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

Statistical Review and Evaluation
Clinical Studies

NDA/BLA	NDA 20351 s44
Drug Name:	**Visipaque (Iohexol)**
Proposed Indication(s):	Visipaque Injection (320 mgI/mL) is indicated for coronary computed tomography angiography (CCTA) to assist in the diagnostic evaluation of patients with suspected coronary artery disease
Applicant:	GE Healthcare Inc.
Date(s):	NDA Submission: October 5, 2016 PDUFA Date: April 5, 2017
Review Priority:	Priority
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Keywords: Sensitivity, Specificity, Efficacy, Safety, Confidence Interval

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1. EXECUTIVE SUMMARY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Inferences:

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

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

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

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

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

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

2. INTRODUCTION

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

2.1 Overview

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

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

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

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

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

2.1.1 Regulatory History

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

A brief regulatory history is as follows:

- End of phase 2 meeting on 27 August 2009

  - GE Healthcare pursued a potential CCTA indication for Visipaque 320 mgI/mL in 2009 "(b) (4)", based on published literature and data from GE Healthcare-sponsored studies supporting its diagnostic value in management of patients with suspected CAD.

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

- Type C Meeting on November 10, 2015

  - To discuss GE's proposed Phase 3 study for proposed indication "(b) (4)"

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

- Type B Meeting on July 13, 2016

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

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

2.2 Data Sources

Data and definition files were provided by the sponsor.

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

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and analysis provided by the sponsor were adequate.

3.2 Evaluation of Efficacy

3.2.1 Study Design

There were two studies evaluating the efficacy and safety.

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

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

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

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

3.2.2 Objective and number of subjects

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

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

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

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

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

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

3.2.3 Demographic and Baseline Characteristics

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

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

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

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

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

3.3 Results and Conclusions

3.3.1 Pivotal Studies

There were two GE sponsored pivotal studies.

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

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

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

Second GE study 2 – registry (2008-2010)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3.3.4 Statistical Analyses

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

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

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

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

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

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

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

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

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

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

3.3.5 Sample Size:

Subject Level Analysis:

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

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

Vessel Level Analysis

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

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

Segment Level Analysis

Efficacy populations - summation of all segments included 2023 segments with 16 discordance for 50% stenosis threshold with with Segments Unevaluable or <2mm by CATH Excluded. The distribution of these segments is given below in Table 7:

Table 7: Efficacy Populations - Reader Discordance

50% Stenosis Threshold	Total (N)	Discordance (n, %)
Summation of all	2023	25 (1.2)
Segment 01: pRCA	219	0 (0)
Segment 02: mRCA	189	3 (1.6)
Segment 03: dRCA	177	2 (1.1)
Segment 04: PDA	82	1 (1.2)
Segment 05: LM	229	2 (0.9)
Segment 06: pLAD	227	4 (1.8)
Segment 07: mLAD	198	2 (1.0)
Segment 08: aLAD	33	0 (0)
Segment 09: D1	82	2 (2.4)
Segment 10: D2	26	0 (0.0)
Segment 11: pLCX	228	2 (0.9)
Segment 12: OM1	156	1 (0.6)
Segment 13: dLCX	149	4 (2.7)
Segment 14: PL	24	2 (8.3)
Segment 15: PD	4	0 (0)

3.3.6 GE Study # 1a - Original Read (GE 189-002, aka VCT 002):

Subject level analysis was pre-specified. Standard of Truth **was q**uantitative assessment of elective ICA.

Original read study “Subject level sensitivity was defined as the proportion of subjects with at least 1 diseased segment by ICA who also had at least 1 diseased segment by CCTA for at least 2 readers.

Original read study "Subject level specificity was defined as the proportion of subjects with no diseased segments by ICA who had none of the same segments diseased by CCTA for at least 2 readers"

3.3.7 GE Study # 1a - Original Read Results:

The original read results for study1a at subject level are given in the following table 8.

