CLINICAL REVIEW

Application Type	Supplemental New Drug Application
Application Number(s)	NDA 201277 (115/397) s011
Priority or Standard	Standard
Submit Date(s)	June 30, 2015
Received Date(s)	June 30, 2015
PDUFA Goal Date	April 30, 2016
Division/Office	Division of Medical Imaging Products/Office of Drug Evaluation IV
Reviewer Name(s)	Anthony Fotenos, MD, PhD
Review Completion Date	March 26, 2016
Established Name	Gadobutrol
(Proposed) Trade Name	Gadavist
Applicant	Bayer HealthCare Pharmaceuticals
Formulation(s)	1.0 M (604.72 g/L) solution
Dosing Regimen	0.1 mL/kg IV at a flow rate of 1.5 mL/s, followed by 30 mL normal saline flush
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For use in magnetic resonance angiography (MRA) in adult and pediatric patients (including term neonates) to evaluate known or suspected supra-aortic or renal artery disease.

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Glossary

AC	*advisory committee*
AE	*adverse event*
BLA	biologics license application
CDER	Center for Drug Evaluation and Research
CEA	Carotid endarectomy
CTA	Computed tomographic angiography
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CRF	case report form
CSR	clinical study report
DMIP	Division of Medical Imaging Products
DSA	digital subtraction angiography
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
FAS	full analysis set
FDA	Food and Drug Administration
GBCA	gadolinium based contrast agent
GCIS	Global Clinical Imaging Services
GCP	good clinical practice
GRAMS	pivotal renal study
GEMSAV	pivotal supra-aortic study
ICA	iodinated contrast agents
IND	Investigational New Drug
MedDRA	Medical Dictionary for Regulatory Activities
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
NDA	new drug application
NNT	number need to treat
OSI	Office of Scientific Investigation
PeRC	Pediatric Review Committee
PPS	per protocol set
PLR	physician labeling rule
PMC	postmarketing commitment
REMS	risk evaluation and mitigation strategy
sNDA	supplementary New Drug Application

SAE	serious adverse event
SPA	Special Protocol Assessment
TEAE	treatment emergent adverse event
US	United States

1 Executive Summary

1.1. Product Introduction

Gadavist is an extracellular, non-ionic, macrocyclic gadolinium-based contrast agent (GBCA). The drug appears bright on T1-weighted magnetic resonance imaging (MRI). Depending on the timing of image acquisition relative to drug administration, potential imaging targets include any waypoint along the path the drug follows as it flows from its site of intravenous injection, makes a first pass through the arterial system, and perfuses into extracellular tissue prior to reaching a state of dynamic equilibrium leading to renal excretion. Gadavist is specifically approved for central nervous system imaging in adult and pediatric patients and for breast imaging in adults. The sponsor here seeks a new indication for magnetic resonance angiography (MRA) in adult and pediatric patients with known or suspected supra-aortic or renal artery disease. The proposed dose of 0.1 mmol/kg is the same as for other Gadavist indications. The proposed injection rate of 1.5 mL/s is slightly slower.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The sponsor has provided adequate evidence to support the following conclusions limited to MRI technology representative of use between 2011 and 2014: Gadavist MRA is superior to non-contrast time-of-flight (TOF) MRA for visualizing the supra-aortic and renal arteries in adults with known or suspected supra-aortic or renal artery disease and, by extrapolation, pediatric patients. Against CTA as the reference standard, and limited to evidence obtained from visualized arterial segments, Gadavist MRA is non-inferior to TOF MRA for distinguishing between normal and abnormal segments. Given non-inferior and better-than-minimum sensitivity plus specificity in two adequate and well-controlled studies, it can be concluded that the clinical meaningfulness of superior-to-TOF arterial segment visualization is self-evident.

Table 1 Reviewer's executive summary of efficacy

Majority-reader endpoints in bold indicate that the sponsor satisfied agreed win criteria. See Tables 15 and 20 for additional details.

	VISUALIZATION (%)			SENSITIVITY (%)			SPECIFICITY (%)		
STUDY	GAD MRA [A]	TOF MRA [B]	[A]-[B] (CI)	GAD MRA [A] [A*]	TOF MRA [B] [B*]	[A]-[B] (CI) [A*]-50 (CI)	GAD MRA [A] [A*]	TOF MRA [B] [B*]	[A]-[B]-7.5 (CI) [A*]-50 (CI)
Supra-aortic	95	73	**22 (20, 24)**	60 62	54 59	**6 (-2, 14)** **12 (5, 18)**	96 98	87 98	**9 (8, 10)** **48 (47, 48)**
Renal	96	78	**18 (15, 21)**	53 55	47 35	**7 (-2, 16)** 5 (-4, 13)	95 96	86 88	**9 (7, 11)** **46 (45, 47)**

*Indicates that non-visualized segments were excluded from the analysis; otherwise, non-visualized segments were imputed to be a 50% match relative to the reference standard.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Supra-aortic and renal vascular diseases are a leading cause of morbidity and mortality in the United States. Ultrasound, computed tomographic angiography (CTA), and magnetic resonance angiography (MRA) already play an important role in guiding patients with known or suspected supra-aortic and renal arterial disease toward effective therapies. Two gadolinium-based contrast agents (GBCAs) have been approved for MRA indications. In this primary clinical review, Gadavist MRA has been found superior to non-contrast time of flight (TOF) MRA for visualizing the supra-aortic and renal arteries. Against CTA as the reference standard, and limited to evidence obtained from visualized arterial segments, Gadavist has been found non-inferior to TOF MRA for distinguishing between normal and abnormal segments. The most important risks associated with Gadavist usage are class-wide, likely independent of efficacy supplement approval, and outweighed by benefit. A risk specific to Gadavist MRA concerns uncertainty with respect to contrast kinetic data. To address this uncertainty, we have proposed a post-marketing commitment. Approval of Gadavist for supra-aortic and renal MRA is thus adequately supported by the available evidence of efficacy and safety.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Vascular disease is a leading cause of morbidity and mortality in the United States. • Supra-aortic and renal arterial disease are leading causes of non-coronary vascular disease. • Medical interventions and surgical carotid endarterectomy are effective. However, surgical interventions can be harmful depending on the degree of arterial narrowing. • Evaluating the degree of arterial narrowing (stenosis) requires imaging.	Imaging of the supra-aortic and renal arteries plays an important role in guiding patients toward appropriate interventions.
Current Treatment Options	• Ultrasound, computed tomographic angiography (CTA), and magnetic resonance arteriography (MRA) are widely used for imaging of the supra-aortic and renal arteries and have generally supplanted use of "gold standard" catheter angiography.	Approval of Gadavist "for MRA in adult and pediatric patients (including term neonates) to evaluate known or suspected supra-aortic or renal artery disease" would represent a "first"

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Contrast drugs are required for arterial visualization with CTA but not with MRA. With MRA, multiple non-contrast imaging techniques are possible, including time-of-flight (TOF). • Ablavar has been approved for adult aortoiliac MRA and Multihance has been approved for adult aortoiliac and renal MRA. • Many gadolinium-based contrast agents (GBCAs) are used off-label for MRA.	with respect to the supra-aortic arteries, the pediatric population, a one molar formulation (other GBCAs are formulated at half molar), and evidence for efficacy using CTA (not catheter angiography) as the reference standard.
Benefit	• The strongest evidence for the benefit of Gadavist comes from the rate at which image readers marked, "Yes, it can be visualized along its entire length..." when responding to the question, "Is this segment assessable?" The majority of three central readers marked "Yes" on 95% vs. 73% of 9597 segment-level survey questions in the supra-aortic arteries and 96% vs. 78% of 1752 segment-level survey questions in the renal arteries. These differences were highly statistically significant. • There is uncertainty associated with extrapolating benefits to clinical practice from those obtained in response to multiple-choice questions and susceptible to bias; however the large magnitude of the reported visualization benefit, its directional consistency across multiple studies, and its plausible technical mechanisms all suggest robustness. • Against CTA as the standard of reference, and limited to visualized segments, there is evidence that Gadavist MRA is non-inferior to TOF MRA for distinguishing between normal and abnormal segments. • The performance of Gadavist MRA for detecting arterial segments with clinically significant stenosis (i.e., Gadavist MRA sensitivity) has not been shown to exceed 50%.	Image readers are more likely to report that supra-aortic and renal arteries are visible after Gadavist administration, when sensitivity plus specificity for visualized segments exceeds chance and is non-inferior to TOF. Given this level of performance, the value of superior arterial visualization is considered self-evident. However, a negative MRA study alone should not be used to rule out significant stenosis.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There is considerable room to improve stenosis measurement reliability for CTA, Gadavist MRA, and TOF MRA.	
Risk	• This review is for an efficacy supplement, in this case meaning Gadavist has already been approved for central nervous system and breast imaging indications. It has been safely used in the U.S. post-market setting since 2011 and, for broader indications, in Europe, since 2000. • The sponsor estimates ~ (b) (4) additional doses of Gadavist will be administered for MRA indications in the first year following MRA approval. The accuracy of this forecast and whether it reflects patients who would otherwise receive another GBCA (likely) or no imaging drug (unlikely) is uncertain. • The most important risks associated with use of Gadavist are class-wide and adequately addressed in prior reviews and current labeling: anaphlactoid reactions that occur within seconds to hours of use and nephrogenic systemic fibrosis that occurs within months to years exclusively or nearly exclusively in patients with renal impairment. • Low-level, chronic gadolinium deposition in all patients following GBCA administration, particularly in bone and brain, is a new safety uncertainty under active class-wide investigation and without any clear clinical correlate identified to date. • The most important Gadavist-MRA-specific risk relates to the interchangeable use of GBCAs in the post-market setting and the uncertainty device operators face when confronted by the question,	Given current practice patterns, approval of an MRA indication for Gadavist may not lead to any net increase in overall GBCA administration, meaning no additional class-wide risk may be associated with approval of this efficacy supplement. If approval leads to a small shift from other GBCAs to Gadavist, this shift would be unlikely to increase net risk, since Gadavist is among the most stable GBCAs. The likelihood of interchangeable use of GBCAs in the post-market setting combined with uncertainty about contrast kinetics for Gadavist represents a risk that the selection of imaging duration at some imaging centers may be poorly informed, suboptimal, or even ineffective for Gadavist MRA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	"What imaging duration should I use for Gadavist MRA of the supra-aortic and renal arteries?". The specification of imaging duration is patient/device specific and inappropriate for drug labeling. Nevertheless, drug contrast kinetic data is necessary (not sufficient) for device operators to approach this imaging duration question. From a clinical perspective, this question is particularly important for MRA applications and likely differs for Gadavist compared to 0.5M GBCAs.	

Risk Management	• From a regulatory perspective, we have previously agreed that the potential for interchangeable use of Gadavist and 0.5M GBCAs in the post-market setting is sufficiently likely to warrant the following exceptional labeling language:
	  • Labeling Section 2.2: "Gadavist is formulated at a higher concentration (1 mmol/mL) compared to certain other GBCAs, resulting in a lower volume of administration. (b) (4) Table 1 to determine the volume to be administered."
	  • Labeling Section 12 (b) (4): "Compared to 0.5 molar GBCAs, the higher concentration of Gadavist results in half the volume of administration and a more compact contrast bolus."
	• The sponsor has submitted contrast kinetic simulations that suggest the imaged bolus in the supra-aortic arteries is less, not more, compact compared to 0.5M GBCAs. These simulations also contradict published data, adding to uncertainty about Gadavist contrast kinetics.
		We have proposed that the sponsor collect clinical or possibly pre-clinical data as a post-marketing commitment to:
		• Inform device operator decision-making around imaging duration, especially since it is likely different compared to other GBCAs;
		• Support the sponsor's contrast kinetic simulations;
		• Quantify qualitative labeling descriptions such as "more compact".

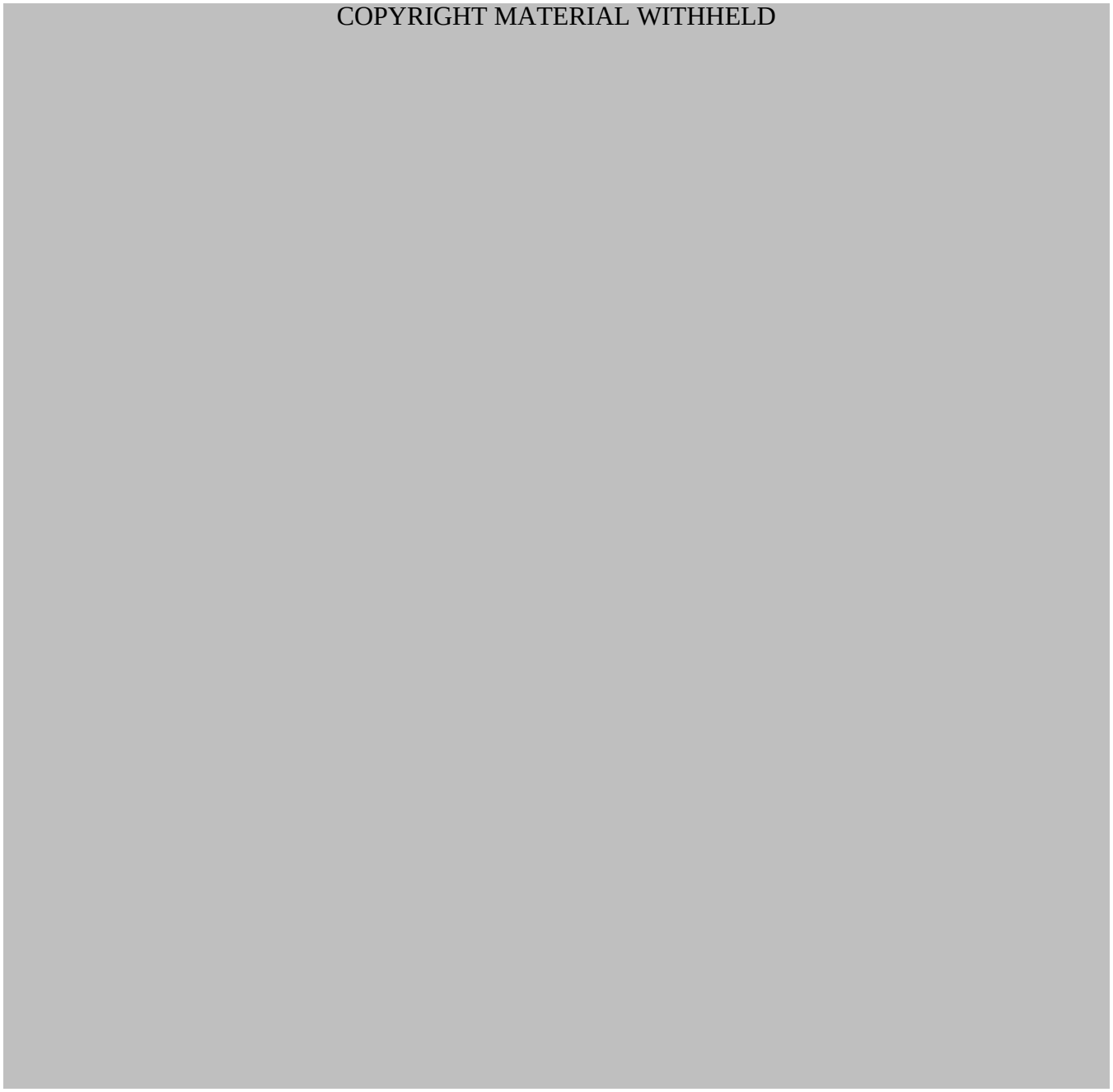
2 Therapeutic Context

2.1. Analysis of Condition

Viewed from the perspective of patients' longitudinal experience, therapeutic activity typically depends on and occurs after diagnostic activity, meaning it is more appropriate to use pathophysiological terms to specify patient populations for therapeutic compared to diagnostic drug indications. Nevertheless, to frame the medical need for MRA of the supra-aortic and renal arteries, the sponsor states that an estimated 795,000 patients suffer from new strokes each year in the United States, resulting in 144,000 deaths, and $69 billion in costs in 2009 (A169). What is the connection to MRA? Characterization of focal atherosclerotic stenosis, a primary aim of supra-aortic MRA, is a prerequisite for effective interventions designed to reduce thromboembolic risk in the internal carotid arteries. In particular, pooled analysis of three landmark trials (NASCET, ECST, AND VA309) on the value of carotid endarterectomy (CEA) estimated that for every seven patients with internal carotid artery stenosis 70-99% (as measured by invasive angiography) plus ipsilateral symptoms (mostly TIA/non-disabling stroke or retinal infarction), one patient would be spared a stroke over a follow-up period up to 10 years compared to medical therapy alone (ie, NNT = 7; Figure 1).

Figure 1 Published therapeutic outcomes related to diagnostic supra-aortic MRA

Carotid endarectomy (CEA) prevents strokes in some symptomatic patients, but harms others. In order from left to right and top to bottom, these five figures show the proportion of patients with near-occlusion, 70-99% stenosis, 50-69% stenosis, 30-49% stenosis, and <30% stenosis who were randomized to medical therapy (thin line, labeled "No surgery") vs. CEA + medical therapy (thick line, labeled "Surgery*") at time 0 and experienced any stroke or operative death over a follow-up period up to 10 years (each tick on the x-axis represents one year). The numbers below the x-axis represent the number of patients at risk at each time point. The degree to which the thick line falls below the thin favors CEA . Note how the magnitude and direction of CEA benefit depends on stenosis grouping. ARR = absolute risk reduction. Source:Rothwell 2003.*

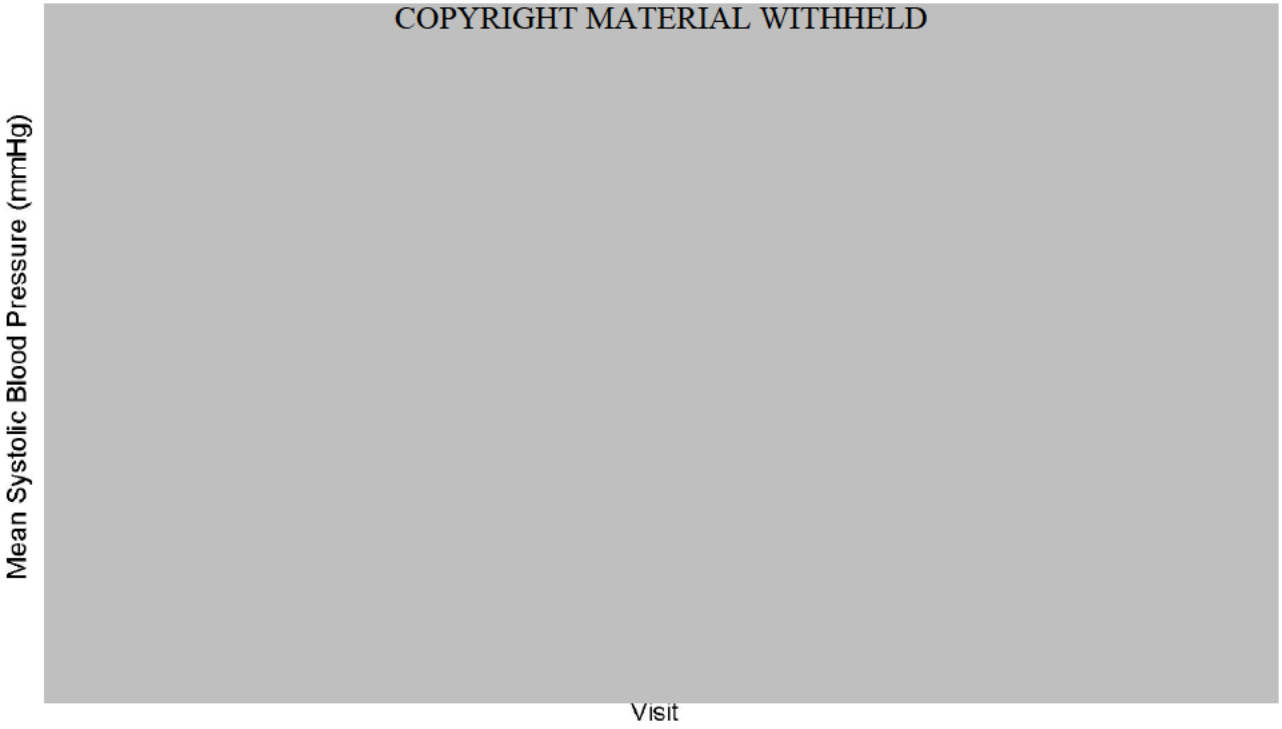


In contrast to CEA (associated with stroke prevention predominantly in the anterior cerebral circulation), recent evidence suggests surgical intervention for symptomatic atherosclerotic stenosis ≥ 50% may be ineffective or harmful compared to medical therapy in the posterior vertebral-basilar arteries (accounting for ~20% of strokes; Compter 2015, Derdeyn 2014). This is despite evidence for vertebrobasilar stenosis ≥ 50% as a predictor for future strokes (Gulli 2013).

