA model). In the re-read study, the same set of CCTAs and ICAs were re-interpreted with the results reported at each segment, based on the subdivision of the coronary 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

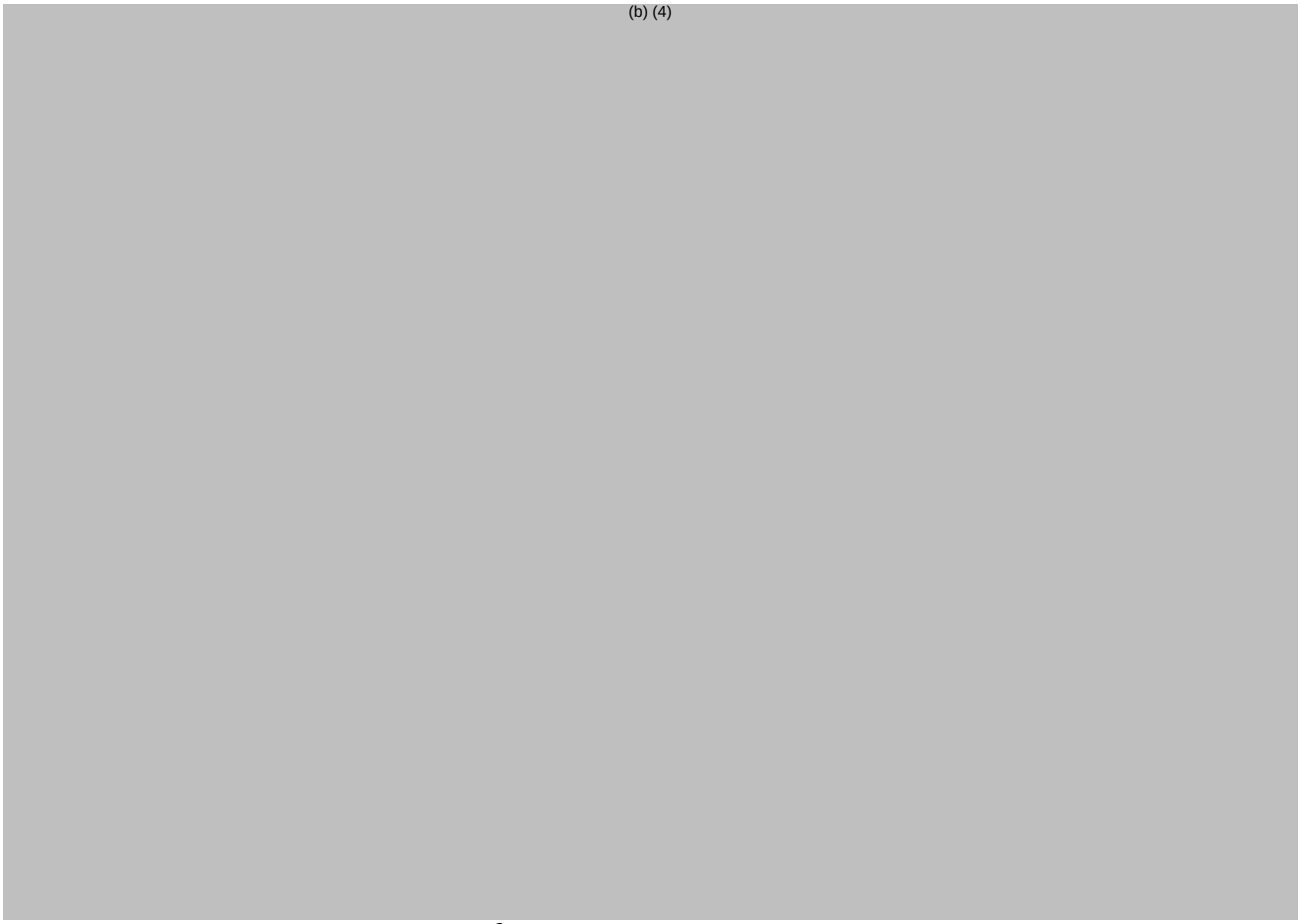
Table 9 Coronary artery segment model comparison: AHA and SCCT

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



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).