Table 8: Study GE-189-002 Subject Level Analysis (Majority Read)

	Primary endpoint (≥ 50%) excluding segments < 2mm by QCA			Additional endpoint (≥ 50%) including segments < 2mm by QCA		
	ICA +	ICA -	Total	ICA +	ICA -	Total
CCTA +	45	38	83	52	30	82
CCTA -	2	142	144	3	142	145
Total	47	180	227	55	172	227
Sensitivity (%) 95% CI	95.7 (85.5, 99.5)			94.6 (84.9, 98.9)		
Specificity (%) 95% CI	78.9 (72.2, 84.6)			82.6 (76.1. 87.9)		
NPV	98.6%			97.9%		

Comment: 3 discordant subjects were excluded, 2 with disease by CATH (ICA), 1 without
Additional endpoint includes segments < 2mm by QCA
CI = 95% exact binomial confidence interval.

3.3.7 GE Study # 1b - Reasons for doing reread study **(GE 102-101):**

- Data analysis
  - "All analyses were to be performed for each reader separately according to the protocol.
  - SAP was changed so that the analyses were performed based on "reader consensus" rather than for each reader separately

- Original study failed to reject the hypothesis that specificity is ≤80% which was a pre-specified :
  - For subject-level sensitivity and specificity, null and alternative hypotheses were tested:
  - H_0: Sensitivity ≤ 0.80 versus H_a: Sensitivity > 0.80, and
  - H_0: Specificity ≤ 0.80 versus H_a: Specificity > 0.80

- FDA feedback on GE-189-002 (Type B Meeting 8-27-2009)

- Study is not adequate as confirmatory or pivotal study forming (in part or in isolation) the basis of an approvable NDA submission

- Lower limit of the CI on both Sensitivity and specificity not greater than 80% Image assessment procedure

- Lack of clarity regarding characterization of non-evaluable segments

3.3.8 Major differences in First read and Re-read analyses:

Major differences in First read and Re-read analysis are given in the following Table 9

Table 9: Original and Reread Analysis Differences

	GE-189-002 original	GE-012-101 Reread
Coronary artery model	AHA 15 segment	SCCT 18 segment (2009)
CCTA read		
3 independent blinded readers		
Consensus	Agreement of 2/3	Agreement of 2/3
Discordant results	Excluded	Counted as FN or FP, depending on SoT
By reader analysis	Not done	Done
Unevaluable segments	Given same result as most adjacent segment	Counted as FN or FP, depending on the SoT
Hypotheses Testing	Done; Failed to reject null for specificity	Not formulated
Intra-reader reliability	Not done	Done for 10% of subjects
ICA read	QCA by one blinded reader	QCA by single reader
Intra-reader reliability	Not done	Done for QCA

3.3.9 Post-hoc Subject Level Per Reader Analysis - original read data:

230 subjects had both CCTA and CATH (ICA) images available for blind read. (59.1% male, 57±10 years). The mean inter-test interval between CCTA and CATH (ICA) was 5.9±4.3 days. On a subject-based model, the sensitivity and specificity to detect ≥50% stenosis and 95% confidence interval based on exact binomial test are provided in Table 10.

Table 10: GE-102-101 (original data) per Subject Level Analysis

	Readers – Original Read Data								
	Reader 1			Reader 2			Reader 3		
	ICA +	ICA -	Total	ICA +	ICA -	Total	ICA +	ICA -	Total
CCTA +	44	33	77	48	54	102	44	33	77
CCTA -	2	137	139	1	126	127	4	147	151
Unevaluable	3	11	14	0	1	1	1	1	2
All Total	49	181	230	49	181	230	49	181	230
Sensitivity (%) 95% CI	44/49 = 89.8 (77.8, 96.6)			48/49 = 98.0 (89.2, 100.0)			44/49 = 89.8 (77.8, 96.6)		
Specificity (%) 95% CI	137/181 = 75.7 (68.8, 81.8)			126/181 = 69.6 (62.4. 76.2)			147/181 = 81.2 (74.8, 86.6)		

Notes: 1> For sensitivity unevaluable were treated as FN and for specificity unevaluable were treated as FP per defined algorithm. (conservative assignment)
2> 95% Confidence Intervals are based on Exact Binomial Test

Sponsor stated that "None of the readers achieved statistical significance for either sensitivity or specificity at the ≥70% stenosis threshold. There were only 28 patients who were diseased by CATH at the ≥70% stenosis threshold.