Turning to the renal arteries, renal artery stenosis ≥ 50% has been observed in up to 7% of unselected older adult populations, but most cases are asymptomatic. The most common causes of symptomatic renal artery stenosis are atherosclerosis (prevalence ~ 0.5%) and fibromuscular dysplasia (prevalence ~ 0.04%); the most common harms are refractory hypertension and chronic kidney disease. Fibromuscular dysplasia is an idiopathic non-inflammatory disease primarily affecting the renal and supra-aortic arteries in younger women; it is also associated with potentially fatal arterial dissections and aneurysms. Again, the benefit of carotid revascularization appears not to apply to the renal arteries. Both the most definitive CORAL trial (Cooper 2014) and a subsequent meta-analysis (Riaz 2014) have failed to demonstrate any benefit of renal artery stenting plus medical therapy compared to medical therapy alone in terms of preventing adverse cardiovascular or renal events in patients with refractory hypertension or chronic kidney disease and atherosclerotic stenosis 60-99% (as measured by invasive angiography 68%, duplex ultrasonography 25%, CTA 5%, and MRA 2%). The only significant positive finding of the CORAL trial was a 2.3 mmHg better decline in systolic blood pressure (Figure 2).

Figure 2 Published therapeutic outcomes related to diagnostic renal MRA

Stenting lowers systolic blood pressure by 2.3 mmHg compared to medical therapy alone in patients treated for renal artery stenosis 60-99% and presumed secondary hypertension or renal insufficiency. Baseline refers to the period just before randomization to stenting + medical therapy vs medical therapy groups. Though the modest degree to which the blue line falls below the red line represents intermediate evidence in favor of stenting, multiple trials, including this one, failed to reject the null hypothesis for stenting based on patient outcomes. Source: Cooper 2014.



In fibromuscular dysplasia, a recent systematic review identified the need for a randomized trial of stenting, estimating that secondary hypertension resolves in one of three patients after stenting against a procedural complication rate of 12% (Trinquart 2010).

Reviewer Comment: Evidence for the potential surgical benefit of diagnosing stenosis 70-99% in the supra-aortic arteries is limited to the internal carotid arteries. There is negative evidence for the potential surgical benefit of diagnosing stenosis 50-99% in the renal and vertebral arteries. This may reflect the differing mechanisms of patient harm in the supra-aortic vs. renal territories (e.g., thromboemboli to the brain from instability of carotid atherosclerotic plaques vs. secondary hypertension and chronic kidney disease from obstructed renal blood flow) and/or differing surgical interventions (stenting vs. CEA). It is also possible that the benefit of CEA, primarily established against medical therapy in the 1980s and 1990s, has diminished and/or will diminish as medical therapy improves. Finally, it should be noted that the tail of the distribution of potential diagnostic outcomes for supra-aortic and renal angiography (differential diagnosis) beyond atherosclerotic stenosis is long, yet common diagnoses are more likely to receive the resources necessary for definitive therapeutic trials. For this reason, a

narrow focus on therapeutic trial outcomes, added to their conceptual one-way dependence on diagnostic procedures, underestimates the scope and potential value of diagnostic imaging.

2.2. Analysis of Current Treatment Options

Of the nine GBCAs approved for use in the United States, two have been approved for MRA and at least four have been reviewed related to supplementary New Drug Applications (NDAs) or Special Protocol Assessments (SPAs), as detailed in Table 2.

Table 2 Reviewer's tabulation of GBCAs approved for MRA and regulatory context

Source: See row L20.

Lines 1-4	Ablavar	(b) (4)	Multihance	(b) (4)
L1. Manufacturer	Lantheus		Bracco	
L2. Year Approved / Reviewed	2008		2012	
L3. Proposed MRA indication	(b) (4)		(b) (4)	
L4. Labeled MRA indication	For use as a contrast agent in MRA to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease.		For use in MRA to evaluate adults with known or suspected renal or aorto-ilio-femoral occlusive vascular disease.	

Lines 5-7	Ablavar	(b) (4)	Multihance	(b) (4)
L5. Dosing / administration	Administer Ablavar injection by an intravenous bolus, manually or by power injector, at a dose of 0.12 mL/kg body weight (0.03 mmol/kg) over a period of time up to 30 seconds followed by a 25-30 mL normal saline flush. Imaging is performed in two stages, the dynamic stage which begins immediately following Ablavar injection and the steady-state stage, which begins following dynamic imaging; generally 5 to 7 minutes after Ablavar injection.		The recommended dose of Multihance is 0.1 mmol/kg (0.2 ml/kg) administered as a rapid bolus intravenous injection. To ensure complete injection of the contrast medium, follow the injection with a saline flush of at least 20 mL in MRA.	
L6. Contrast (C) images	First pass + steady state		First pass	
L7. Non-contrast (NC) comparator	2D-TOF		2D-TOF	

Lines 8-17	Ablavar	(b) (4)	Multihance	(b) (4)
L8. Sn: C – NC win criteria	Superiority		• Non-inferiority (supra-aortic; C – NC > -5) • Superiority (renal and pelvis)	
L9. Sp criteria: C – NC win criteria	Non-inferiority (C – NC > -5%)		• Superiority (supra-aortic) • Non-inferiority (renal and pelvis; C – NC > -5%)	
L10. Additional primary win criteria	Sn and Sp > 50% for segments visualized by Ablavar but not TOF		None	
L11. Standard of reference (SOR)	Catheter angiography		Catheter angiography	
L12. Imputation for blanks	All wrong (blank=-SOR)		Half wrong (blank=50%SOR)	
L13. Central reader aggregation	Same 2 of 3		Same 2 of 3	
L14. Level of pivotal efficacy analysis	Segment		Segment	
L15. Analysis set for pivotal efficacy	C+NC+SOR complete		C+NC+SOR complete	
L16. Use of calipers for stenosis	Yes (unclear if for all or subset of segments)		Yes (unclear if for all or subset of segments)	
L17. Definition of positive stenosis	Unclear: 50-99% or 50-100%		• 51-99% renal and pelvis • 60-99% supra-aortic	

Line 18	Ablavar	(b) (4)	Multihance	(b) (4)
L18. Sponsor's claimed MRA efficacy outcomes • *s = segments (subdivided by number positive + negative, if available)* • *n = patients (number positive + number negative, if available)* • *R = central reader* • *In all expressions of the form C – NC = D, C = performance with contrast, NC = performance without contrast, and D = difference* • ** = win criterion achieved*	<u>Calf (n=72+53,s=200+116)</u> R1* • Sn:93-77=16* • Sp:60-38=22* R2 • Sn:78-87=-9 • Sp:66-39=27* R3 • Sn:79-78=1 • Sp:63-28=35* <u>Pelvis 1* (n=140+250, s=237+1409)</u> R1* • Sn:80-62=18* • Sp:85-72=13* R2 • Sn:73-67=6 • Sp:93-85=8* R3* • Sn:70-42=28* • Sp:95-75=20* <u>Pelvis 2* (n=85+172,s=146+1018)</u> R1* • Sn:83-52=31* • Sp:80-71=9* R2* • Sn:84-60=24* • Sp:83-75=8* R3* • Sn:71-49=21* • Sp:90-78=12* <u>Renal* (n=40+116,s=53+229)</u> R1* • Sn:57-30=27* • Sp:77-48=29* R2* • Sn:66-42=24* • Sp:82-59=23* R3* • Sn:64-23=41* • Sp:83-57=26*		<u>Calf* (original read with half-wrong imputation, n=164)</u> R1* • Sn:45-4=41* • Sp:89-64=25* R2* • Sn:79-48=31* • Sp:74-65=9* R3* • Sn:68-33=35* • Sp:83-75=8* <u>Pelvis* (re-read, n=274, s=2949+8886)</u> R1* • Sn:78-74=4* • Sp:88-79=9* R2* • Sn:65-53=12* • Sp:94-89=5* R3* • Sn:69-59=10* • Sp:90-75=15* <u>Renal* (re-read, n=268, s=600+960)</u> R1* • Sn:68-47=21* • Sp:94-86=8* R2* • Sn:62-47=15* • Sp:94-84=10* R3* • Sn:66-40=26* • Sp:95-87=8* <u>Supra-aortic (re-read, n=237, s=912+7338)</u> R1 • Sn:61-67=-6 • Sp:93-88=5* R2 • Sn:75-78=-3 • Sp:89-89=0 R3 • Sn:66-69=-3 • Sp:95-93=2*	

Lines 19-20	Ablavar	(b) (4)	Multihance	(b) (4)
L19. Labeled outcomes supporting MRA efficacy indications • *s = segments (subdivided by number positive + negative, if available)* • *n = patients (number positive + number negative, if available)* • *R = central reader* • *In all expressions of the form C – NC = D, C =performance with contrast, NC=performance without contrast, and D= difference*	<u>Pelvis (n=215+411,s=316 +2230)</u> R1 • Sn:89-69=20 • Sp:72-71=1 R2 • Sn:82-70=12 • Sp:81-73=8 R3 • Sn:79-64=15 • Sp:85-85=0 <u>TOF Blanks (n=25+93, s=28+202)</u> R1 • Sn:97 • Sp:72 R2 • Sn:91 • Sp:84 R3 • Sn:72 • Sp:82		<u>Pelvis</u> R1 • Sn:78-74=4 • Sp:88-79= R2 • Sn:65-53=12 • Sp:94-89=5 R3 • Sn:69-59=10 • Sp:90-75=15 <u>Renal</u> R1 • Sn:68-47=21 • Sp:94-86=8 R2 • Sn:62-47=15 • Sp:94-84=10 R3 • Sn:66-40=26 • Sp:95-87=8	
L20. Source	NDA 21711 primary clinical reviews		NDA 21357 s11 primary clinical and biometric reviews	

Line 21	Ablavar	(b) (4)	Multihance	(b) (4)
L21. Reviewer comments	*1) Win criteria were not achieved using alternative imputation strategies (including no imputation). 2) Win criteria were not achieved for steady-state Ablavar MRA when interpreted separately from first-pass images by site readers (first-pass and steady-state images were read together by central readers).*		*1) It is unclear whether win criteria would have been achieved using alternative imputation strategies. 2) It is unclear why the sponsor hypothesized that Multihance would be superior to TOF for sensitivity in some regions and for specificity in others. 3) Injection rate for the pivotal studies was 2 mL/s.*	

Table 2 shows that Ablavar (aortoiliac) and Multihance (aortoiliac+ renal) have been approved for MRA indications. (b) (4)

Table 2 also shows variation in the win criteria against which past GBCA MRA studies have been reviewed. Variation in win criteria is associated with variation in the likelihood of winning. In particular, the following heuristics apply for variations that increase the likelihood:

- Non-inferiority (compared to superiority) endpoints and larger (compared to smaller) non-inferiority margins for relative performance;
- None or fewer (compared to more) additional win criteria (all else being equal);
- Use of catheter angiography (compared to CTA) as the standard of reference (SOR; state-of-the art catheter angiography has superior spatial resolution and is less susceptible to vascular calcification artifacts for measuring arterial stenosis);
- All-wrong or half-wrong imputation (compared to no imputation, i.e., exclusion of blank stenosis measurements) and all-wrong (compared to half-wrong) imputation;
- Same 2/3 readers (compared to majority read) for aggregating performance across multiple readers;
- Segment-level (compared to vessel- or patient-level) analysis of positive/negative reads;

- Caliper (compared to eyeballing) stenosis measurements, assuming generalizability of available evidence (for example, Schmittling 2005) that additional measurement precision reduces variability;
- Broader (compared to narrower) definitions of positive stenosis measurements, assuming generalizability of asymmetric study recruitment (negative cases > positive cases) in studies reviewed to date and association with wider confidence intervals for sensitivity comparisons.

In comparison to the two GBCAs (Ablavar and Multihance) approved for MRA indications, I am aware of no ICA approved for CTA. For example, with respect to CT imaging, Ultravist is approved in adult and pediatric patients age ≥ 2 years for, "Imaging of head and body (intrathoracic, intra-abdominal and retroperitoneal regions) for evaluation of neoplastic and non-neoplastic lesions. The usefulness of contrast enhancement for the investigation of the retrobulbar space and of low grade or infiltrative glioma has not been demonstrated" (Ultravist 2016 label). Ultravist is explicitly approved for intra-arterial angiography (ie, planar radiography), and the clinical studies described in labeling to support Ultravist's use with CT note that approval was based on reader ratings of "good" or "excellent" in 477 patients. No SOR was used for performance assessment.

Reviewer Comment: 1) CTA, MRA, and ultrasound are widely used for arterial imaging in the United States, meaning off-label use of ICAs and GBCAs for arterial imaging is common (this pattern does not yet hold for ultrasound contrast agents). 2) Two non-approvable letters for Ablavar hinged on contrast minus non-contrast Sn/Sp performance with all-wrong imputation vs. no imputation for blank segments. Subsequently, half-wrong imputation (compared to no imputation) has been accepted as a de facto standard. The rationale for this remains unclear to me. 3) In our 2004 guidance on imaging drugs, we recommend C + NC > NC (compared to C ≥ NC) as the basic schema for demonstrating efficacy in terms of performance of a new contrast agent/indication (C = imaging with contrast drug; NC = imaging without contrast drug). Acquisition of GBCA MRA and TOF MRA are not mutually exclusive; indeed, their serial acquisition in the same patient at one MRI session is universal in comparative MRA studies and their interpretation together is common in routine clinical practice. The rationale for using a C ≥ NC criterion is thus also unclear to me. 4) Table 2 may serve as a helpful reference when reviewing future Phase 3 GBCA MRA studies in order to ensure that variation compared to historical regulatory standards is justified.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Table 3 itemizes major milestones in Gadavist's overall U.S. regulatory history from a primary clinical reviewer perspective.

Table 3 Reviewer's tabulation of regulatory history underlying approved new indications
Source: DAARTS.

Date	Application	Description
01/27/2011	NDA 201277	Barbara Stinson recommends approval "for intravenous use in diagnostic MRI in adults and children (2 years of age and older) to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system (CNS)." Original NDA approved 3/14/2011.
4/11/2014	NDA 201277	Barbara Stinson recommends approval "for contrast-enhanced MRI of the breast to detect the presence and extent of malignant breast disease." Gadavist receives approval 6/11/2014. Supplement 7 approved 6/11/2014.
11/7/2014	NDA 201277	I recommend approval "for intravenous use in diagnostic magnetic resonance imaging (MRI) in adults and children *of all ages (including term neonates)* to detect and visualize areas with disrupted blood brain barrier (BBB) and/or abnormal vascularity of the central nervous system" (italics indicate new language). Supplement 8 approved 12/29/2014.

Reviewer Comment: If approved for its proposed indication, Gadavist would represent the only GBCA indicated for MRA of the supra-aortic arteries and in pediatric patients.

3.2. Summary of Presubmission Regulatory Activity

On January 14, 2009, Elizabeth Jones, Associate Director in the Department of Radiology and Imaging Sciences at the NIH's Clinical Center, wrote the following in an e-mail to Alex Gorovets, Lead Medical Officer at the time and now Deputy Director in DMIP (quoted in the indented text below):

> All the neuroradiologists I have spoken to agree that conventional cerebral angiography has been replaced in practice by CTA (and MRA). They feel comfortable, as do I, that comparison of MRA vs CTA for trials of most clinical indications is fine. Cerebral angiography is still superior to the other exams in selected clinical situations such as the detection of intracranial vaculitis or vascular malformations.

This consultation, in response to another GBCA sponsor proposing to use CTA rather than catheter angiography as an SOR, confirmed the prevailing opinion of clinical reviewers within our division that the continued use of catheter angiography, based on precedent studies was no

longer necessary or feasible.

On the other hand, based on use of catheter angiography as the SOR, available evidence comparing the general diagnostic performance of MRA with contrast, MRA without contrast, CTA, and ultrasound has failed to support the hypothesis that CTA is superior. For example, the following figure (Figure 3) suggests MRA with contrast may be superior or equivalent compared to CTA.

Figure 3 Published meta-analysis of carotid imaging modalities against catheter angiography
For diagnosing patients as positive or negative for carotid artery stenosis 70-99%, MRA with contrast was found to be more sensitive than CTA (better at identifying positive cases, purple curve higher than blue) and overall efficacy was comparable (area under curve similar for purple and blue curves) in a meta-analysis of 2541 patients and 4876 carotid arteries using catheter angiography as the SOR. DMIP agreed to replace catheter angiography with CTA as the SOR for MRA studies starting in 2009. True Sn/Sp may be better than measured for studies in which the SOR is equivalent or worse compared to variables under study. Source: Wardlaw 2006.