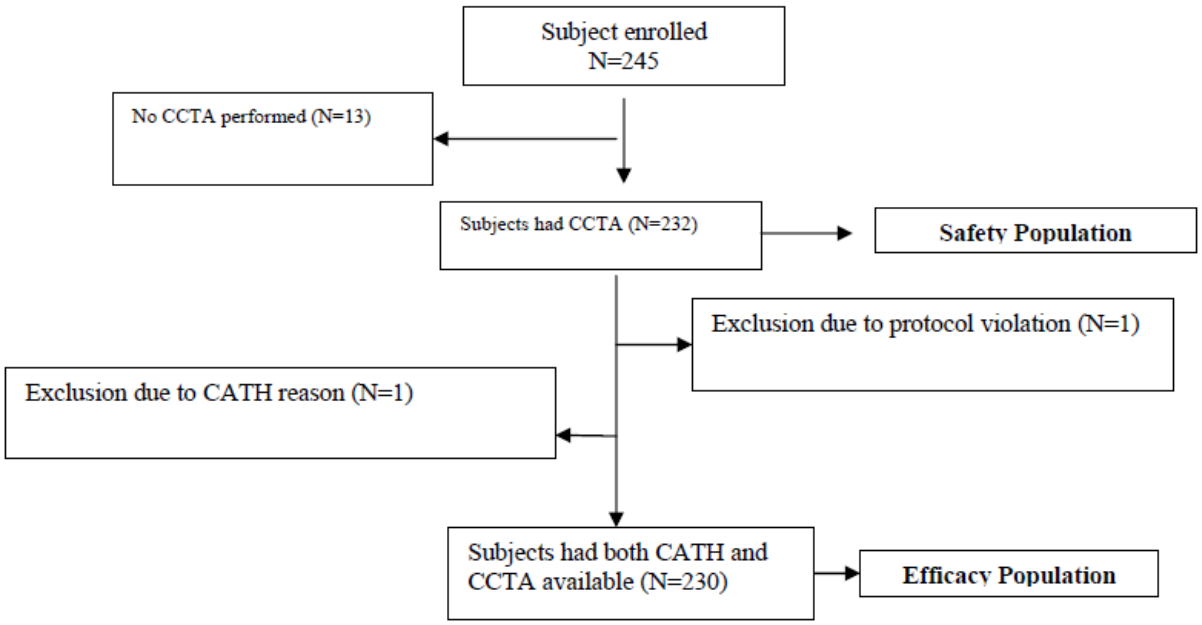
Financial Disclosure

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 1/3rd 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:

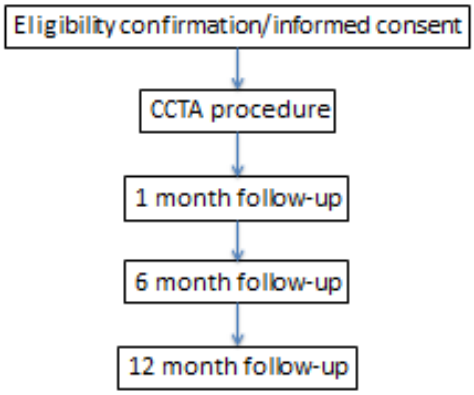
- Subjects with chest pain syndrome scheduled to undergo a Visipaque-enhanced CCTA examination for 1 of the following reasons:
    - Intermediate pre-test probability of CAD
    - An uninterpretable/equivocal stress test (exercise, perfusion, or stress echo).
- The subject was willing to allow the study 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	Deviation Type	Actual Deviation
001-0019	minor	After the subject signed the informed consent, it was discovered that the subject did not meet the inclusion criteria.
002-0053	major	Prior catheterization documents coronary calcification.
005-0054	minor	Subject did not mention history of CABG during interview.
006-0003	major	Left heart catheterization procedure performed 1997, mild CAD of LAD.
006-0010	major	Left heart catheterization less than 50% plaque found in LAD.
006-0013	major	Left heart catheterization done in 2006, less than 30% disease in LAD.
006-0023	major	Left heart catheterization done in 2001, no intervention done, less than 50% CAD.
011-0026	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 001-0008 was a 52-year-old male who had the study CCTA procedure on June 12, 2006. At the month 6 follow-up check, medical records indicated that he died on (b) (6). The death was not cardiac related.
>
> Subject 001-0041 was a 67-year-old male who had the study CCTA procedure on October 30, 2006. 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 004-0006 was a 54-year-old female who had the study CCTA procedure on July 11, 2006. 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 (b) (5) 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) (5) .