3.3.10 Subject Level, Per Reader Analysis – re-read data:

230 subjects had both CCTA and CATH (ICA) images available for blind reread. (59.1% male, 57±10 years). The mean inter-test interval between CCTA and CATH (ICA) was 5.9±4.3 days. On a subject-based model, the sensitivity and specificity to detect ≥50% stenosis and 95% confidence interval based on exact binomial test are provided in Table 11.

Table 11: Study 012-101 (reread Data) per Patient Level

	Readers – Reread data GE-012-101								
	Reader A			Reader B			Reader C		
	ICA +	ICA -	Total	ICA +	ICA -	Total	ICA +	ICA -	Total
CCTA +	48	6	54	56	17	73	63	20	83
CCTA -	23	152	175	15	151	156	8	138	146
Total	71	158	229	71	158	229	71	158	229
Sensitivity %) 95% CI	67.6 (55.5, 78.2)			78.9 (67.6, 87.7)			88.7 (79.0, 95.0)		
Specificity (%) 95% CI	96.2 (91.9, 98.6)			89.2 (83.3, 93.6)			87.3 (81.1, 92.1)		

3.3.11 Post-hoc Vessel Level Analysis - Original read data - by reader analysis:

Table 12 provides VISIPAQUE™-enhanced CCTA Visual Assessments Compared to CATH (ICA) as Standard of Truth by Reader with Segments Unevaluable or <2mm by CATH (ICA) Excluded (Summation of All Vessels Assuming Independent Vessels) (Stenosis ≥ 50%) (Efficacy Population). The Sensitivity estimates for readers 1, 2 and 3 are 76% , 89% and 77% respectively and the Specificity estimates for readers 1, 2 and 3 are 85% , 84% and 89% respectively

Table 12: Summation of All Vessels (Stenosis ≥ 50%) by reader for original data

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

*based on exact binomial confidence interval assuming independent vessels

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

Notes: 1> For sensitivity unevaluable were treated as FN and for specificity unevaluable were treated as FP per defined algorithm. (a conservative assignment)

2> A vessel was categorized as diseased if there was at least 1 diseased segment by CATH (ICA) within the vessel and not diseased if there were no diseased segments within the vessel.

Table 13 provides VISIPAQUE™-enhanced CCTA Visual Assessments Compared to CATH (ICA) as Standard of Truth by Reader with Segments Unevaluable or <2mm by CATH (ICA) Excluded (Summation of All Vessels Assuming Independent Vessels) (Stenosis ≥ 70%) (Efficacy Population). The Sensitivity estimates for readers 1, 2 and 3 are 76% , 88% and 88% respectively and the Specificity estimates for readers 1, 2 and 3 are 89% , 87% and 90% respectively

Table 13: Summation of All Vessels (Stenosis ≥ 70%) by reader for original data

	Readers Original Read Data (Stenosis ≥ 70%)								
	Reader 1			Reader 2			Reader 3		
	CATH +	CATH -	Total	CATH +	CATH -	Total	CATH +	CATH -	Total
CCTA +	25	34	59	29	105	133	29	66	95
CCTA -	7	781	788	4	762	766	3	788	791
Unevaluable	1	58	59	0	6	6	1	19	20
All Total	33	873	906	33	873	906	33	873	906
Sensitivity %)	25/33 = 75.8			29/33 = 87.9			29/33 = 87.9		
95% CI*	(57.7, 59.1)			(71.8, 96.6)			(71.8, 96.6)		
95% CI**	(56.9, 88.1)			(70.9, 95.6)			(71.6, 95.4)		
Specificity (%)	781/873 = 89.5			762/873 = 87.3			788/873 = 90.3		
95% CI*	(87.2, 91.4)			(84.9, 89.4)			(88.1, 92.2)		
95% CI**	(85.5, 92.4)			(84.1, 89.9)			(87.4, 92.6)		

*based on exact binomial confidence interval assuming independent vessels

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

Notes: 1> For sensitivity unevaluable were treated as FN and for specificity unevaluable were treated as FP per defined algorithm. (a conservative assignment)

2> A vessel was categorized as diseased if there was at least 1 diseased segment by CATH (ICA) within the vessel and not diseased if there were no diseased segments within the vessel.