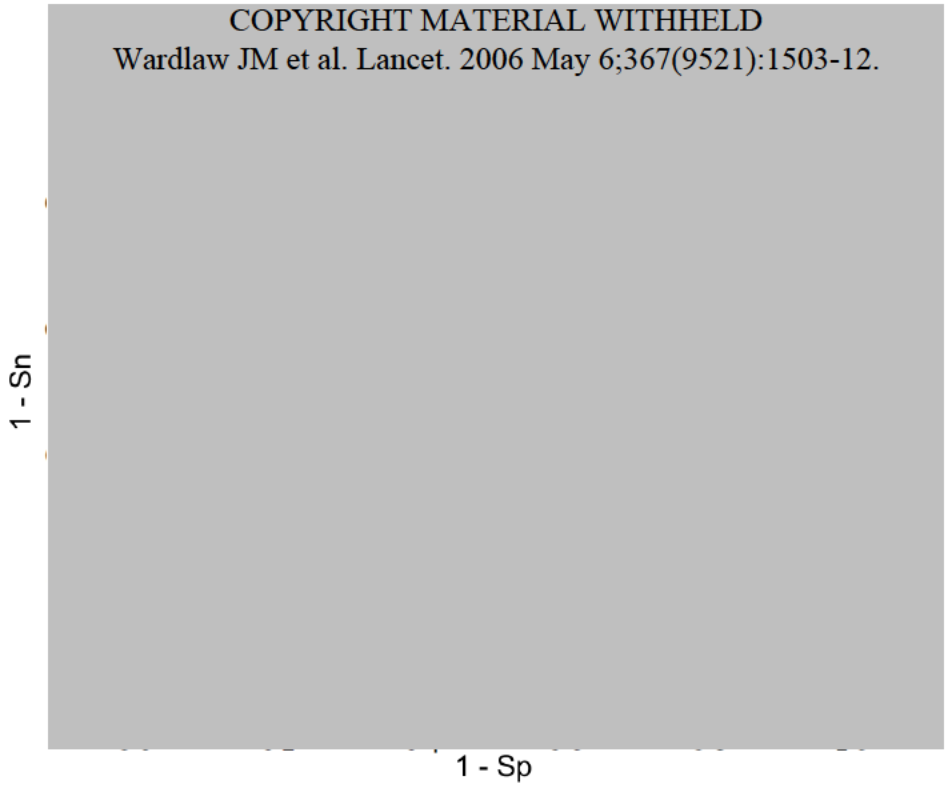


Table 4 provides a timeline of additional regulatory events leading up to this sNDA submission. The sponsor's originally proposed indication was, "Gadobutrol Injection is indicated for Magnetic Resonance Angiography (MRA) in adults with known or suspected vascular disease for visualization and diagnosis of clinically significant disease involving the renal arteries and supra-aortic vessels."

Table 4 Reviewer's tabulation of regulatory milestones leading up to current submission

Source: DARRTS.

Date	Application	Description
03/24/2010	IND (b) (4)	Written responses in preparation for face-to-face meeting 3/25/2010 (minutes 6/28/2010) regarding sponsor's plans for two Phase 3 MRA studies. We accept Visualization: GAD – TOF > 0 as an acceptable criterion at the segment level. Other highlights: 1. We recommend all-wrong ("no-credit", opposite of SOR) imputation for blanks as part of a new "minimum performance" criterion, Sn/Sp: GAD – 50% > 0; 2. We recommend that all criteria be met by at least the same two of three central readers (not majority reader); 3. We recommend half-wrong ("half-credit", 50% match to SOR) imputation (not conditional, all-wrong imputation) for blank segments against the "relative performance" criterion, Sn/Sp: GAD – TOF > -7.5 (not -10% margin).
09/09/2010	IND (b) (4)	Non-agreement letter referencing Special Protocol received 7/20/2010 (SPA-5) and 7/21/2010 (SPA-6) primarily around statistical methods for accounting for within-subject correlations and re-sampling/bootstrapping methods for estimation of confidence intervals.
12/21/2010	IND	Agreement letter referencing Special Protocol – Resubmission received 11/3/2010 (SPA-5) and 11/4/2010 (SPA-6). The final SPA agreement reflects protocol revision by the sponsor in non-conformance with recommendations 1 and 2 and conformance with recommendation 3 (see 3/24/2010 line, above).
5/23/2013	IND	Agreement letter referencing Special Protocol Amendment (SPA-6) received 4/18/2013 and containing alteration of eligibility from subjects with ≥ 50% to subjects with ≥ 70% stenosis on pre-MRA supra-aortic imaging.
12/15/2014	NDA 201277	Written responses in preparation for pre-sNDA teleconference 12/17/2014 (minutes 1/8/2015)
3/25/2015	IND (b) (4)	Agreement to Initial Pediatric Study Plan (Agreed iPSP) proposing to use the same primary PK pediatric data (used to support extrapolation of CNS efficacy from adults to pediatric patients) as the basis to extrapolate adult MRA outcomes.
6/30/2015	NDA 201277	Receipt of sNDA 11 and start of 21st Century Review clock.

Reviewer Comment: 1) (b) (4) *a specification for win criteria against which to determine whether Gadavist is effective for MRA of the renal and supra-aortic arteries.* (b) (4) *A) We recommended all-wrong*

imputation (blank=-SOR) for the minimum performance criterion: GAD Sn/Sp – 50% > 0. However, we agreed to no imputation, meaning on an "intention-to-interpret" basis at the segment level, we might accept worse-than-chance performance. B) We recommended use of the same-2/3 central reader criterion used for all prior GBCA MRA studies. However, we agreed to base pivotal analyses on the majority reader, meaning we might accept outcomes only generalizable to the unusual clinical situation in which the blinded second opinions of multiple independent radiologists would be solicited and synthesized. 2) I agree with the new precedent DMIP set in 2009 that CTA may be used as the SOR for MRA studies going forward, primarily based on a feasibility/safety rationale. However, it is important to recognize that the use of a "bronze standard" (compared to a "gold standard") has multiple downstream consequences for diagnostic performance evaluation (also referred to as "imperfect SOR bias"). In particular, true Sp and especially Sn may be higher for MRA than it appears when measured against CTA.

3.3. Foreign Regulatory Actions and Marketing History

Gadavist (known as Gadovist or Gadograf in Europe) was first approved for marketing in Germany in 2000. An indication for MRA was added in 2003. The indication section of its current EMA-approved label reads as follows:

> This medicinal product is for diagnostic use only. Gadovist is indicated in adults and children of all ages (including term neonates) for:
>
> - Contrast enhancement in cranial and spinal MRI.
> - Contrast enhanced MRI of liver or kidneys in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant.
> - Contrast enhancement in magnetic resonance angiography (CE-MRA).
>
> Gadovist can also be used for MR imaging of pathologies of the whole body.
>
> It facilitates visualisation of abnormal structures or lesions and helps in differentiation between healthy and pathological tissue.

With respect to Gadovist MRA, the EMA-approved label reads as follows:

> Optimal signal enhancement is observed during arterial first pass for CE-MRA.
>
> T1-weighted scanning sequences are particularly suitable for contrast-enhanced examinations.
>
> Intravascular administration of contrast media should, if possible, be done with the patient lying down. After the administration, the patient should be kept under observation for at least half an hour, since experience shows that the majority of

undesirable effects occur within this time.

Adults: Imaging of 1 field of view (FOV): 7.5 mL for body weight below 75 kg; 10 mL for body weight of 75 kg (corresponding to 0.1-0.15 mmol/kg BW).

Adults: Imaging of > 1 field of view (FOV): 15 mL for body weight below 75 kg; 20 mL for body weight of 75 kg and higher (corresponding to 0.2-0.3 mmol/kg BW).

Peadiatric population: For children of all ages (including term neonates) the recommended dose is 0.1 mmol gadobutrol per kg body weight (equivalent to 0.1 mL/kg BW) for all indications.

Reviewer Comment: The sponsor has proposed a 0.1 mmol/kg dose for Gadavist MRA of the supra-aortic and renal arteries (single FOV MRA), based on the protocol used for two pivotal studies under review. If approved, dosage instructions in the United States would thus differ compared to the volume-based EMA-approved dosage instructions for adults, as follows: 0.1 mmol/kg vs 7.5/10 mL (depending on how body weight compares to 75 kg). In contrast, the proposed MRA dosage for pediatric patients in the United States matches EMA-approved labeling.

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 Division of Pediatric and Maternal Health (DPMH, Erica Radden), Office of Scientific Investigations (OSI, John Lee), Office of Product Quality (OPQ, James Laurenson), and Office of Surveillance and Biometrics (OSB, Anthony Mucci) would also write primary reviews. The specific findings of the biometrics team relevant to my clinical review of efficacy will be incorporated into Sections 5-7. However, the implications of a more general biometrics finding related to this submission will be discussed here.

In short, in his primary biometrics review, Dr. Mucci has highlighted the problem that when a reader renders multiple positive/negative diagnostic determinations within the same patient, the reader's patient-independent knowledge (for example, which segments are associated with higher true positive rates than others) is sufficient to achieve Sn/Sp performance well above chance, defined as Sn + Sp = 100%. This is relevant to the current review because we recommended and agreed to the "minimum performance" criterion: GAD Sn/Sp – 50% > 0. The general question is whether this "minimum performance" threshold is too low, meaning imaging drugs may achieve it yet actually be ineffective or even diagnostically misleading.

It is beyond the present scope to attempt to resolve this question here. Suffice it to sketch the following: A) I agree with Dr. Mucci that "minimum performance" in any clinically meaningful sense is usually underestimated by a Sn/Sp – 50% > 0 criterion. B) The problem of pre-specifying true "minimum performance" is not restricted to segment-level endpoints; patient-independent expert knowledge almost certainly drives reader performance above chance at the regional anatomical and patient levels, too. C) A more ideal design would likely incorporate Bayesian logic. For example:

F1. It is reasonable to paraphrase the question motivating referring physicians to consult radiologists in the pivotal studies under review as, "Is this patient likely to benefit from surgical or endovascular intervention compared to medical therapy alone?"
F2. Call the referring physician's pre-imaging Sn + Sp performance A, where A represents the accuracy of the referring physician's answer to F1 prior to imaging.
F3. Call the referring physician's post-imaging Sn + Sp control performance B, where B represents the accuracy of the referring physician's answer to F1 after reviewing the site reader's TOF report.
F4. Call the referring physician's post-imaging Sn + Sp test performance C, where C represents the accuracy of the referring physician's answer to C1 after reviewing the site reader's report of GAD + TOF.
F5. Randomize patients to GAD + TOF vs TOF and mask patient assignment in the site reader's report.
F6. The use of multiple central readers may be used to obtain separate estimates of reader variation.

Using this design sketch, efficacy may be estimated as $E_{TOF} = B - A$ and $E_{GAD+TOF} = C - A$. The higher of B or C represents a more clinically meaningful estimate of "minimum performance" (compared to a fair coin toss) and, according to our 2004 guidance on imaging drugs, determination of Gadavist's efficacy would depend on whether the following superiority criterion were achieved: $E_{GAD + TOF} - E_{TOF} > 0$.

4.1. Office of Scientific Investigations (OSI)

On November 9, 2015, DMIP requested that OSI's Division of Good Clinical Practice Compliance (DGCPC) audit the image core lab, based on the following rationale (quoted from our consult request [A5399] in the indented text):

> We have requested inspection of the central imaging laboratory because all images are funneled through the central laboratory for generation of primary sensitivity and specificity endpoints; in addition, we have no specific site-level concerns at present.
>
> In addition to inspecting the central reading laboratory for verification of standard

> procedures described in the "Blinded Reading Manual" for pivotal studies 14607 and 91759 (image quality control, segmentation, and labeling; reader preparation, training, and conduct; image visualization system and electronic case report forms), we have preliminarily found a surprising degree of within- and between-reader variability for measurements of vascular stenosis. Any insight inspectors may be able to provide on the sources of measurement variability, including documentation of images showing digital caliper measurements, would be very helpful for our review.

With respect to quality-control issues in its supra-aortic study, the sponsor also reports the following interim finding (quoted from A479 in the indented text below):

> The interim analysis could not be performed until 150 subjects were enrolled and read by the blinded readers. The interim analysis was to be performed solely for futility by an independent statistician to maintain the blinding of the sponsor.
>
> Before the interim analysis, the data to be used for the interim analysis was checked for quality and was noted that the vessel diameters were disproportionately large and therefore, the derived percent stenosis and sensitivity based on the aggregate blinded data was exceedingly low compared to the literature and expectations, which was brought to the attention of the image core lab. This raised questions about a potential systematic inaccuracy related to the quantification of thin vessels by the blinded read system. Therefore, an additional quality check of the blinded read system and the blinded reader measurement tools for quantification of vessel diameters was performed by the core lab. This review revealed that the blinded read software consistently produced vessel diameter measurements that were larger than expected. This required a correction and revalidation of the software considering the partial volume effect for measurement of thin vessels. During this time the study was placed on hold until the core lab finished implementation of the revised measurement tool.
>
> Subsequently, these subjects were read with the revised and validated software. The blinded reading with the revised and validated software started approximately 6 months later, before the interim analysis could take place by the independent statistician. The blind was maintained throughout and the original blinded read data with the inaccurate diameter measurements has remained blinded.

My understanding, as of mid-cycle in this review, is that OSI plans to audit Bayer's core imaging lab, (b) (4), and that no significant study-conduct issues have been identified to date.

4.2. Product Quality

A finding of no significant impact (FONSI) has been made based on review of the sponsor's 14-

page Environmental Assessment. The sponsor forecasts that global Gadavist usage for MRA will (b) (4) doses per year from 2015 to 2016 (A136). Otherwise, the sponsor submitted no new chemistry, manufacturing, or control (CMC) information compared to primary reviews signed 12/30/2014, 12/11/2013, 7/31/2013, 3/19/2012, and 2/25/2011.

4.3. Clinical Microbiology

The sponsor submitted no new clinical microbiology information compared to primary reviews signed 12/11/2013, 7/27/2011, and 1/31/2011.

4.4. Nonclinical Pharmacology/Toxicology

The sponsor submitted no new nonclinical pharmacology/toxicology information compared to primary reviews signed 4/9/2014, 10/19/2014, 10/1/2012, 9/12/2012, and 5/2/2011.

4.5. Clinical Pharmacology

The sponsor submitted no new clinical pharmacology information compared to primary reviews signed 11/20/2014, 4/16/2014, and 3/22/2013.

4.5.1. Mechanism of Action

Gadolinium can carry up to 7 unpaired electrons and thus forms a strong internal, induced magnetic field in the presence of an externally applied magnetic field. This paramagnetism forms the basis for Gadavist's mechanism of action as an imaging contrast agent in the 0.1 to 1 nm range of each of gadolinium atom. Specifically, the slope with which spin-lattice (T1) and spin-spin (T2) relaxation rates increase as a function of drug concentration under specified conditions defines relaxivity, the key physical correlate of contrast or how much brighter regions of an image become due to the proximity of imaged tissue and drug.

4.5.2. Pharmacodynamics

Gadavist is designed to be physiologically inert. Thus, from the perspective of an image reader, intravenously administered Gadavist can potentially highlight any waypoint within perfused tissue along the drug's course from injection site to urinary excretion. The localization of Gadavist in a single static image depends on the timing of image acquisition relative to drug administration.

4.5.3. Pharmacokinetics

Gadavist is predominantly non-metabolized and renally excreted with a clearance rate comparable to inulin. The mean terminal half-life for plasma clearance is 1.8 hours. Based on

increasing evidence of low level chronic gadolinium deposition in multiple anatomical regions of patients prescribed GBCAs, some researchers have begun to hypothesize that a 3-compartment model (plasma, interstitial fluid, bone) may better describe the pharmacokinetics of GBCAs compared to the 2-compartment model (plasma, interstitial fluid) understood to date (Murata 2016).

4.6. Devices and Companion Diagnostic Issues

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

4.7. Consumer Study Reviews

From a clinical perspective, relative to many other drug categories, GBCA selection is typically governed more at the health care organizational level than by patient-provider discussion on a case-by-case basis of available options within the drug class. The sponsor submitted no label comprehension, patient self-selection, or other human factors studies in its submission.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 5 Reviewer's tabulation of sponsor's Gadavist MRA clinical studies

i.a. DSA = intra-arterial digital subtraction angiography. Source: A2895-5175.

	GEMSAV	GRAMS	98178/B204	99011/A02885	97099/A04519	309376/A40727	304300/A04542
Year Reported	2015	2015	2001	2001	2001	2008	2003
Patients in FAS: Supra-aortic, Renal, Other, Total	457, 0, 0, 457	0, 292, 0, 292	0, 69, 146 (aorto-iliac), 215	0, 0, 182 (aorto-iliac-femoral), 182	~50, 0, ~126 (aorto-iliac), 176	17, 15, 34 (aorto-iliac), 66	~5,~7,~32 (aorto-iliac-femoral), 44
Study Title	Multicenter, open-label study to evaluate the safety and efficacy (by blinded reading) of contrast-enhanced MRA after a single intravenous injection of 0.1 mmol/kg gadobutrol in subjects with known or suspected vascular disease of the supra-aortlc vessels	Multicenter, open-label study to evaluate the safety and efficacy (by blinded reading) of Gadobutrol-enhanced MRA after a single injection of 0.1 mmol/kg of Gadobutrol in subjects with known or suspected renal artery disease	A double-blind, randomized, multicenter dose comparative study with corresponding blinded reading to evaluate SH L 562 BB (1.0 molar) for Magnetic Resonance Angiography (MRA) in patients with known or suspected disease of the abdominal aorta and its branches	Open, multicenter contrast-enhanced MRA study of pelvic and peripheral arteries using SH L 562 BB in comparison to i.a. DSA followed by blinded reader evaluation	Open, multicenter contrast-enhanced MRA study of body arteries using SH L 562 BB in comparison to i.a. DSA followed by blinded reader evaluation	A single-blind, intra-individual, crossover, multicenter study of the efficacy,safety and tolerability of Gadovist (1.0 M) in comparison with Magnevist (0.5 M) as contrast agent in the enhanced MR Angiography in Chinese patients	Open, multi-center contrast-enhanced MRA study of body and peripheral arteries using SH L 562 BB with extended safety follow-up
Gadavist injection (mmol/kg @mL/s)	0.1@1.5	0.1@1.5	0.05@0.5-4* 0.15@0.5-4* 0.25@0.5-4* *rate varied to target fixed 6-8s injection duration	0.2-0.3@0.2-1 *rate varied to target half 0.5M-GBCA rate	0.1-0.15@0.5-2 *rate varied to target injection duration ≥ 50-70% imaging duration	0.2-0.3@1-3 *rationale for rate variation unspecified (MAG: 0.4-0.6@1-3)	0.1-0.3 *rated varied to target injection duration ≥ 40-70% imaging duration
SOR	CTA	CTA	Catheter angiography	Catheter angiography	Catheter angiography	Catheter angiography	None
Other Comparator	TOF	TOF	None	None	None	Magnevist	
Primary Endpoints	Visualization and Sn/Sp for significant stenosis	Visualization and Sn/Sp for significant stenosis	Agreement with SOR: location, degree, and length of most severe stenosis	Agreement with SOR for significant stenosis / aneurysm	Agreement with SOR for significant stenosis / aneurysm	Visualization	Visualization
Level of 1° Analysis	Segments	Segments	Segments	Patient (segments matched)	Patient (segments matched)	Segments	Segments
Outcome	GAD vs. TOF: Superior visualization, non-inferior Sn/Sp, and GAD Sn/Sp better than minimum	GAD vs. TOF: Superior visualization, non-inferior Sn/Sp, and GAD Sp but not Sn better than minimum	Dose groups*: 71% (0.05 mmol/kg), 86% (0.15 mmol/kg), and 81% (0.25 mmol/kg) *differences not significant	GAD vs. SOR: Agreement > 80%	GAD vs. SOR: Agreement > 80%	GAD vs. MAG: Non-inferior (7.3 segments visualized per patient with MAG vs 6.8 for GAD)	Visualization ratings reported
Publication				Hentsch 2003	Schaefer 2007		
Reviewer Comment			Rate and dose confounded	No comparator; Sn and Sp confounded	No comparator; Sn and Sp confounded	Rate and dose confounded	No SOR/comparator

5.2. Review Strategy

This primary clinical review is focused on the question of whether Gadavist's approved CNS and breast indications should be expanded to include a new MRA indication for supra-aortic and renal arteries. My review strategy was primarily governed by criteria agreed to in DMIP's SPA of 12/21/2010 and pre-sNDA discussion of 12/17/2014. Accordingly, determination of safety and efficacy hinged on GRAMS and GEMSAV and sponsor's updated integrated safety summary. For the studies in Table 5 reported between 2001-2008 (right five columns), the sponsor submitted only Clinical Study Reports (no patient-level data). In addition, none of these studies was focused on patients under the proposed supra-aortic/renal indications, and none tested for superiority of Gadavist over non-contrast MRA. These supplementary studies were thus reviewed mainly for directional consistency in terms of reported top-line efficacy outcomes and for safety. I also placed special emphasis on the implications of using CTA as the reference standard for these pivotal studies, since relevant prior NDAs used catheter angiography. Finally, relative to other GBCAs, Gadavist is formulated at a higher concentration. Since MRA applications are especially sensitive to contrast kinetic issues, typical MRI imaging protocols are not GBCA-specific, and current labeling is explicit that the bolus for Gadavist is "more compact," I also paid particular attention to the question of how the time-intensity curve for full vs half-concentration Gadavist MRA may differ.