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 "Main Bolus Volume."

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

Abbara S, Arbab-Zadeh A, Callister TQ, Desai MY, Mamuya W, Thomson L, Weigold WG. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. Journal of cardiovascular computed tomography. 2009 Jun 30;3(3):190-204

American College of Radiology. *ACR manual on contrast media*. 2015.

Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, Mcgoon DC, Murphy ML, Roe BB. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation. 1975 Apr 1;51(4):5-40.

Brieger DB, Mak KH, Kottke-Marchant K, Topol EJ. Heparin-induced thrombocytopenia. Journal of the American College of Cardiology. 1998 Jun 30;31(7):1449-59.

Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, Scherer M, Bellinger R, Martin A, Benton R, Delago A. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. Journal of the American College of Cardiology. 2008 Nov 18;52(21):1724-32.

Cerqueira MD, Allman KC, Ficaro EP, Hansen CL, Nichols KJ, Thompson RC, Van Decker WA, Yakovlevitch M. Recommendations for reducing radiation exposure in myocardial perfusion

imaging. Journal of nuclear cardiology. 2010 Aug 1;17(4):709-18.

Chen MY, Shanbhag SM, Arai AE. Submillisievert median radiation dose for coronary angiography with a second-generation 320–detector row CT scanner in 107 consecutive patients. Radiology. 2013 Apr;267(1):76-85.

Coles DR, Smail MA, Negus IS, Wilde P, Oberhoff M, Karsch KR, Baumbach A. Comparison of radiation doses from multislice computed tomography coronary angiography and conventional diagnostic angiography. Journal of the American College of Cardiology. 2006 May 2;47(9):1840-5.

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.

Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, Fonarow GC, Lange RA, Levine GN, Maddox TM, Naidu SS. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Journal of the American College of Cardiology. 2014 Nov 4;64(18):1929-49.

Hamon M, Biondi-Zoccai GG, Malagutti P, Agostoni P, Morello R, Valgimigli M, Hamon M. Diagnostic performance of multislice spiral computed tomography of coronary arteries as compared with conventional invasive coronary angiography: a meta-analysis. Journal of the American College of Cardiology. 2006 Nov 7;48(9):1896-910.

Han BK, Lesser A, Rosenthal K, Dummer K, Grant K, Newell M. Coronary computed tomographic angiographic findings in patients with Kawasaki disease. The American journal of cardiology. 2014 Dec 1;114(11):1676-81.

Hausleiter J, Meyer T, Hadamitzky M, Zankl M, Gerein P, Dörrler K, Kastrati A, Martinoff S, Schömig A. Non-invasive coronary computed tomographic angiography for patients with suspected coronary artery disease: the Coronary Angiography by Computed Tomography with the Use of a Submillimeter resolution (CACTUS) trial. European heart journal. 2007 Dec 1;28(24):3034-41.

Hendel RC, Patel MR, Kramer CM, Poon M, Carr JC, Gerstad NA, Gillam LD, Hodgson JM, Kim RJ, Lesser JR, Martin ET. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 Appropriateness

Criteria for Cardiac Computed Tomography and Cardiac Magnetic Resonance Imaging: A Report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for .... Journal of the American College of Cardiology. 2006 Oct 3;48(7):1475-97.

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.

Javeed N, Javeed H, Javeed S, Moussa G, Wong P, Rezai F. Refractory anaphylactoid shock potentiated by beta-blockers. Catheterization and cardiovascular diagnosis. 1996 Dec 1;39(4):383-4.

Kanamaru H, Sato Y, Takayama T, Ayusawa M, Karasawa K, Sumitomo N, Harada K. Assessment of coronary artery abnormalities by multislice spiral computed tomography in adolescents and young adults with Kawasaki disease. The American journal of cardiology. 2005 Feb 15;95(4):522-5.

Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, Dunning A, DeFrance T, Lansky A, Leipsic J, Min JK. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms: results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. Journal of the American College of Cardiology. 2011 Nov 1;58(19):1989-97.

Ladapo JA, Blecker S, Douglas PS. Physician decision making and trends in the use of cardiac stress testing in the United States: an analysis of repeated cross-sectional data. Annals of internal medicine. 2014 Oct 7;161(7):482-90.

Landau C, Lange RA, Hillis LD. Percutaneous transluminal coronary angioplasty. New England Journal of Medicine. 1994 Apr 7;330(14):981-93.

Lang DM, Alpern MB, Visintainer PF, Smith ST. Increased risk for anaphylactoid reaction from contrast media in patients on β-adrenergic blockers or with asthma. Annals of internal medicine. 1991 Aug 15;115(4):270-6.

Lang DM, Alpern MB, Visintainer PF, Smith ST. Elevated risk of anaphylactoid reaction from

radiographic contrast media is associated with both ß-blocker exposure and cardiovascular disorders. Archives of internal medicine. 1993 Sep 13;153(17):2033-40.

Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, Nieman K, Pontone G, Raff GL. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. Journal of cardiovascular computed tomography. 2014 Sep 1;8(5):342-58.

Lieberman PL, Seigle RL. Reactions to radiocontrast material. Clinical reviews in allergy & immunology. 1999 Dec 1;17(4):469-96

Mark DB, Berman DS, Budoff MJ, Carr JJ, Gerber TC, Hecht HS, Hlatky MA, Hodgson JM, Lauer MS, Miller JM, Morin RL. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. Journal of the American College of Cardiology. 2010 Jun 8;55(23):2663-99.

Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Després JP, Fullerton HJ, Howard VJ. Executive Summary: Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016 Jan 26;133(4):447

Newburger JW, Takahashi M, Burns JC. Kawasaki disease. Journal of the American College of Cardiology. 2016 Apr 12;67(14):1738-49.

Raff GL, Abidov A, Achenbach S, Berman DS, Boxt LM, Budoff MJ, Cheng V, DeFrance T, Hellinger JC, Karlsberg RP. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. Journal of cardiovascular computed tomography. 2009 Mar 1;3(2):122-36.

Raff GL, Chinnaiyan KM, Cury RC, Garcia MT, Hecht HS, Hollander JE, O'Neil B, Taylor AJ, Hoffmann U. SCCT guidelines on the use of coronary computed tomographic angiography for patients presenting with acute chest pain to the emergency department: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. Journal of cardiovascular computed tomography. 2014 Jul 1;8(4):254-71.

Seifarth H, Schlett CL, Truong QA, Hoffmann U. Cardiac CT in the emergency department. Cardiol Clin. 2012 Feb;30(1):117-33.

Shuman WP, Branch KR, May JM, Mitsumori LM, Lockhart DW, Dubinsky TJ, Warren BH, Caldwell JH. Prospective versus Retrospective ECG Gating for 64-Detector CT of the Coronary

Arteries: Comparison of Image Quality and Patient Radiation Dose 1. Radiology. 2008 Aug;248(2):431-7.

Sun J, Zhang Z, Lu B, Yu W, Yang Y, Zhou Y, Wang Y, Fan Z. Identification and quantification of coronary atherosclerotic plaques: a comparison of 64-MDCT and intravascular ultrasound. American Journal of Roentgenology. 2008 Mar;190(3):748-54.

Tavakol M, Ashraf S, Brener SJ. Risks and complications of coronary angiography: a comprehensive review. Global journal of health science. 2012 Jan;4(1):65.

Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, Rubin GD. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography: a report of the American college of cardiology foundation appropriate use criteria task force, the society of cardiovascular computed tomography, the American college of radiology, the American heart association, the American society of echocardiography, the American society of nuclear cardiology, the north American society for cardiovascular imaging, the society for cardiovascular angiography and .... Journal of the American College of Cardiology. 2010 Nov 23;56(22):1864-94.

Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, vant Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. New England Journal of Medicine. 2009 Jan 15;360(3):213-24.

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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