95% Confidence Interval are based on sponsor's analysis

Comparing side-by-side 50% Stenosis vs. 70% Stenosis, sensitivity & specificity are similar.

3.3.12 Post-hoc Vessel Level Analysis - read and reread data summary by reader:

Table 14 provides VISIPAQUE™-enhanced CCTA Visual Assessments Compared to CATH as Standard of Truth by Reader with Segments Unevaluable or <2mm by CATH Excluded (Summation of All Vessels) (Stenosis ≥ 50%) (Efficacy Population). This table provides sensitivity and specificity for summation of all vessels by readers and by majority read for both original read data and reread data.

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

Table 14: Summation of All Vessels (Stenosis ≥ 50%) by reader for original and reread data

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

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

3.3.13 Post-hoc Segment Level Analysis - Original and reread data summary by reader:

Table 15 provides VISIPAQUE™-enhanced CCTA Visual Assessments Compared to CATH (ICA) as Standard of Truth by Reader with Segments Unevaluable or <2mm by CATH (ICA) Excluded (Summation of All Segments) (Stenosis ≥ 50%) (Efficacy Population). This table provides sensitivity and specificity for summation of all segments by readers and by majority read for both original read data and reread data.

This table shows showed moderate sensitivity ranging from 55% to 77 % for the original data and 40% to 60% for reread data. It also showed specificity ranging from 88% to 91% for the original data and 94% to 96% for reread data.

Table 15: Post-hoc Summation of All Segments for original and reread data

Segment-level Analysis (Summation of all segments)(Stenosis ≥ 50%)								
	GE-189-002 (Read)				GE-012-101 (Reread)			
Readers	Reader 1	Reader 2	Reader 3	Majority	Reader A	Reader B	Reader C	Majority
Sens. (%) 95% CI**	62.1 (50.5, 72.4)	77.0 (66.9, 84.7)	55.2 (43.8, 66.0)	64.7 (52.6, 75.2)	40.0 (31.4, 49.3)	47.4 (37.7, 57.4)	60.0 (50.9, 68.4)	47.4 (38.0, 57.0)
Spec (%) 95% CI**	87.6 (83.6, 90.7)	89.4 (87.0, 91.4)	91.4 (89.3, 93.1)	92.9 (90.8, 94.6)	95.5 (94.1, 96.5)	95.6 (94.5, 96.5)	93.8 (92.1, 95.2)	96.2 (95.0, 97.1)

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

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

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

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

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

The purpose of the Visipaque-enhanced CCTA registry study was to evaluate the usefulness of CCTA findings in predicting patient outcome in routine clinical practice. The study was conducted between September 2008 and September 2010 with 885 patients enrolled at 17 centers. 11 had no CCTA, 874 underwent CCT and 17 were excluded. This resulted in the efficacy population of 857 subjects and 850 subjects completed the study.

The Primary endpoint was to assess prognostic value (sensitivity, specificity, PPV and NPV) of CCTA compared to subsequent ICA findings (if performed) or subject outcomes (MACE, death, revascularization). After eligibility confirmation/informed consent CCTA procedure was performed. Follow-up clinical outcome was assessed at 1, 6, and 12 month follow-up. This study evaluated prognostic value of CCTA. The clinical outcome for the follow-up period is given in the following table 16:

Table 16: Clinical Outcomes Follow-up Period

Clinical Outcome	Follow-up Period		
	1 month	6 month	12 month
	N = 857	N = 853	N = 843
Positive	51 (6%)	71 (8%)	76 (9%)
Negative	806 (94%)	782 (92%)	767 (91%)

The diagnostic accuracy of Visipaque-enhanced CCTA results (positive finding of ≥50% stenosis) on predicting downstream cardiovascular events at each follow-up period when compared to the actual occurrence of events are summarized in Table 17. The sensitivity of Visipaque-enhanced CCTA for detection of downstream cardiac events was 96.1%, 95.8%, and 94.7% at the 1-, 6-, and 12-month follow-up time points, respectively, and the specificity was 84.5%, 86.6%, and 87.0%.