All parenthetical references to page numbers in the sponsor's submission refer to reviewer's Appendix A, a concatenated pdf containing all referenced sponsor-submitted and other primary (non-published) review material. Page numbering in the pdf starts at 1 and ends on 5500.

Table 6 summarizes regulatory milestones occurring between the sponsor's June 30, 2015 submission and mid-March, 2016.

Table 6 Reviewer's tabulation of post-submission regulatory milestones

Date	Description	Appendix A page reference
6/30/2015	Receipt of sNDA 11 and start of 21st Century Review clock	1
7/21/2015	JumpStart data fitness session	5214
7/24/2015	Data submission error resolved	
7/30/2015	Filing meeting	5271
7/30/2015	JumpStart analysis session	5275
9/1/2015	Applicant orientation meeting	5326
9/8/2015	74-day-letter specifies standard review goal date of April 30	5375
10/5/2015	Response to two-question information request focused on pediatric extrapolation	5381
11/9/2015	Request for clinical site inspections	5396
11/25/2015	Mid-cycle practice #1	
12/3/2015	Mid-cycle practice #2	
12/15/2015	Response to two-question information request focused on high-level contrast kinetic and measurement reliability questions	5402
12/17/2015	Mid-cycle meeting	5409
1/19/2016	Internal team meeting to discuss biometrics issues	
2/1/2016	Internal team meeting to discuss PeRC assessment	
2/1/2016	Response to three-question information request focused on more specific contrast kinetic, measurement reliability, and safety data analysis issues	5469
2/12/2016	Educationally oriented teleconference with sponsor to clarify 2/1 response	5472
2/23/2016	Pediatric assessment meeting	5478
2/24/2016	Response to three-question information request following up on 2/12 teleconference	5497
3/9/2016	Labeling meeting #1	
3/15/2016	Wrap-up and labeling meeting #2	

A few notes about nomenclature are in order. Throughout this review, I prefer and have used the term “visualized” in place of the sponsor’s “assessable”, “central reader” in place of the sponsor’s “blinded reader”, and post-contrast in place of the sponsor’s “contrast-enhanced.” Prior reviewers have used the term “half-credit” for assigning hits and misses to blank segments with equal frequency. This is potentially confusing, since some might interpret “half-credit” as implying better-than-chance performance, assuming chance (i.e., fair coin flip) is the general floor for evaluating the quality of all diagnostic information. I have used the term “all-wrong (blank=-SOR)” and “half-wrong (blank=50%SOR)” in reference to imputation options.

The formatting and sequencing of this review follows CDER's Clinical Review Template 2015 Edition (Version 11/5/2015).

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Supra-aortic study

6.1.1. Study Design

Overview and Objective

This section covers the trial design of the sponsor's pivotal supra-aortic study, entitled, "Multicenter, open-label study to evaluate the safety and efficacy (by blinded reading) of contrast-enhanced magnetic resonance angiography (MRA) after a single intravenous injection of 0.1 mmol/kg gadobutrol in subjects with known or suspected vascular disease of the supra-aortIc vessels." The sponsor also refers to this study as GEMSAV (Study 14607, PH-38001). The protocol available for review at the time of SPA agreement was received 11/4/2010 (see A2330-2613). I used this document (and comparison to the final protocol included in the sNDA submission) as my main source for understanding study design.

The sponsor states its primary objective, as follows: "To evaluate the efficacy of gadobutrol-enhanced MRA over 2-dimensional-time-of-flight (2D-ToF) MRA in subjects with known or suspected vascular disease of the supra-aortic arteries...using computed tomographic angiography (CTA) as the standard of reference (SOR) excluding the first objective (structural delineation)" (A2333).

Trial Design

The sponsor summarizes this study design as "multi-center," "single-arm," "open-label," and with "blinded reading." Unpacking these in turn, the study was multi-center because the sponsor planned to recruit patients for both MRA and CTA imaging at more than one site.

The study was single-arm because all enrolled patients received Gadavist. They also all received iodinated contrast for CTA, which we agreed to treat as the SOR. The "comparator" was 2D-TOF, a non-contrast MRA technique. (It is important to understand that there is no TOF equivalent for CT imaging: CTpre ~ MRIpre, CTpost ~ MRIpost, but TOF is additional and unique to MRI). Thus, though the study was "single-arm," the sponsor planned for all patients to receive GAD MRA, TOF MRA, and CTA with iodinated contrast in order to perform an analysis of Gadavist-to-SOR vs. TOF-to-SOR across patients. Such "comparison-of-comparisons" designs are typical of performance studies involving diagnostic imaging drugs.

The study was open-label because patients and readers were aware that all patients in the study received Gadavist.

The study involved "blinded reading" insofar as patient identity was masked for central (but not site) readers. It is also reasonable to assume that most expert readers recognize the identity of CTA, TOF MRA, and GBCA MRA images by their appearance. By analogy to drug therapy trials, in which blinding has meaning only insofar as it refers to masking the identity of the key allocated variables (drug vs. placebo), central and site readers were both likely aware of the identity of the key variables allocated in this study (GAD vs. TOF). In addition, readers directly controlled the multiple-choice or quantitative values assigned to all study variables.

Turning to design details, the sponsor reports that patient enrollment began May, 2011 and ended May, 2014, involving 56 centers in 14 countries. The sponsor itemizes six inclusion criteria, mainly the following (quoted from A2351):

> Male or female subjects, age ≥ 18 years with known or suspected supra-aortic arterial artery disease based on any of the following:
> - Prior stroke;
> - Transient ischemic attack (TIA);
> - Amaurosis Fugax (transient monocular blindness);
> - Referred for evaluation of any supra-aortic vessel (for clinically significant stenosis);
> - Follow-up for a metallic stent in a supra-aortic vessel;
> - Prior imaging study (CTA or ultrasound) showing ≥ 50% stenosis of a supra-aortic vessel segment (within 60 days before consent).

The sponsor itemizes 12 exclusion criteria, mainly eGFR < 30 mL/min/1.73 m^2 and acute renal insufficiency of any intensity (A2352).

For patients with acceptable CTA imaging within 60 days of enrollment, patients were enrolled in the study for 1-8 days; otherwise, 8-13 days. The sponsor's schedule of evaluations is provided in Table 7.

Table 7 Sponsor's schedule of evaluations for supra-aortic study

Source: A2360.

Table 8 summarizes the sponsor's protocol with respect to drug administration:

Table 8 Reviewer's tabulation of imaging drug administration for supra-aortic study
Source: A2330

	Gadavist for MRA	Iodinated contrast for CTA
Dose	0.1 mmol/kg (0.1 mL/kg)	≥75 mL of ≥300 mg/ml
Preferred vein, cannula	Antecubital, 20 Gg	Antecubital (opposite to lesion), 18 Gg
Rate	1.5 mL/s	≥ 4 mL/s
Injection duration for 75 kg patient	5 s	~20 s
Approximate scan duration	20 s	2 s
Approximate voxel size	1.75 mm	0.75 mm (CT ≥ 64-slice)
Saline chaser	30 mL @ 1.5 mL/s	Unspecified

With respect to image acquisition, the sponsor specifies a dedicated cervical or head/neck coil with at least eight parallel channels for MRA. Use of 3T devices was recorded as a minor protocol deviation. For CTA, scanners were expected to be 64-slice or better. The field of view for both CTA and MRA encompasses the neck, extending at least from the aortic arch to the level of the basilar artery, with arterial anatomy subsequently grouped into 21 segments for analysis (see Figure 9). Additional minimum and maximum MR acquisition paramaters (pulse sequences) are detailed in Tables 9-10.

Table 9 Sponsor's tabulation of TOF MRA acquisition parameters

Source: A2372.

PARAMETER	Value	Maximum	Minimum
Plane	axial		
Mode	2D		
Pulse Sequence	TOF		
Timing	non-contrast		
TE	typically minimum	typically 6 ms	
TR		typically 50 ms	
Flip angle	(optimize)		
NEX		1.0	0.5
Matrix (frequency x phase)	Prefer 320 x 192 or 256 x 256 minimum		256 x 192
Slice thickness		2.5 mm	
Spacing	overlap of 1 suggested		
Voxel size		1.5 x 1.75 x 2.5 mm	

Table 10 Sponsor's tabulation Gadavist MRA acquisition parameters

Annotated to show few differences with acquisition parameters for renal study, as well. Source: A2373.

PARAMETER	Value	Maximum	Minimum
Plane	Coronal		
Mode	3D		
Pulse Sequence (SPGR, T1FFE, FLASH etc)	Incoherent gradient echo (spoiled)		
Timing	Fluoro triggered / bolus tracking method		
TE	minimum	2 ms	
TR	minimum	4 ms	
Flip angle	(optimize) 25 preferred	40	20
NEX		1.0	0.5
Matrix (frequency x phase)	Prefer 512 x 256 (renal 320 x 192)		320 x 192 or 256 x 256 (renal 256 x 192)
Slice thickness		2 mm (renal 2.25)	
Spacing	Overlap 1 suggested		
Voxel size (coronal)		1.25 x 1.75 x 2.0 mm	
k-space	Elliptical centric filling		
Acceleration factor (iPAT, ASSET, SENSE, GRAPPA, etc)		4	2

Finally, with respect to central reading, the sponsor provides a schematic illustrating the physical arrangement of a central reader with respect to three monitors used for image interpretation and primary data recording in an electronic case report form (eCRF; Figure 4).

Figure 4 Sponsor's illustration of blinded reading layout

Source: A966.

Denoting site readers as R0, six board-certified, sub-specialized neuroradiologist central readers also participated, three for interpretation of the MRA images (R1, R2, R3) and three for interpretation of the CTA images (R4, R5, R6) in minimum batch sizes of 40 patients. For central MRA interpretation, TOF and GAD images were randomly intermixed, including 5% recycling for re-reads (MRA only) to estimate intra-reader variability (not for reader exclusion). No intra-reader variability criterion was specified, despite the sponsor stating in its protocol, "A refresher training session may be provided prior to each subsequent blinded reading session, if applicable. And any reader who did not meet the intra-reader variability criteria will be required to participate in a reader re-training as per the protocol" (A973). The sponsor provided central reader training by randomly selecting a small number of patient images (and then excluding them from subsequent analysis) or using images from other MRA studies. No quantified minimum post-training performance threshold was specified.

Reviewer Comment: 1) Supra-aortic MRA radiology protocols vary from site to site. A representative protocol in current use specifies serial acquisition of 3DTOF + 3DT1wPre + 3DT1wPost in the same patient with side-by-side interpretation. The sponsor's 2DTOF vs. 3DT1wPost design would be more appropriate if the clinical choice between GAD MRA and TOF were mutually exclusive. It also raises questions about the specification of 2DTOF (compared to 3DTOF or "best available non-contrast MRA protocol" as the comparator in a field of rapid technological advancement) and the role of 3DT1wPre imaging in the study. 2) Limited to the

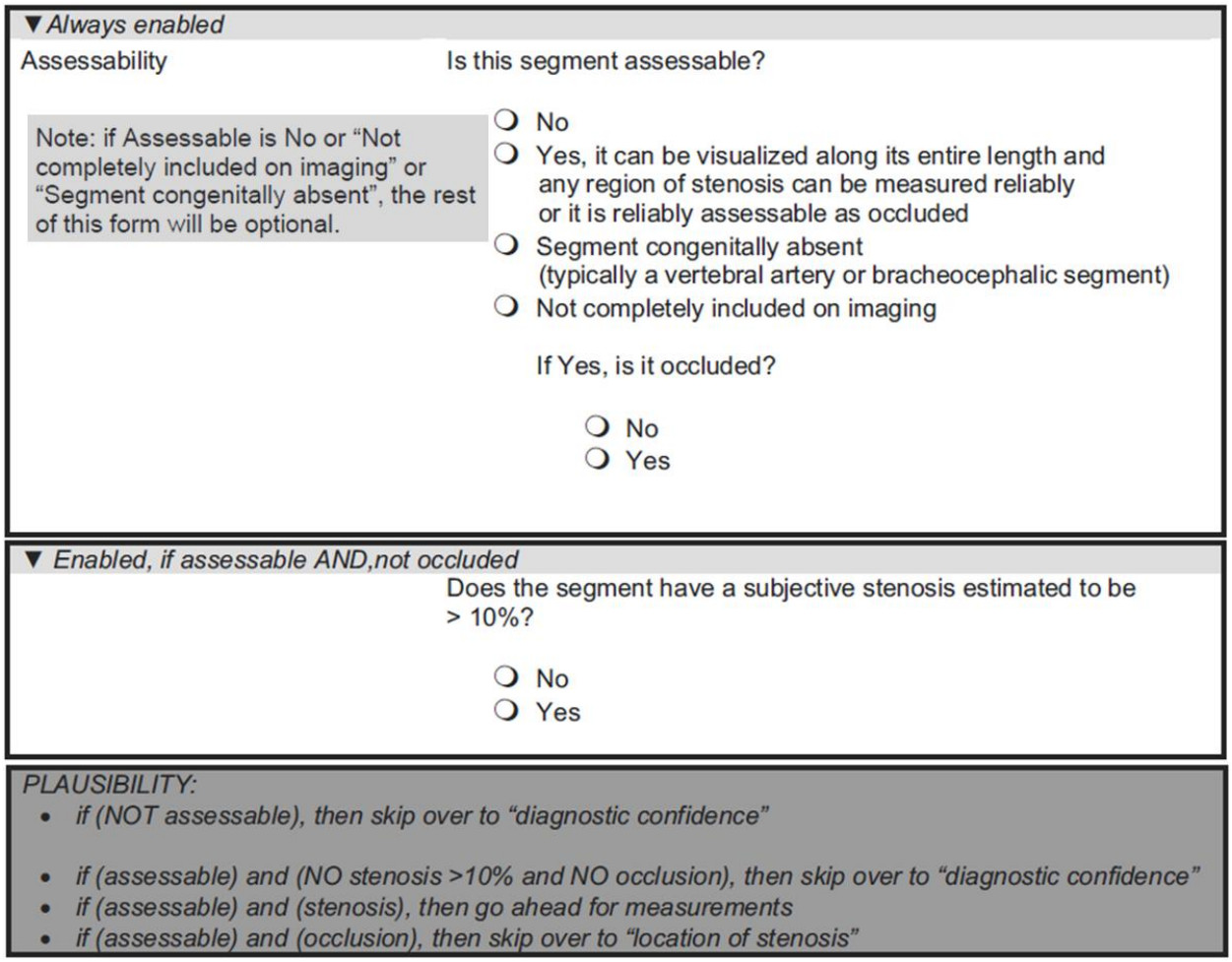
context of this study, I prefer the term "central" over "blinded" readers and caution against the potential for miscommunication when using the term "blinded reading" as a descriptor for this study. 3) Representative MRA times are ~20 s for GAD MRA (breath-hold) vs. ~ 5 minutes for TOF MRA, a fundamental difference that partially explains why it is reasonable to hypothesize that GAD MRA has lower susceptibility to artifacts than TOF MRA. 4) During my residency training in radiology between 2009-2012, several of the central readers involved with this study supervised me as attending physicians.

Study Endpoints

This study's three primary endpoints trace directly to multiple-choice questions posed to image readers in the eCRF on a per-segment basis, with segment presentation grouped per patient. The most pivotal question was posed first, as shown in the following eCRF snapshot from the sponsor's submission (Figure 5):

Figure 5 eCRF excerpt underpinning visualization endpoint from supra-aortic study

Shaded text not shown to readers. In the shaded "Plausability" box, the sponsor almost certainly meant to write, "If (NOT assessable), then skip over to 'artifacts'", rather than "If (NOT assessable), then skip over to 'diagnostic confidence'" (see A1913). Source: A977 and sdtm/blankcrf.



Note the conditional logic (gray background in Figure 5), such that if readers mark "No..." to the first question, most of the remaining segment-level questions were set to blank or other automated responses. To underscore this conditional logic and to avoid the potential for a misleading degree of objectivity to be associated with the term "assessable" in reference to an arterial segment viz-a-viz a reader's essentially unblinded forced selection of one of four multiple choices on a form, I prefer the term "visualization" as a description of the "Yes..." marking, which underpins the sponsor's first win criterion:

- Endpoint #1 Visualization: GAD – TOF > 0

Within the context of our 2004 guidance on imaging drugs, I categorize this endpoint as predominantly subjective and potentially supportive of an indication statement under the

heading, “Structure Delineation – Locating and Outlining Normal Anatomic Structures.”

If and only if the reader marks a segment as visualized, the reader next indicates whether the segment is occluded (stenosis = 100%) and, if not, whether the segment appears to have a magnitude of stenosis > 10% (eyeball threshold). If it does, the reader records two diameter measurements, leading to automated calculation of percent stenosis and automated categorization of the segment as positive/negative. The following eCRF snapshot illustrates the format for this recording (Figure 6).

Figure 6 eCRF snapshot underpinning performance endpoints from supra-aortic study

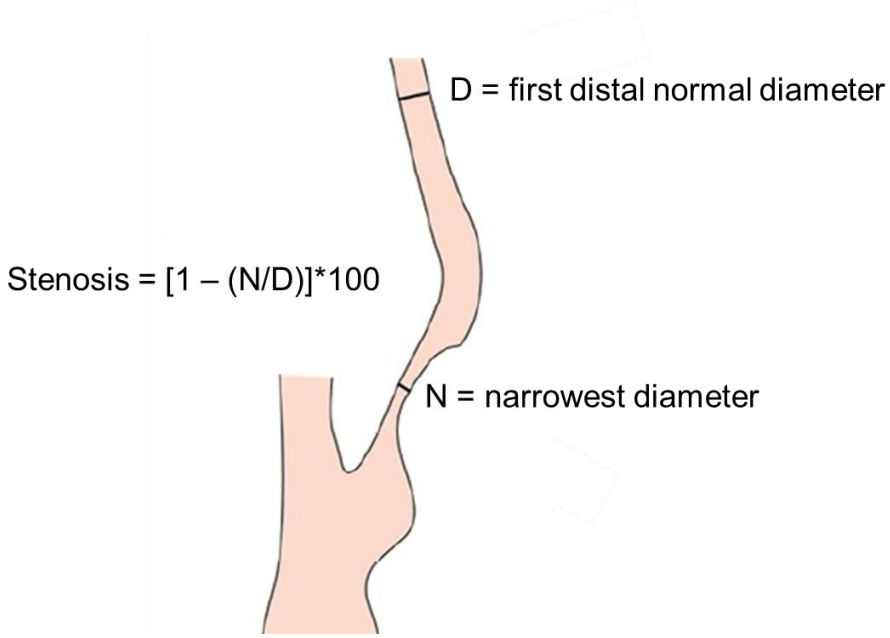
Source: A977.

▼*Enabled, if* ***stenosis*** *> 10%*		
Diagnosis of clinically significant disease	In case of multiple stenoses, assess the most severe stenosis in the segment.	
Vessel diameter at narrowest point	Vessel diameter at narrowest point:	[99.9] mm
	Vessel diameter at normal point:	[99.9] mm
Percent stenosis	Percent stenosis: [0-100] %	
	(Note: By definition a stenosis of 70-99% is clinically significant disease)	

The sponsor states, in reference to central readers, “The readers used a validated work station [MEVIS 1.3] for review of images and quantitation of stenosis that provided semi-automated as well as electronic calipers for measurements of vessel diameter” (A227), according to the following method established in the NASCET trial (Figure 7).

Figure 7 Method of calculating percent stenosis

Source: A2368 (annotations added by reviewer).



Synthesizing across Figures 5-7, note the sponsor's protocol was designed to focus reader interpretation not on whether to call a stenosis clinically significant, but on whether a segment appeared essentially normal (stenosis ≤ 10%), and where/how to place/interpret electronic calipers in order to measure narrowest and normal luminal diameters (in the event of multiple stenoses, the reader was instructed to measure the most severe). The number of positive/negative segments underpinned the second and third win criteria:

- Endpoint #2 Relative Performance: Sn/Sp GAD – TOF > -7.5%
- Endpoint #3 Minimum Performance: Sn/Sp GAD – 50% > 0

Within the context of our 2004 guidance on imaging drugs, I categorize these performance endpoints as objective and, had they been designed for superiority over TOF and independence from Endpoint #1, potentially supportive of an indication claim categorized under the heading, "Structure Delineation – Distinguishing Between Normal and Abnormal Anatomy."

For secondary endpoints, the sponsor planned to analyze primary endpoints on a per-reader basis and to provide descriptive statistics related mostly to central reader multiple-choice responses to additional eCRF questions, as detailed in Table 11.

Table 11 Sponsor's tabulation of secondary endpoints for supra-aortic study

Source: A2367.

	Non-contrast 2d-ToF		Gadobutrol-enhanced MRA	
Segmental analysis unless specified **Secondary endpoints**	Investigator	3 Blinded readers	Investigator	3 Blinded readers
Artifacts		•		•
Minimum diameter of the segment	•	•	•	•
Length and location of stenosis		•		•
Secondary radiologic indicators for diagnosis of clinically significant disease		•		•
Diagnostic confidence		•		•
Additional imaging studies (subject)	•	•	•	•

The eCRF questions underpinning these six secondary endpoints are outlined below (reviewer notes bracketed). Note that only the "Artifacts," "Secondary Signs," and "Additional Imaging" questions were asked if the reader's response to the first question, "Is this segment assessable?" was "No":

- Artifacts [Show unless segment already marked "congenitally absent" or "not completely included"]
    - Do artifacts exist? [Mark 1 of 2]
        - Yes
        - No
    - If yes, select all applicable [Mark 0-7 of 7]
        - Motion artifact (including pulsatitility, breathing, swallowing)
        - Venous opacification
        - Saturation artifact (e.g. in-plane flow, turbulence, dephasing, saturation band)
        - Susceptibility artifacts (including devices, e.g. stents)
        - Ring artifact (e.g. bands)
        - Bolus timing error
        - Other (artifact not specified above)
- Minimum diameter of the segment [See Figure 7]
- Length and location of stenosis [Show if 70-100%]

    - Length of stenosis [Show if 70-99%]
        - Length of stenosis = X mm [Write X, stenosis 10% or segment boundary defines start and end-point]
    - The location of stenosis is [Show if 70-100%, mark 1 of 3]
        - at the bifurcation or proximal origin of the segment (occlusion proximal to the origin of the segment)
        - within 5 mm of the bifurcation or proximal origin of the segment
        - beyond 5 mm from the bifurcation or proximal origin of the segment
- Secondary radiologic indicators for diagnosis of clinically significant disease [Show unless segment already marked "congenitally absent"]
    - Do secondary signs of stenosis exist [Mark 1 of 2]
        - No
        - Yes
    - If yes, please specify which secondary signs are present [Mark 0-3 of 3]
        - Post-stenotic dilation or ulceration (segmental)
        - Post-stenotic signal dropout, narrowing and intensity
        - Thrombus
- Diagnostic confidence [Show if segment marked "can be visualized"]
    - Confidence in diagnosis [Mark 1 of 4]
        - Not confident
        - Somewhat confident
        - Confident
        - Very confident
- Patient-level: additional imaging [Show for all patients]
    - Do you recommend an additional imaging study? [Mark 1 of 2]
        - No
        - Yes
    - If yes, please specify [Mark 1 of 6]
        - Non-contrast MRA
        - Contrast-enhanced MRA
        - Computed tomographic angiography
        - Ultrasound
        - Digital subtraction catheter angiogram
        - Nuclear medicine study

Reviewer Comment: 1) The subjective visualization endpoint was categorized as a secondary, not primary, in DMIP's reviews of the two GBCAs approved for MRA indications to date (see Table 2). 2) The sponsor does not specify how matching was performed between segment identification in the eCRF relative to the displayed images, nor how variant anatomy (e.g. bovine arch, etc.), meaning variation in anatomical identification may or may not contribute to overall measurement variation. 3) I consider the sponsor's secondary endpoints minimally interpretable

for multiple reasons. For example: i-The sponsor does not specify any criteria or training for readers to assign one or more of seven artefact categories to imaging, and it is unreasonable to assume standardized expertise for this highly technical "differential diagnosis" even amongst subspecialized MR readers. ii-The clinical benefit, if any, of quantitating stenosis length, location, and secondary signs is both uncertain and unspecified. iii-Recommendations for additional imaging likely differ in the context of practice and central reading, especially given the potential confusion of readers with full awareness that they are reading "Non-contrast MRA" and "Contrast-enhanced MRA" yet see them listed as options for additional imaging. 4) For future MRA studies designed primarily to test whether use of a contrast drug adds to the robustness of image acquisition, I strongly recommend revising the conditional eCRF approach used here in order to improve interpretability. In particular, readers can and should provide lumen diameter estimates for testing performance and address questions about visualization/artifacts/confidence for testing visualization in all segments.

Statistical Analysis Plan

Table 12 summarizes the sponsor's statistical analysis plan with respect to the primary endpoints.

Table 12 Reviewer's tabulation of statistical analysis plan for supra-aortic study
Source: A2408-2430, particularly A2422.

Endpoint	Type	Win Criterion	Imputation for blanks	Analysis Set
Choice-to-assess (% presented)	Superior	GAD -TOF > 0 (2-sided, alpha 0.05)	N/A	Full
Relative performance (Sn/Sp)	Non-inferior	GAD - TOF - 7.5 > 0 (1-sided, alpha 0.05)	50% match to SOR (half wrong)	Full
Minimum performance (Sn/Sp)	Superior	GAD - 50 > 0 (1-sided, alpha 0.05)	Exclude	Full

The pre-specified sample size of 398 was powered (80%) for the visualization endpoint, assuming visualization rates of 90 vs 85%. The sponsor also assumed segment-level MRA Sn/Sp of GAD vs TOF would be 83/93% vs. 80/93% (A2399).

In the agreed SPA, the sponsor states, "An interim analysis is planned after about 150 patients have been enrolled in the study. The interim analysis is not being undertaken for a safety

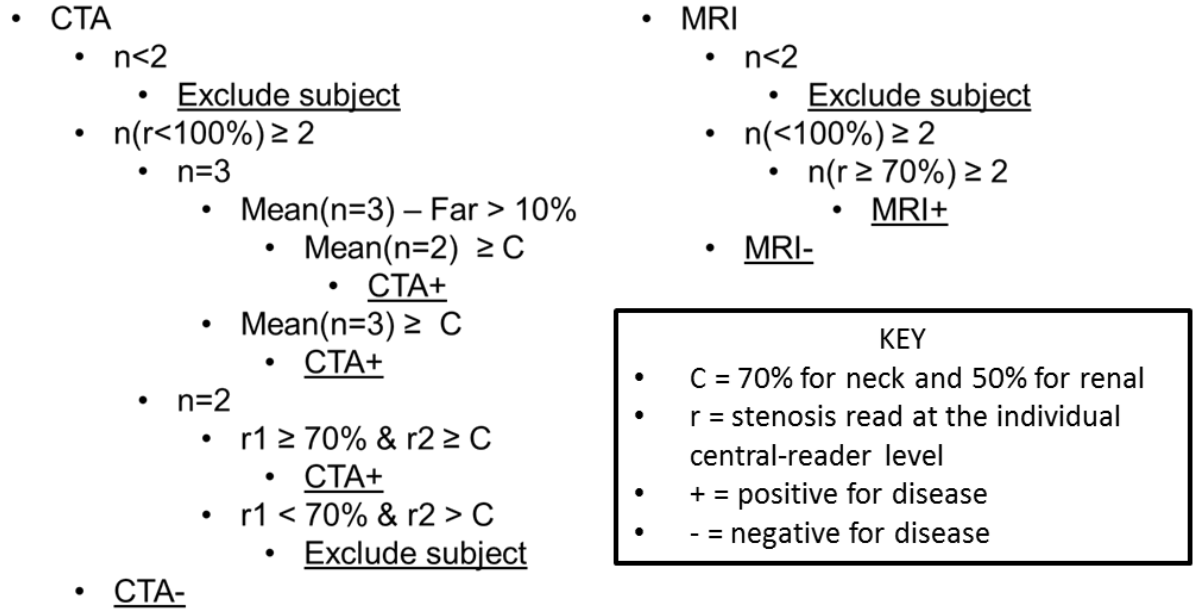
review and the study will not be stopped during the analysis" (A2398). In slight contrast (italicized), in its study report, the sponsor states (A489):

> An interim analysis was performed in February 2013 by an independent statistician at (b) (4), on blinded reader efficacy data from 150 subjects. Enrollment was placed on hold until the interim analysis result was provided. The information provided by (b) (4) to Bayer from the interim analysis at this time was that the conditional power for all 5 efficacy endpoints was greater than 67%. Therefore, the study was not stopped for futility and *enrollment was re-started*. (b) (4) in a communication letter to Bayer only communicated whether the conditional powers for the five primary endpoints exceeded a cut-off of 67%.

Although also not described in the agreed protocol, the sponsor deducted a 0.001 "alpha penalty" as a result of this interim analysis, meaning familiar 95% confidence intervals are subsequently reported as 95.1% confidence intervals (a tiny bit narrower).

Figure 8 provides the pseudo-code reflecting my understanding of the algorithm the sponsor describes for its complex aggregation of central reader's eCRF responses:

Figure 8 Reviewer's understanding of sponsor's algorithm for aggregating reader data
Source: A2376 (see also A2639).



Reviewer Comment: 1) Due to the conditional logic of the eCRF, the subjective number of segments that readers marked as visualized confounds objective reader measurements, reducing the value of performance endpoints as an independent and interpretable outcome. Nevertheless, if TOF – GAD > 0 (2-sided, 95% CI) for Sn and Sp without imputation, I would consider it a loss for Gadavist MRA, whether or not the pre-specified non-inferiority criterion were achieved under the agreed imputation scheme. 2) The sponsor planned to enroll 398 subjects, but actually enrolled 487 (22% more).

Protocol Amendments

Regarding protocol amendments, the sponsor provides the following succinct summary of minor changes that were also explicitly discussed in correspondence leading up to our SPA agreement (quoted from A60):

> Protocol 14607 (GEMSAV) Amendment 2 was submitted as SPA on April 18, 2013 and the FDA agreement letter was received on May 23, 2013. Amendment 2 allowed for further restriction of the protocol inclusion criteria from 50% to 70% stenosis to allow for adequate enrollment of subjects with disease. NOTE: Amendment 1 was a country specific amendment.

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

Regarding Good Clinical Practice (GCP), the sponsor states, "All clinical studies performed in the framework of this submission were conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), the principles of the Declaration of Helsinki, and all applicable national regulations valid at the time the studies were performed" (A294, see also A1301).

Financial Disclosure

The sponsor provides adequate documentation of having collected financial disclosure forms and reports no disclosable information for any investigator/sub-investigator (A20-37).

Patient Disposition

A total of 504 patients were screened for the supra-aortic study. I reviewed the sponsor's

explanations for screening failures and the reasons for excluding patients from the pivotal Full Analysis Set (FAS) and Per Protocol Set (PPS) compared to criteria pre-specified in the protocol. I identified no notable inconsistencies. Table 13 summarizes the reasons for post-consent exclusion from the FAS.

Table 13 Reviewer's tabulation of patient's excluded from supra-aortic efficacy analysis
Source: A484.

Enrolled: 487 subjects	Excluded from efficacy analysis:
No GAD MRA (A)	14
No TOF MRA (B)	11
No CTA (C)	8
Patients with A, B, or C	30 (3 with > 1)
Full Analysis Set (FAS)	457 = 487 - 30

Protocol Violations/Deviations

The sponsor reports that protocol deviations occurred in a total of 413 subjects (86%), in whom 47 met criteria for exclusion from the Per Protocol Set (PPS; n: 440 = 487 – 47). No primary analyses hinged on the PPS.

Table of Demographic Characteristics

The study was conducted at 56 sites, spanning 14 countries, with the largest number of subjects enrolled from Poland (120) and the United States (94). The demographics of all 479 patients who received Gadavist is detailed in Table 14.

Table 14 Sponsor's tabulation of patient demographics from supra-aortic study

Source: A485.

Sex	
Male	312 (65.1%)
Female	167 (34.9%)
Age	
Mean	68.2
SD	10.0
Min	25
Median	69.0
Max	93
Race	
White	385 (80.4%)
Black	14 (2.9%)
Asian	73 (15.2%)
Not reported	7 (1.5%)
Ethnicity	
Not hispanic or Latino	450 (93.9%)
Hispanic or Latino	21 (4.4%)
Not reported	8 (1.7%)
Baseline Weight (kg)	
Mean	76.0
SD	14.5
Min	41
Median	75.0
Max	130
Age Group (N)	
<45 years	9 (1.9%)
45-64 years	155 (32.4%)
>=65 years	315 (65.8%)

Efficacy Results – Primary Endpoint

Table 15 provides study results on both a majority and individual reader basis in terms of all primary endpoints: visualization, sensitivity (relative and minimum), and specificity (relative and minimum).

Table 15 Reviewer's tabulation of primary endpoints reported for supra-aortic study

To use this table to interpret whether the sponsor achieved its pre-specified win criteria, focus on the cells at the intersection of the "Majority Reader" row and "[A]-[B]" columns. Is 20.4 greater than 0 (visualization)? Are -2.1 and 7.8 greater than -7.5 (relative performance)? Are 5.3 and 47.3 greater than 0 (minimum performance)? The answer to all three questions is "yes," so the sponsor achieved its pivotal win criteria. Source: A491-498.

SUPRA-AORTIC ARTERIES (457 patients) Performance at the segment level Majority reader: 9597 presented, 158 positive for stenosis 70-99%, and 9321 negative by SoR[1]									
	VISUALIZATION (%)			SENSITIVITY (%)			SPECIFICITY (%)		
READER	GAD MRA [A]	TOF MRA [B]	[A]-[B] (CI[2])	GAD MRA [A] [A*]	TOF MRA [B] [B*[3]]	[A]-[B] (CI[3]) [A*]-50 (CI[4])	GAD MRA [A] [A*]	TOF MRA [B] [B*[3]]	[A]-[B]-7.5 (CI[3]) [A*]-50 (CI[4])
Majority	95.0	72.7	22.3 (20.4, 24.2)	60.1 61.7	54.4 59.1	5.7 (-2.1, 13.5) 11.7 (5.3, 18.1)	96.1 98.0	87.3 98.2	8.8 (7.8, 9.8) 48.0 (47.3, 48.3)
1	88.2	24.4	63.8 (60.9, 66.7)	59.5 60.3	54.4 71.8	5.1 (-3.8, 14.0) 10.3 (3.6, 17.0)	92.0 97.6	61.7 98.0	30.3 (28.8, 31.8) 47.6 (47.3, 47.9)
2	94.9	75.3	19.6 (17.8, 21.4)	59.5 59.6	53.8 55.1	5.7 (-2.5, 13.9) 9.6 (3.1, 16.1)	94.8 97.2	85.1 96.5	9.7 (8.7, 10.7) 47.2 (46.9, 47.5)
3	97.4	82.4	15.0 (13.3, 16.7)	58.2 58.7	55.1 56.7	3.2 (-4.4, 10.8) 8.7 (2.2, 15.2)	96.7 98.0	89.1 97.4	7.6 (6.7, 8.5) 48 (47.4, 48.6)
Site	97.0	78.6	18.5 (16.5, 20.5)	60.9 61.5	39.1 56.1	21.9 (15.6, 28.2) 11.5 (6.7, 16.3)	98.1 99.2	89.0 97.3	9.1 (8.1, 10.1) 49.2 (48.9, 49.5)

*Indicates that non-visualized segments were excluded from the analysis; otherwise, non-visualized segments were imputed to be a 50% match relative to the SoR.
[1]Standard of Reference, based on aggregate interpretation of three central CTA readers.
[2]95.1% confidence interval for two-sided comparison.
[3]The primary biometrics reviewer provided these estimates; the sponsor only estimated TOF performance with imputation.
[4]90.1% confidence interval for one-sided comparison; non-inferiority margin of -7.5 was pre-specified for [A]-[B].

In reference to this table (Table 15), note how the confidence intervals for sensitivity compared to specificity are wider, reflecting the large difference in the number of corresponding CTA-positive vs. negative segments (158 vs. 9321). Also, performance values better than 50% tend

to improve without imputation, demonstrating how winning on visualization made the sponsor more likely to win on relative performance (i.e., note how the Sp: [A] – [B] > 0, but [A*] – [B*] ≈ 0).

Turning to central tendencies, in most MRA efficacy studies that DMIP has reviewed, GBCA specificity has exceeded GBCA sensitivity (see Table 2). For this study, the sponsor hypothesized that GAD MRA Sn would be 83% and GAD MRA Sp would be 90%. The observed point estimates were 60% and 96%.

Finally, note that "24.4%" (reflecting Reader 1's choice not to assess TOF segments) and "39.1%" (reflecting the site readers' low Sn performance for TOF) are outlying values in terms of the magnitude but not the direction in which they favor the sponsor.