Table 17: Diagnostic Efficacy of CCTA for Prediction of Cardiac Events

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

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

3.3.15 Pediatric Subjects:

There are no GE-sponsored studies in the pediatric population for this indication. The sponsor refers to the current Visipaque Injection package insert for information to pediatric subjects.

3.4 Evaluation of Safety

Study 1: In the GE-189-002 study, the VISIPAQUE™- enhanced CCTA procedure was well tolerated. There were no reported deaths nor any serious, significant or severe in intensity AEs. Of the 232 subjects in the safety population of the GE-189-002 study, 24 subjects experienced a total of 34 AEs: 25 were mild in intensity and 9 were moderate. Eleven subjects experienced AEs classified as cardiac disorders: 7 subjects experienced a mild cardiac disorder, and 4 subjects experienced a moderate cardiac disorder.

Study 2: Of the 874 subjects included in the Safety population, 17 (2%) subjects experienced 1 or more TEAEs and 5/874 (1%) subjects had TEAEs that were considered related to VISIPAQUE administration. There were 10 SAEs reported for 8 (1%) subjects. None of the SAEs were considered related to VISIPAQUE administration. A total of 27 TEAEs occurred in 17 of 874 subjects (2%) in this registry study. The most commonly reported TEAEs were hypersensitivity, followed by angina pectoris, CAD and coronary artery stenosis. There were no TEAEs leading to death or discontinuation during the study. Results are summarized in Table 18.

Table 18: Overall Summary of TEAEs (Safety Population) Study 2

	All Event	Causal Relations
Subjects with at Least 1 AE, n (%)	17 (2%)	5
Number of AEs, n	27	10
Subjects with Related AEs, n (%)	5	5
Number of Related AEs, n	10	10
Subjects with SAEs, n (%)	8	0
Number of SAEs, n	10	0
Subjects with AEs Leading to Discontinuation from	0	0
Deaths, n (%)	0	0

N = number of subjects in the safety population; n = number in category; % = n/N*100%. Adverse events (AEs) summarized in this table are treatment-emergent unexpected AEs or serious adverse events (SAEs) occurring within 48 hours following administration of VISIPAQUE.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant stated that no comparison of results in sub-populations has been performed. Patients included in the pivotal studies discussed here were from similar populations. As such, comparison of results in sub-populations is not applicable. There were no special groups identified by the clinical team.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

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

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

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

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

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

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

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

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

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

Table 19 provides VISIPAQUE™-enhanced CCTA Visual Assessments Compared to CATH as Standard of Truth by Reader with Segments Unevaluable or <2mm by CATH Excluded (Summation of All Vessels) (Stenosis ≥ 50%) (Efficacy Population). This table provides sensitivity and specificity for summation of all vessels by readers and by majority read for both original read data and reread data.

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

Table 19: Summation of All Vessels (Stenosis ≥ 50%) by reader for original and reread data

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

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

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

The diagnostic accuracy of Visipaque-enhanced CCTA results (positive finding of ≥50% stenosis) on predicting downstream cardiovascular events at each follow-up period when compared to the actual occurrence of events are summarized in Table 20. The sensitivity of Visipaque-enhanced CCTA for detection of downstream cardiac events was 96.1%, 95.8%, and 94.7% at the 1-, 6-, and 12-month follow-up time points, respectively, and the specificity was 84.5%, 86.6%, and 87.0%.

Table 20: Diagnostic Efficacy of CCTA for Prediction of Cardiac Events

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

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

Inferences:

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

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

  Summary of most relevant results of Visipaque-enhanced CCTA, compared to ICA, at the vessel-level, with ≥ 50% stenosis threshold, and with segments < 2 mm by ICA excluded are given in the following Table 21

Table 21: Summary of Visipaque-enhanced CCTA at the vessel-level

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

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

SIGNATURES/DISTRIBUTION LIST

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Secondary Statistical Reviewer:	Jyoti Zalkikar, Ph. D.
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/s/

SATISH C MISRA
03/17/2017

JYOTI ZALKIKAR
03/17/2017
This primary review for the medical imaging drug Visipaque is satisfactory. I concur with its findings.

PEILING YANG
03/18/2017
Signed for Dr. H.M. James Hung.