Reviewer Comment: 1) The sponsor achieved all SPA-agreed win criteria for the supra-aortic study. In addition, all win criteria were achieved by each central reader. 2) Generalizing from the implicit cut-points of readers across multiple GBCA MRA studies, including this one, I conclude that GAD MRA is better used to rule in (compared to rule out) stenosis 70-99% in the supra-aortic arteries.

Data Quality and Integrity – Reviewers' Assessment

I have identified no significant quality/integrity review issues that would undermine the sponsor's reported results.

Efficacy Results – Secondary and other relevant endpoints

Table 16 summarizes the sponsor's report on secondary efficacy variables, with the scope limited to analyses pre-specified in the agreed SPA.

Table 16 Reviewer's tabulation of secondary endpoints reported for supra-aortic study
Numbers reflect point estimates based on computation of the simple mean across central readers. Source: A500-514.

Endpoint	CTA	GAD	TOF	Units	CTA nearest GAD vs TOF
Artifacts		26	64	%segs	
Diameter (min)	3.0	3.2	2.7	mm	GAD
Diameter (normal)	5.0	4.9	4.3	mm	GAD
Location (near)	66	58	49	%segs+	GAD
Secondary signs		284	154	segs	
Confidence		3.0	2.2	(1,2…5)	
Additional imaging		46	94	%subjs	

See Section 6.1.1 for a discussion of limitations related to the interpretation of these secondary results. At a qualitative, directional level, however, they support the same efficacy conclusions supported by the primary endpoints.

Additional Analyses Conducted on the Individual Trial

I performed three exploratory/visualization analyses using the sponsor's raw sdtm datasets (primarily ya.xpt and suppya.xpt) in order to obtain an overview and hands-on understanding of the primary data.

Figure 9 shows how all measurements of lumen diameter varied by segment.

Figure 9 Reviewer's data visualization for 21 supra-aortic segments

The outer solid lines represent the median normal diameter for all 27,639 measurements recorded in the eCRF across readers, organized by segment. The sponsor called for quantitative measurements if and only if readers first chose to assess the segment in response to a visualization question and then eyeballed a stenosis in the 10-99% range. The inner solid lines represent the median derived from 27,607 minimum diameter stenosis measurements, with dashed lines representing 95th-percentile intervals. Reading from left to right first down the left side and then down the right side of the figure: L and R vertebral C1 loop, L and R vertebral foraminal, L and R pre-foraminal, brachiocephalic, R subclavian, L and R internal carotid cavernous, L and R internal carotid lacerum, L and R internal carotid petrous, L and R internal carotid, L and R external carotid, L subclavian, and L and R common carotid artery segments. All circles are drawn to scale relative to 5 mm, shown at top. Note how the smallest measurements concentrate in the internal carotid and pre-foraminal vertebral segments. Source: A441, YA n154271.xlsx, 654271_bot27639.jmp, 654271_top27607.jmp

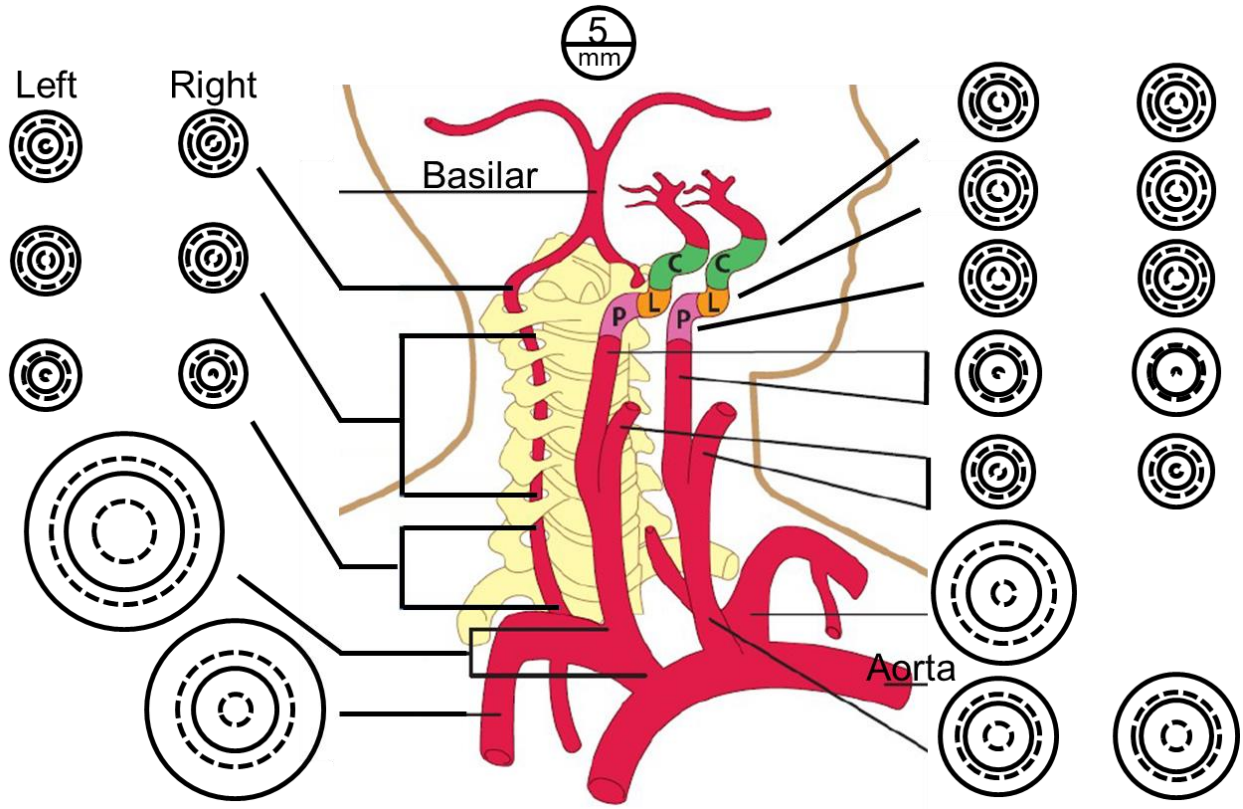


Figure 10 shows how readers responded to key eCRF questions with respect to the internal carotid artery.

Figure 10 Reviewer's data visualization for key eCRF responses: internal carotid artery

How readers visualized segments is shown by the bars on the right, with each bar representing the intersection of reader and study variable (CTA, GAD, TOF). The height of the bar represents the number of segments presented to each reader. The distance between the height of the bar and the horizontal marking represents the number of segments readers did not visualize. The distance between the horizontal marking and the colored bar represents the number of segments eyeballed as patent (ie, stenosis 0-99%). Conversely, the height of the colored bars represents the number of segments eyeballed as occluded (stenosis = 100%). The height of the bars on the left represents the number of patent segments eyeballed as essentially normal (stenosis 0-10%). The height of the lines represents the cumulative number of segments measured with stenosis >10% at the corresponding point on the x-axis (range: 10.1-99%). In summary: presented = non-visualized + occluded + normal + line height. Note how CTA readers visualized nearly all segments compared to MRA readers, and GAD readers visualized more segments compared to TOF readers. R1 is an outlier, both in terms of visualizing a minority of TOF segments and measuring tighter stenoses for GAD compared to TOF (height of R1 line: red >> black). R2 is an outlier in terms of measuring tighter stenoses. R0 (red and black) = MRA site reader; R1-3 = MRA central readers; R0 (blue) = CTA site reader; R4-6 = CTA central readers. Source: YA n154271.xlsx, 654271_assess4loc21c111282.jmp, 654271_occ2loc21c110316.jmp, 654271_sten1-99loc21c16514.jmp, 654271_sten2loc21c19921.jmp.

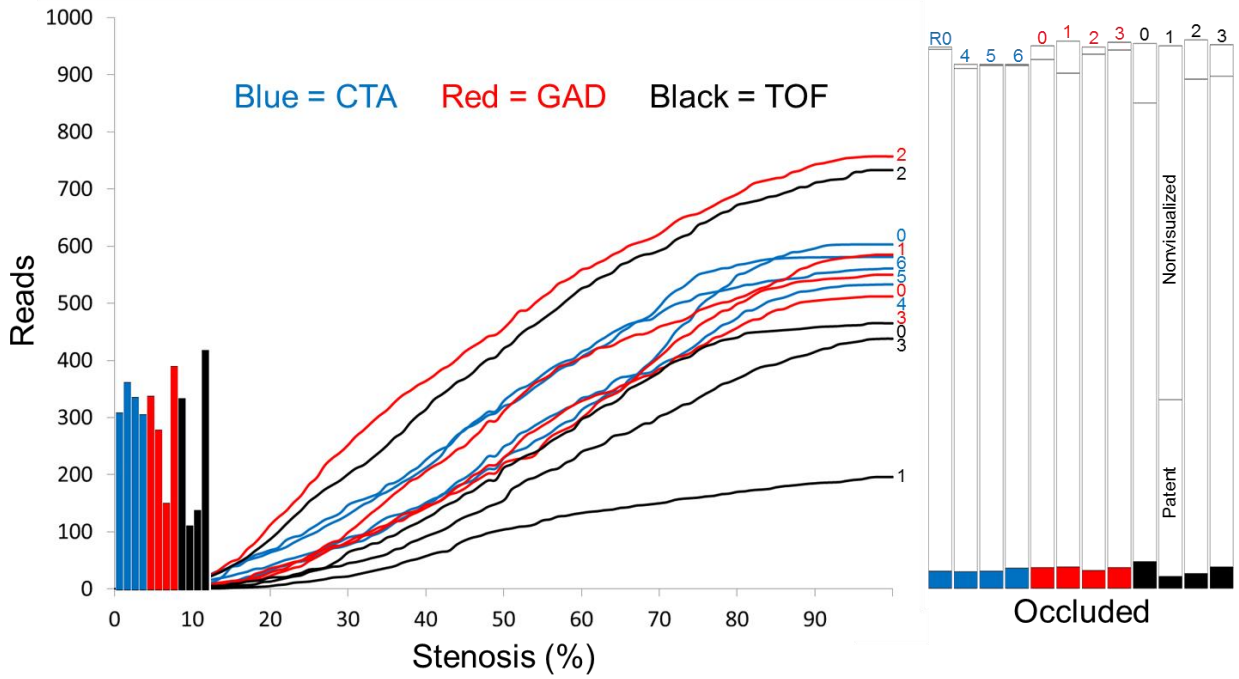
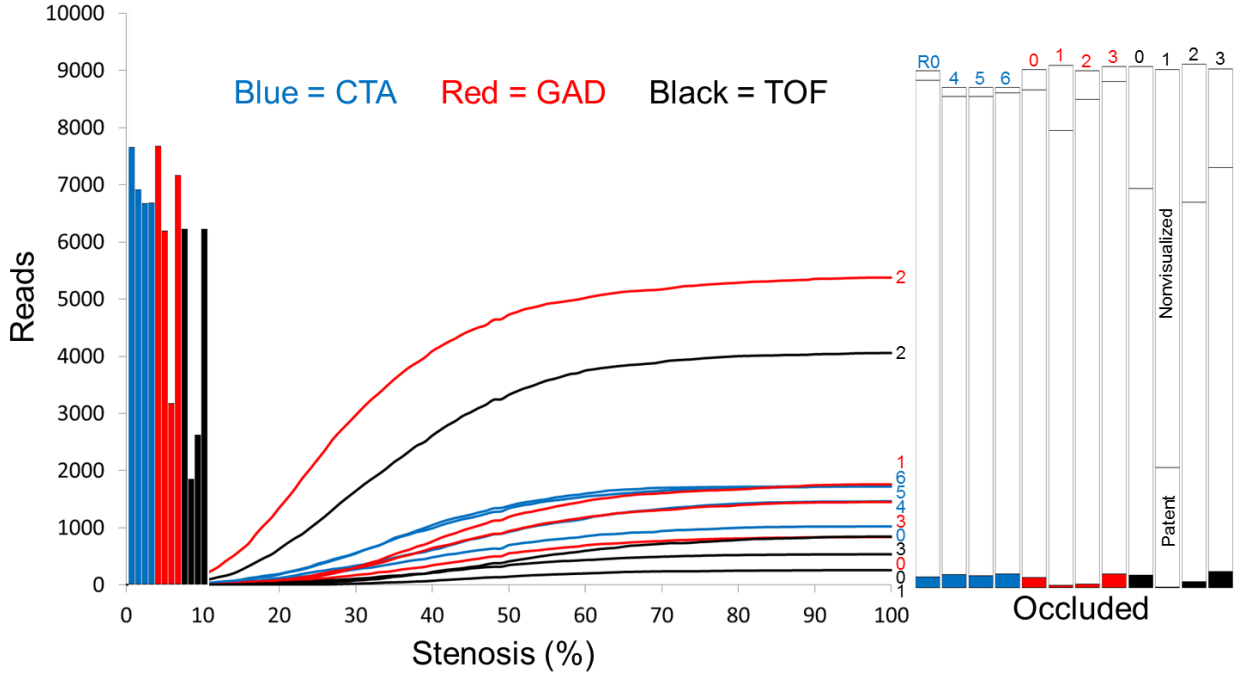


Figure 11 is analogous to Figure 10, showing how readers responded to key eCRF questions with respect to all non-internal-carotid segments. Not the lower disease burden, fewer

visualizations, and how the magnitude of stenosis appears to plateau around 50% in these segments.

Figure 11 Reviewer's data visualization for key eCRF responses: non-internal carotid arteries
See Figure 10 for detailed explanation. Note CTA readers visualized nearly all segments compared to MRA readers, and GAD readers visualized more segments than TOF readers. R1 is an outlier, both in terms of visualizing a minority of TOF segments and measuring tighter stenoses for GAD compared to TOF (height of R1 line: red >> black). R2 is an outlier in terms of measuring tighter stenoses. R0 (red and black) = MRA site reader; R1-3 = MRA central readers; R0 (blue) = CTA site reader; R4-6 = CTA central readers. Source: YA n154271.xlsx, 654271_assess4loc21NOT1107179.jmp, 654271_occ2loc21NOTc191278.jmp, 654271_sten1-99loc21NOTc121072.jmp, 654271_sten2loc21NOTc189265.jmp.



6.2. Renal study

6.2.1. Study Design

Section 6.1.1 provides a detailed description of the design of the sponsor's supra-aortic study. All descriptions and comments apply identically to the design of the renal study, entitled, "Multicenter, open-label study to evaluate the safety and efficacy (by blinded reading) of Gadobutrol-enhanced magnetic resonance angiography (MRA) after a single injection of 0.1 mmol/kg of Gadobutrol in subjects with known or suspected renal artery disease," except for the following differences:

- Pivotal renal study referred to as GRAMS (Study 91759/PH-27337);

- Patient enrollment from May, 2011 to July, 2012 (55 sites, 13 countries);
- Three main inclusion criteria in adults age ≥ 18 years with known or suspected renal artery disease based on any of the following (quoted below from A2634):
    - Referred for evaluation of the renal arteries for clinically significant stenosis
    - Follow-up for a metallic stent in a renal artery
    - Prior imaging study (CTA) showing ≥ 50% renal artery stenosis (within 60 days prior to consent);
- Scheduling of safety blood sampling, vital signs, and adverse event monitoring at 72 ± 6 (not 24 ± 6) hours post Gadavist;
- Minimum MRI specification: body coil with at least 6 parallel channels;
- Field of view from T12 (superior end plate) through renal hilum;
- Left and right renal arteries divided into three equally sized segments each;
- Stenosis 50-99% categorized as "positive";
- Central reading by six board-certified, body-MRI-subspecialized radiologists, three for MRA (R1, R2, R3) and three for CTA (R4, R5, R6);
- Patient-level first eCRF question for central readers (A1912; reviewer notes bracketed):
    - Are renal arteries present? (Note: Absent does not mean occluded) [Mark 0-2 of 2]
        - Right renal artery is absent
        - Left renal artery is absent
    - Does the scan include a transplant kidney? [Mark 1 of 2]
        - No
        - Yes;
- Additional secondary endpoints (see Table 17):

Table 17 Sponsor's tabulation of secondary endpoints for renal study

Source: A2696.

Segmental analysis unless specified	Non-contrast 2D-ToF		Gadobutrol-enhanced MRA	
	Investigator	3 Blinded readers	Investigator	3 Blinded readers
Artifacts		•		•
Narrowest diameter of a segment	•	•	•	•
Location of stenoses in the proximal segments		•		•
Length of right and left renal arteries (subject NOT segmental)		•		•
Accessory (duplicate) renal arteries on right and left (subject NOT segmental)	•	•	•	•
Aneurysmal dilatation	•		•	
Diagnosis: FMD vs. arteriosclerosis (subject NOT segmental)	•	•	•	•
Diagnostic confidence		•		•
Additional imaging studies recommended (subject NOT segmental)	•	•	•	•

- eCRF questions for the four different secondary endpoints ("Length of arteries", "Accessory visualization," "Aneurysmal dilatation", "fibromuscular dysplasia vs. arteriosclerosis"; reviewer notes bracketed; A1912-1915):
  - Vessel-level: Length of renal artery [Show unless marked "absent"]
    - Length of renal artery visualized = X mm [Write X, start and end-points unspecified]
  - Vessel-level: Accessory renal arteries [Show unless marked "absent"]
    - Is accessory (duplicate) renal artery present [Mark 0 or 1 of 2]
      - No
      - Yes
  - Aneurysmal dilatation [Show if segment marked "can be visualized"]
    - Does aneurysmal focal dilatation exist and is > 10%? [Mark 1 of 2]
      - No
      - Yes
    - If yes, vessel diameter at widest point = X mm [Write X]
  - Patient-level: Diagnosis [Show if aneurysmal dilatation and/or stenosis > 10% for any segment]
    - Diagnosis only if aneurysmal dilatation and/or stenosis > 10%
      - Arteriosclerotic
      - Fibromuscular dysplasia

- Not specified above or non-specific

- Pre-specified sample size of 336 powered (80%) for the primary visualization endpoint, assuming (GAD vs. TOF) visualization rates of 85-88% vs. 80-82% and Sn/Sp 70/98% vs. 60/92%; 317 patients were enrolled;
- No planned interim analysis and no "alpha penalty";
- No notable protocol amendments.

Reviewer Comment: 1) For the same reasons explained in Section 6.1.1 with respect to the sponsor's supra-aortic study, I consider most of the sponsor's secondary endpoints in this renal study to be minimally interpretable (most are the same between the two studies). With respect to the novel secondary endpoints, a notable exception is visualization of accessory renal arteries. Here, the clinical value of visualizing normal anatomy can be categorized as self-evident. In addition, identification of accessory renal arteries has particular value in pre-surgical planning. In contrast, I consider the "arteriosclerosis vs. fibromuscular dysplasia" uninterpretable, as it is secondary from a statistical/design perspective, incidental with respect to the sponsor's eligibility criteria, present in only one study, and not reliably established by CTA (compared to pathology or clinical correlation).

6.2.2. Study Results

Given the nearly identical designs of the sponsor's supra-aortic and renal studies, in this section, for efficiency, I have focused on study-specific results and review findings (see Section 6.1.2 for more comprehensive discussion, including of generally applicable findings).

Patient Disposition

Of 338 patients screened for participation in the renal study, 317 enrolled. Table 18 summarizes the reasons why subjects were subsequently excluded from efficacy analysis (i.e., not in the FAS):

Table 18 Reviewer's tabulation of patients excluded from renal efficacy analysis
Source: A1451.

Enrolled: 317 subjects	Excluded from efficacy analysis
No GAD MRA	9
No TOF MRA	10
No CTA	4
Ineligible	3
TOTAL	25
Full Analysis Set (FAS)	292 = 317 - 25

Protocol Violations/Deviations

The sponsor provides the following explanation regarding why its Clinical Study Report (CSR) for the renal study is titled Amended Clinical Study Report (indented text quoted from A1383):

> It was noted upon completion of the CSR that some of the efficacy tables were reported in a manner inconsistent with the specification provided in the protocol and statistical analysis plan (SAP) for the primary analysis of non-inferiority for sensitivity and specificity. Specifically, selected 95% confidence intervals (CIs) were reported as two-sided CIs rather than one-sided CIs as specified in the protocol and the SAP. The two-sided CIs were corrected by one-sided CIs for the primary analysis. The already performed two-sided CIs were then provided as a supplement to the SAP to fulfill the International Conference on Harmonisation (ICH) E9 recommendations.
>
> Selected tables (in Section 14.2) related to the primary variables were revised and the text accompanying the revised tables was modified. Some descriptive values for sensitivity and specificity for the non-inferiority comparisons also changed slightly. This was due to the resampling procedure based on random imputations having been run again to implement the change in the 95% CIs.

Table of Demographic Characteristics

The study was conducted at 55 sites, spanning 13 countries, with the largest number of subjects enrolled from South Korea (58) and the United States (52). The demographics of all patients who received Gadavist is detailed in Table 19.

Table 19 Sponsor's tabulation of patient demographics from renal study

Source: A1454.

Sex	
n	315 (100.0%)
Male	170 (54.0%)
Female	145 (46.0%)
Age	
n	315
Mean	54.9
SD	16.9
Min	18
Median	59.0
Max	88
Race	
n	315 (100.0%)
White	215 (68.3%)
Black	22 (7.0%)
Asian	69 (21.9%)
White, Black	1 (0.3%)
Not Reported	8 (2.5%)
Ethnicity	
n	315 (100.0%)
Not Hispanic or Latino	224 (71.1%)
Hispanic or Latino	87 (27.6%)
Not Reported	4 (1.3%)
Baseline Weight (kg)	
n	315
Mean	77.5
SD	16.9
Min	37
Median	75.0
Max	145
Age Group (N)	
n	315 (100.0%)
< 45 years	92 (29.2%)
45-64 years	111 (35.2%)
≥ 65 years	112 (35.6%)
Number of Subjects Enrolled by Country	
Argentina	37
Austria	6
Brazil	31
Colombia	15
Czech Republic	15
Germany	11
France	31
Poland	35
South Korea	58
Switzerland	4
Taiwan	7
Turkey	13
United States	52

Efficacy Results - Primary Endpoint

Table 20 provides study results on both a majority and individual reader basis in terms of all primary endpoints: visualization, sensitivity (relative and minimum), and specificity (relative and minimum).

Table 20 Reviewer's tabulation of primary endpoints reported for renal study

To use this table to interpret whether the sponsor achieved its pre-specified win criteria, focus on the cells at the intersection of the "Majority Reader" row and "[A]-[B]" columns. Is 15.2 greater than 0 (visualization)? Are -2.2 and 7.1 greater than -7.5 (relative performance)? Are -3.8 and 44.9 greater than 0 (minimum performance)? The answer to 2.5 of these three questions is "yes," so the sponsor achieved most but not all of its pivotal win criteria. Source: A1461-1467.

RENAL ARTERIES (292 patients) Performance at the segment level Majority reader: 1752 presented, 133 positive for stenosis 50-99%, and 1605 negative by SoR[1]									
	VISUALIZATION (%)			SENSITIVITY (%)			SPECIFICITY (%)		
READER	GAD MRA [A]	TOF MRA [B]	[A]-[B] (CI[2])	GAD MRA [A] [A*]	TOF MRA [B] [B*[3]]	[A]-[B] (CI[3]) [A*]-50 (CI[3])	GAD MRA [A] [A*]	TOF MRA [B] [B*[3]]	[A]-[B]-7.5 (CI[3]) [A*]-50 (CI[4])
Majority	95.9	77.6	18.3 (15.2, 21.4)	53.4 54.6	46.6 35.0	6.8[5] (-2.2, 15.8) 4.6 (-3.8, 13.0)	94.8 95.9	85.7 88.7	9.1[5] (7.1, 11.1) 45.9 (44.9, 46.9)
1	98.1	81.7	16.4 (13.2, 19.6)	51.9 51.6	51.1 55.4	0.8[5] (-8.9, 10.5) 1.6 (-6.4, 9.6)	94.4 95.0	83.1 90.4	11.3[5] (9.1, 13.5) 45 (43.8, 46.2)
2	95.5	71.5	24.0 (20.5, 27.5)	54.1 54.4	39.1 33.3	15.0[5] (5.8, 24.2) 4.4 (-4.5, 13.3)	94.8 96.2	85.0 98.3	9.8[5] (7.7, 11.9) 46.2 (45.2, 47.2)
3	95.5	78.1	17.4 (14.3, 20.5)	52.6 53.4	50.4 50.6	2.2[5] (-6.6, 11) 3.4 (-5.2, 12.0)	94.0 95.8	80.7 89.3	13.3[5] (11.1, 15.5) 45.8 (44.8, 46.8)
Site	94.4	68.9	25.6 (21.9, 29.3)	69.3 71.3	50.0 52.9	19.3[5] (11.0, 27.6) 21.3 (14.7, 27.9)	96.5	83.5 97.1	13.0[5] (10.9, 15.1) 48.4 (47.8, 49.0)

*Indicates that non-visualized segments were excluded from the analysis; otherwise, non-visualized segments were imputed to be a 50% match relative to the SoR.

[1]Standard of Reference, based on aggregate interpretation of three central CTA readers.

[2]95.1% confidence interval for two-sided comparison.

[3]The primary biometrics reviewer provided these estimates; the sponsor only estimated TOF performance with imputation.

[4]90.1% confidence interval for one-sided comparison; non-inferiority margin of -7.5 was pre-specified for [A]-[B].

[5]The sponsor reported [A]-[B] values containing multiple small arithmetic errors, likely related to its late report amendment (see Submission p. 1383); the values displayed reflect my own computation of [A]-[B].

In reference to this table (Table 20), note that the same patterns identified for the primary supra-aortic endpoints (Table 15) also hold for the renal study. Confidence intervals for sensitivity compared to specificity are wider (133 positive vs 1605 negative segments). The point estimate for GBCA specificity exceeds sensitivity. Relative specificity is superior for GAD with imputation, but not without. The sponsor hypothesized that GAD Sn would be 70% and GAD Sp would be 98%. The point estimates observed were 53% and 95%.

Also, note that "69.3%" (reflecting the site readers' high Sn performance for GAD) is an outlying value in terms of the magnitude but not the direction in which it favors the sponsor.

Reviewer Comment: 1) The sponsor achieved 2.5 of the three SPA-agreed win criteria for the renal study. In particular, on the agreed majority-reader basis, superiority was achieved for visualization; non-inferiority was achieved for relative performance; and superiority was achieved for minimum performance in terms of Sp. At the level of individual central readers, 3/3 achieved superiority for visualization; 2/3 achieved non-inferiority for relative performance; and 0/3 achieved minimum performance due to low Sn. 2) Independent of secondary outcomes, two factors argue against the decisiveness of the sponsor's partial loss: i-It is likely attributable to imperfect reference standard bias; ii-Sn + Sp = 148% >> 100% (the pre-specified sum).

Efficacy Results - Secondary and other relevant endpoints

Table 21 summarizes the sponsor's report on secondary efficacy variables, with the scope limited to analyses pre-specified in the agreed SPA.

Table 21 Reviewer's tabulation of secondary endpoints reported for renal study

Numbers reflect point estimates only based on calculation of the simple mean across the reported means for each central reader. For comparison, on a per-visualized artery basis, the overall point estimates for visualization of the accessory artery are CTA: 266/1752 (15%), GAD: 243/1838 (15%), and TOF: 56/1766 (3%). Source: A1470-1484 and 156782_acc12756_noR05412.jmp.

Endpoint	CTA	GAD	TOF	Units	CTA nearest GAD vs TOF
Artifacts		78	96	%segs	
Diameter (min)	2.5	2.6	2.2	mm	GAD
Diameter (normal)	5.2	5.2	4.8	mm	GAD
Location (near)	39	42	39	%segs+	TOF
Length (artery)	43	41	38	mm	GAD
Accessory	15	13	3	%subjs	GAD
Aneurysmal dilatation		11	2	%segs	
Fibromuscular dysplasia	2.3	4.3	0.5	%subjs	GAD
Confidence		3.3	2.1	(1,2…5)	
Additional imaging		21	73	%subjs	

See Section 6.2.1 for a discussion of limitations related to the interpretation of these secondary endpoints. At a qualitative, directional level, however, they mostly support the same efficacy conclusion suggested by the primary endpoints.

Reviewer Comment: 1) Table 21 shows that CTA readers (aggregated) identified accessory renal arteries in 15% of patients (SOR value) compared to 13% and 3% for GAD and TOF MRA readers, respectively, a notable difference albeit in terms of point estimates, both for its apparent magnitude and potential clinical utility. 2) Without a standard against which to establish disease diagnosis, the prevalence of fibromuscular dysplasia in the study population is unknown, yet the sponsor's highest point estimate of 4% provides additional evidence for why this study design is inadequate as the basis for a disease diagnostic indication.

Additional Analyses Conducted on the Individual Trial

As with the supra-aortic study, I performed three exploratory/visualization analyses using the sponsor's raw sdtm datasets (primarily ya.xpt and suppya.xpt) in order to obtain an overview and hands-on understanding of the primary data.

Figure 12 shows how all measurements of lumen diameter varied by segment.

Figure 12 Reviewer's data visualization for 6 renal segments

The outer solid lines represent the median normal diameter for all 3924 measurements recorded in the eCRF across readers, organized by segment. See Figure 9 for a more detailed description. Note how the smallest measured diameters concentrate in the proximal segments. Source: 156782.xlsx, 156782_bot3924.jmp, 156782_top3505.jmp

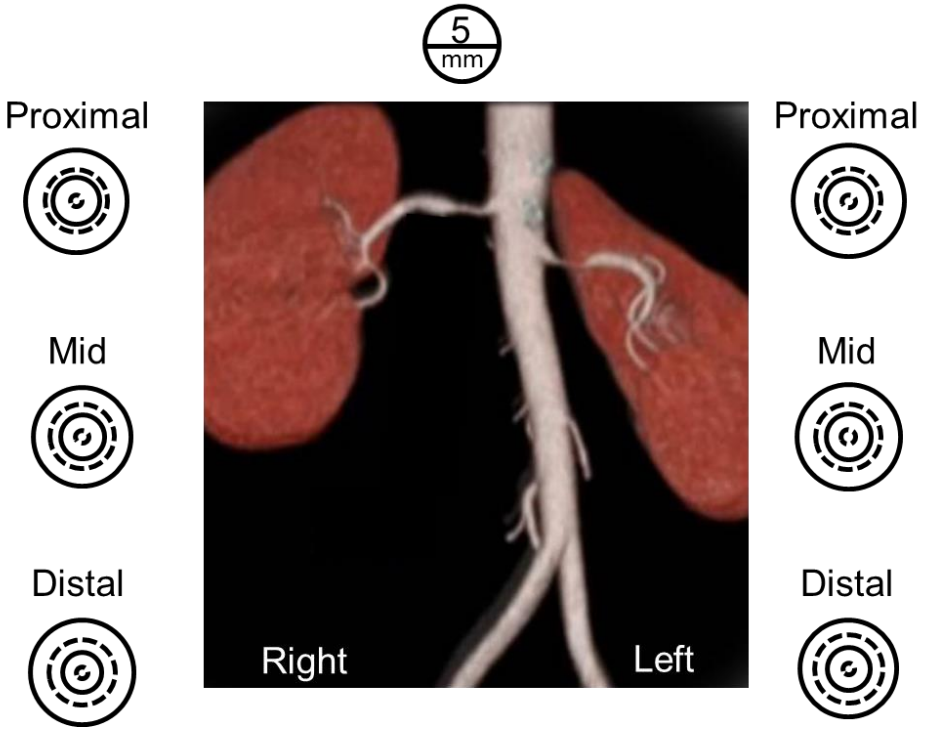


Figure 13 shows how readers responded to key eCRF questions with respect to the proximal renal artery. Note how stenosis distribution more closely resembles that of the non-internal- compared to internal carotid segments (comparing Figure 13 to Figures 10 vs. 11).

Figure 13 Reviewer's data visualization for key eCRF responses: proximal main renal artery

See Figure 10 for a detailed explanation. Note how CTA readers visualized nearly all segments compared to MRA readers, and GAD readers visualized more segments compared to TOF readers. R4 is an outlier in terms of measuring tighter stenoses. R0 (red and black) = MRA site reader; R1-3 = MRA central readers; R0 (blue) = CTA site reader; R4-6 = CTA central readers. Source: 156782.xlsx, 156782_assess3loc24m17251.jmp, 156782_occ2loc24m16691.jmp, 156782_sten1-99loc24m12115.jmp, 156782_sten2loc24m16641.jmp.

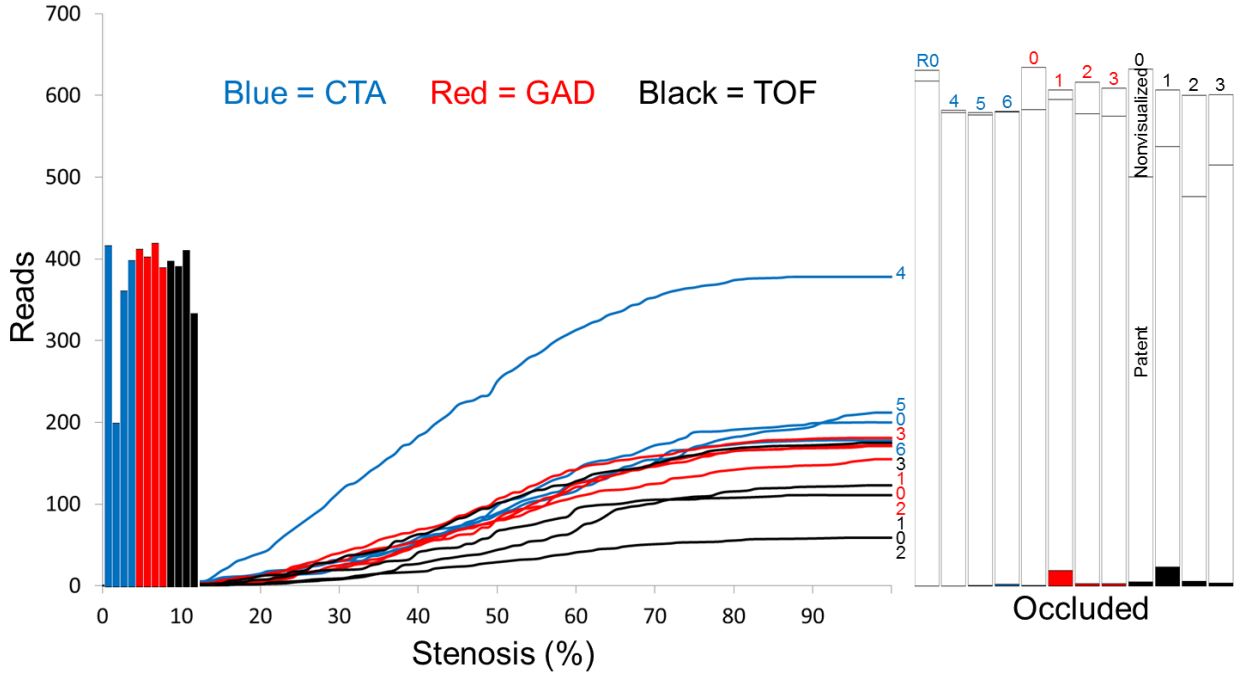
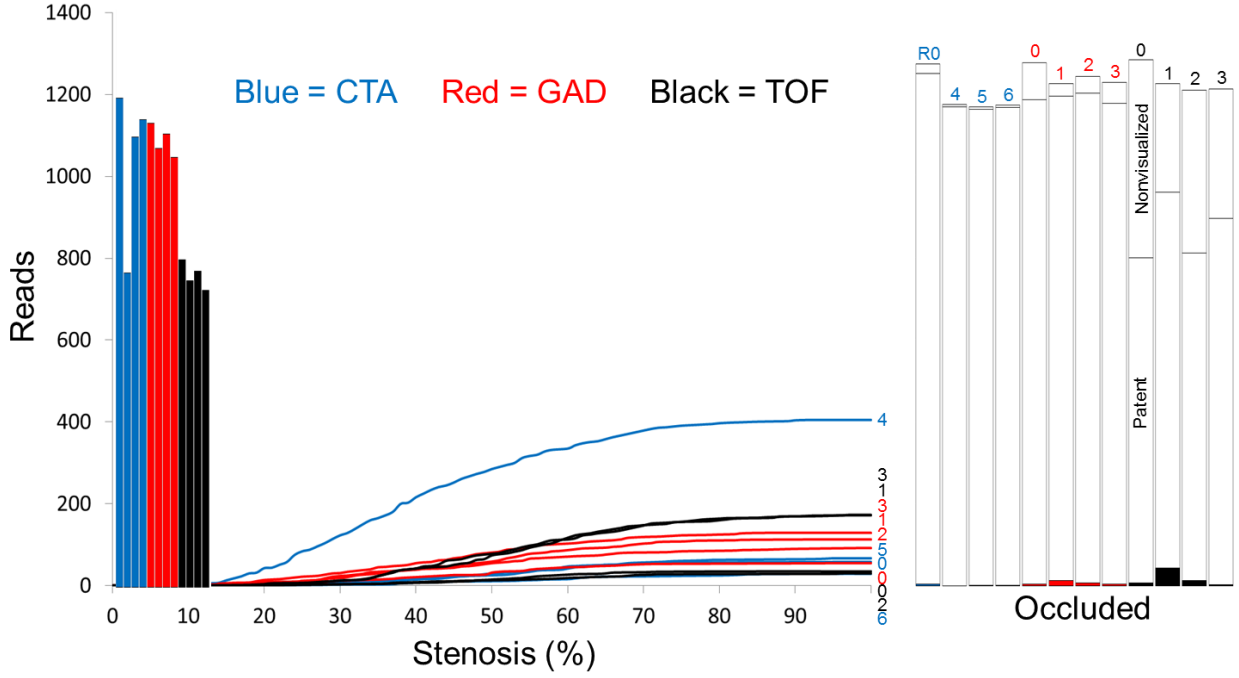


Figure 14 shows how readers responded to key eCRF questions with respect to the mid and and distal renal arteries. Note the lower stenosis burden and fewer visualizations in these compared to proximal segments.

Figure 14 Reviewer's data visualization for key eCRF responses: mid/distal main renal artery
See Figure 10 for a detailed explanation. Note how CTA readers visualized nearly all segments compared to MRA readers, and GAD readers visualized more segments compared to TOF readers. R4 is an outlier in terms of measuring tighter stenoses. R0 (red and black) = MRA site reader; R1-3 = MRA central readers; R0 (blue) = CTA site reader; R4-6 = CTA central readers. Source: 156782.xlsx, 156782_assess3loc24NOTm114645.jmp, 156782_occ2loc24NOTm112950.jmp, 156782_sten1-99loc24NOTm11358.jmp, 156782_sten2loc24NOTm112887.jmp.



7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Table 22 places the sponsor's primary endpoints in the same tabular context as precedent studies introduced in Section 2.

Table 22 Reviewer's tabulation of GBCAs approved for MRA, including Gadavist

The Ablavar and Multihance columns are identical to those in Table 2. The Gadavist column is added here so integrated efficacy endpoints can be viewed in regulatory context.

Lines 1-4	Ablavar	Multihance	Gadavist
L1. Manufacturer	Lantheus	Bracco	Bayer
L2. Year Approved / Reviewed	2008	2012	2016
L3. Proposed MRA indication			(b) (4)
L4. Labeled MRA indication	For use as a contrast agent in MRA to evaluate aortoiliac occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease.	For use in MRA to evaluate adults with known or suspected renal or aorto-ilio-femoral occlusive vascular disease.	For use in magnetic resonance angiography (MRA) in adult and pediatric patients (including term neonates) to evaluate known or suspected supra-aortic or renal artery disease.

Lines 5-7	Ablavar	Multihance	Gadavist
L5. Dosing / administration	Administer Ablavar injection by an intravenous bolus, manually or by power injector, at a dose of 0.12 mL/kg body weight (0.03 mmol/kg) over a period of time up to 30 seconds followed by a 25-30 mL normal saline flush. Imaging is performed in two stages, the dynamic stage which begins immediately following Ablavar injection and the steady-state stage, which begins following dynamic imaging; generally 5 to 7 minutes after Ablavar injection.	The recommended dose of Multihance is 0.1 mmol/kg (0.2 ml/kg) administered as a rapid bolus intravenous injection. To ensure complete injection of the contrast medium, follow the injection with a saline flush of at least 20 mL in MRA.	Image acquisition should coincide with peak arterial concentration, which varies among patients. Adults • Administer Gadavist by power injector, at a flow rate of approximately 1.5 mL/second, followed by a 30 mL normal saline flush at the same rate to ensure complete administration of the contrast. Pediatric patients • Administer Gadavist by power injector or manually, followed by a normal saline flush to ensure complete administration of the contrast.
L6. Contrast (C) images	First pass + steady state	First pass	First pass
L7. Non-contrast (NC) comparator	2D-TOF	2D-TOF	2D TOF

Lines 8-17	Ablavar	Multihance	Gadavist
L8. Sn: C – NC win criteria	Superiority	• Non-inferiority (supra-aortic; C – NC > -5) • Superiority (renal and pelvis)	Non-inferiority (C – NC > -10%
L9. Sp criteria: C – NC win criteria	Non-inferiority (C – NC > -5%)	• Superiority (supra-aortic) • Non-inferiority (renal and pelvis; C – NC > -5%)	Non-inferiority (C – NC > -7.5%)
L10. Additional primary win criteria	Sn and Sp > 50% for segments visualized by Ablavar but not TOF	None	Visualization (C – NC > 0) Minimum performance (C – 50 > 0)
L11. Standard of reference (SOR)	Catheter angiography	Catheter angiography	CTA
L12. Imputation for blanks	All wrong (blank=-SOR)	Half wrong (blank=50%SOR)	Half wrong (blank=50%SOR)
L13. Central reader aggregation	Same 2 of 3	Same 2 of 3	Majority
L14. Level of pivotal efficacy analysis	Segment	Segment	Segment
L15. Analysis set for pivotal efficacy	C+NC+SOR complete	C+NC+SOR complete	C+NC+SOR complete
L16. Use of calipers for stenosis	Yes (unclear if for all or subset of segments)	Yes (unclear if for all or subset of segments)	Yes (if eyeballed stenosis > 10%)
L17. Definition of positive stenosis	Unclear: 50-99% or 50-100%	• 51-99% renal and pelvis • 60-99% supra-aortic	• 70-99% supra-aortic • 50-99% renal

Line 18	Ablavar	Multihance	Gadavist
L18. Sponsor's claimed MRA efficacy outcomes • *s = segments (subdivided by number positive + negative, if available)* • *n = patients (number positive + number negative, if available)* • *R = central reader* • *In all expressions of the form C – NC = D, C =performance with contrast, NC=performance without contrast, and D= difference* • ** = win criterion achieved*	Calf (n=72+53,s=200+116) R1* • Sn:93-77=16* • Sp:60-38=22* R2 • Sn:78-87=-9 • Sp:66-39=27* R3 • Sn:79-78=1 • Sp:63-28=35* Pelvis 1* (n=140+250, s=237+1409) R1* • Sn:80-62=18* • Sp:85-72=13* R2 • Sn:73-67=6 • Sp:93-85=8* R3* • Sn:70-42=28* • Sp:95-75=20* Pelvis 2* (n=85+172,s=146+1018) R1* • Sn:83-52=31* • Sp:80-71=9* R2* • Sn:84-60=24* • Sp:83-75=8* R3* • Sn:71-49=21* • Sp:90-78=12* Renal* (n=40+116,s=53+229) R1* • Sn:57-30=27* • Sp:77-48=29* R2* • Sn:66-42=24* • Sp:82-59=23* R3* • Sn:64-23=41* • Sp:83-57=26*	Calf* (original read with half-wrong imputation, n=164) R1* • Sn:45-4=41* • Sp:89-64=25* R2* • Sn:79-48=31* • Sp:74-65=9* R3* • Sn:68-33=35* • Sp:83-75=8* Pelvis* (re-read, n=274, s=2949+8886) R1* • Sn:78-74=4* • Sp:88-79=9* R2* • Sn:65-53=12* • Sp:94-89=5* R3* • Sn:69-59=10* • Sp:90-75=15* Renal* (re-read, n=268, s=600+960) R1* • Sn:68-47=21* • Sp:94-86=8* R2* • Sn:62-47=15* • Sp:94-84=10* R3* • Sn:66-40=26* • Sp:95-87=8* Supra-aortic (re-read, n=237, s=912+7338) R1 • Sn:61-67=-6 • Sp:93-88=5* R2 • Sn:75-78=-3 • Sp:89-89=0 R3 • Sn:66-69=-3 • Sp:95-93=2*	Renal* (n=292, s=133+1605) R1 • Sn:52-51=1 • Sp:94-83=11* R2* • Sn:54-39=15* • Sp:95-85=10* R3* • Sn:53-50=3* • Sp:94-81=13* Supra-aortic* (n=457, s=158+9321) R1* • Sn:60-64=6* • Sp:96-87=9* R2* • Sn:60-54=6* • Sp:95-85=10* R3* • Sn:58-55=3* • Sp:97-89=8*

Lines 19-20	Ablavar	Multihance	Gadavist
L19. Labeled outcomes supporting MRA efficacy indications • *s = segments (subdivided by number positive + negative, if available)* • *n = patients (number positive + number negative, if available)* • *R = central reader* • *In all expressions of the form C – NC = D, C =performance with contrast, NC=performance without contrast, and D= difference*	<u>Pelvis (n=215+411,s=316+223)</u> R1 • Sn:89-69=20 • Sp:72-71=1 R2 • Sn:82-70=12 • Sp:81-73=8 R3 • Sn:79-64=15 • Sp:85-85=0 <u>TOF Blanks (n=25+93, s=28+202)</u> R1 • Sn:97 • Sp:72 R2 • Sn:91 • Sp:84 R3 • Sn:72 • Sp:82	<u>Pelvis</u> R1 • Sn:78-74=4 • Sp:88-79= R2 • Sn:65-53=12 • Sp:94-89=5 R3 • Sn:69-59=10 • Sp:90-75=15 <u>Renal</u> R1 • Sn:68-47=21 • Sp:94-86=8 R2 • Sn:62-47=15 • Sp:94-84=10 R3 • Sn:66-40=26 • Sp:95-87=8	<u>Renal (n=292, s=133+1605)</u> R1 • Vis:98-82=16 • Sn:52-51=1 • Sp:94-83=11 R2 • Vis:96-72=24 • Sn:54-39=15 • Sp:95-85=10 R3 • Vis 96-78=17 • Sn: 53-50=3 • Sp: 94-81=13 <u>Supra-aortic*(n=457, s=158+9321)</u> R1 • Vis:88-24=64 • Sn: 60-64=6 • Sp: 96-87=9 R2 • Vis:95-75=20 • Sn: 60-54=6 • Sp: 95-85=10 R3 • Vis 97-82=15 • Sn: 58-55=3 • Sp: 97-89=8 "For all three renal artery readers, the lower bound of confidence for the sensitivity of Gadavist MRA did not exceed 50%."

Reviewer Comment: Across multiple pivotal MRA studies, performance of GBCA MRA in the renal and supra-aortic arteries has consistently been estimated in the 60-70% range when measured against catheter angiography and in the 50-60% range when measured against CTA (see Tables 2 and 22). This supports the hypothesis of an imperfect gold standard bias. It also suggests that variable regulatory outcomes may reflect, at least in part, variability in agreed win criteria, imputation schemes, and TOF performance (more than GBCA performance).

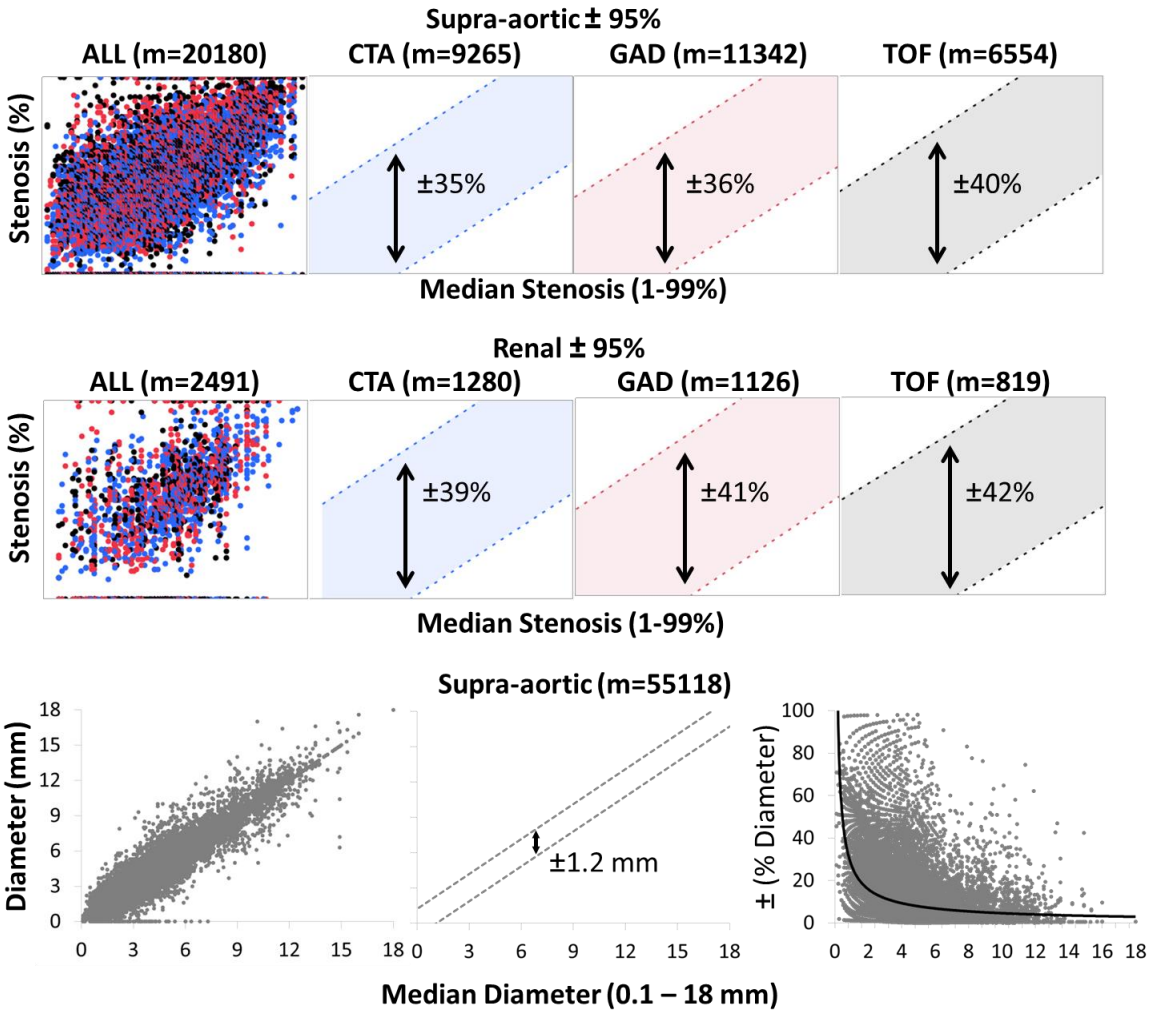
7.1.2. Secondary and Other Endpoints

See Sections 6.1.2 and 6.2.2. for discussion of study-level secondary endpoints, which are not amenable to further pooled/integrated analysis.

See Section 3.2 for background on our agreement to use CTA rather than catheter angiography as the SOR for this efficacy supplement. I considered this the most important change compared to prior MRA reviews and thought it merited special analysis. I reasoned that a gold standard should be both more accurate and precise than its comparators. It is not possible, in the absence of catheter angiography, to explore the relative accuracy of CTA and MRA (see Figure 3). It is possible, however, to explore CTA and MRA reliability. I compared stenosis measurements across at least four measurements per segment per patient (1 site reader + 3 central readers). Figure 15 shows the outcome of this secondary exploratory analysis.

Figure 15 Reviewer's data visualization of measurement reliability

Each dot represents one measurement (m) of stenosis (top two rows) or diameter (bottom row), as recorded in the sponsor's eCRF. Measurements were recorded only if readers first reported that they could visualize a segment. Segments eyeballed as occluded were assigned a stenosis value of 100% and those eyeballed as < 10% stenosed were assigned a value of 0%. All other stenosis measurements represent the ratio of two diameter measurements. At least four repeated measurements were recorded for each well visualized segment, one per patient per reader, for CTA (blue), Gadavist MRA (GAD, red), and TOF MRA (TOF, black) images. The median of these ~4 measurements was used to position each dot on the x-axis; the recorded value was used to position each dot on the y-axis. The spread of dots away from a line connecting the lower left and upper right corners of each graph thus represents measurement variability. Note the very large spread of stenosis measurements. The vertical range across which 95% of the blue, red, and black dots fall is shown in the three graphs toward the right of the top and middle rows.The graph on the bottom left shows that measurement variability appears considerably reduced when numerator and denominator measurements are disentangled (propagation-of-error effect). The graph on the bottom right highlights the observation that spread is roughly fixed across the range of diameter measurements from 0.1 to 18 mm. As a consequence, measurement error, expressed in percentage terms, is highly non-linear. Source: 645271_sten101922_STEN501-9920180, 156782_sten19726_STEN501-992491.jmp, 14607_figs.xls.



This secondary analysis supplements the sponsor's report on kappa statistics, which require positive/negative dichotomization of stenosis measurements according to SOR-match and re-reading to compute intra-reader reliability (5% re-read rate for central readers only). The sponsor reported an intra-reader kappa of 0.535 and 0.589 and an inter-reader kappa of 0.67 and 0.51 for the supra-aortic and renal studies, respectively (A500 and A1468).

In its response to our information request, response dated February 1, 2016, the sponsor provided the following tabular summary of stenosis measurement variability across its two pivotal studies (Table 23).

Table 23 Sponsor's tabulation of measurement variation

Source: A5468.

Left or Right Internal Carotid Segment

Patients with range in percent stenosis measurements ≥ 10, 30, 50, 70, 90%

	Range ≥ 10%	Range ≥ 30%	Range ≥ 50%	Range ≥ 70%	Range ≥ 90%
GAD (N=454)	89.87%	47.36%	13.44%	3.96%	1.98%
TOF (N=443)	89.84%	55.30%	22.12%	8.80%	3.84%
CTA (N=456)	85.09%	39.69%	11.18%	3.73%	1.10%

Left or Right Proximal Renal Artery

Patients with range in percent stenosis measurements ≥ 10, 30, 50, 70, 90%

	Range ≥ 10%	Range ≥ 30%	Range ≥ 50%	Range ≥ 70%	Range ≥ 90%
GAD (N=286)	52.80%	34.27%	14.34%	3.50%	1.05%
TOF (N=270)	59.26%	44.44%	22.22%	8.52%	1.85%
CTA (N=292)	82.19%	58.90%	33.22%	8.90%	0.34%

Reviewer Comment: Quantitative lumenography, as a metric of vascular wall disease, is indirect, raising multiple metrological challenges, including multiplicative error propagation for ratios and relative error that increases in proportion to disease severity. The development and use of normal-population nomograms against which to compare single narrowest-lumen measurements may represent a partial solution to the large magnitude of unreliability illustrated in Figure 15 (upper left) and Table 23. (Development of methods for direct imaging and quantification of mural disease likely represents the best solution.)

7.1.3. Subpopulations

See Section 4, primary biometrics review, and Figures 10 vs. 11 and 13 vs. 14 for discussion of efficacy in high- vs low-prevalence segments.

With respect to the sponsor's proposal to include pediatric patients in its MRA indication, on June 24, 2015, the Pediatric Review Committee (PeRC) agreed with the sponsor's proposal to extrapolate efficacy for magnetic resonance angiography (MRA) from adults and leverage

pharmacokinetic and safety studies performed for the approved CNS indication in pediatric patients down to birth. We agreed that no dedicated pediatric MRA studies were required, based on the following rationale: "The mode of action of gadobutrol and other contrast agents of this class (extracellular GBCAs) is the same. Gadavist works by enhancing the vessels and by being rapidly distributed into the extracellular space thereby enhancing body regions. Thus, diagnostic information is provided in different body regions independent of organs and body parts. The PK profile (together with relaxivity) is the basis for all conditions related to the different body regions and indications" (A5195). To confirm this strategy, I also reviewed published literature (Young 2013, Chavhan 2015), which generally supports the sponsor's position that supra-aortic and renal MRA is feasible down to birth (see A5179, A5381).

7.1.4. Dose and Dose-Response

The sponsor provided no rationale for its decision to test a 0.1 mmol/kg Gadavist dose administered at a rate of 1.5 mL/s, except for the following December 15 response to our information request (quoted in the indented text from A5405):

> Request: Our understanding is the maximum labeled dose for Gadavist MRA in Europe is 0.3 mmol/kg. Justify why your proposed 0.1 mmol/kg maximum for U.S. labeling is different and optimal.
>
> Response: The labeling in Europe for up to 0.3 mmol/kg is for a multi-station MRA exam, i.e. an MRA exam for lower extremity requiring three (3) separate/consecutive MRA scans to be performed over the pelvis, thighs, and calves. This does not apply to the vascular territories in this sNDA requiring a single station MRA scan of the supra-aortic territory (GEMSAV) or the renal artery territory (GRAMS).
>
> The older Phase 2 and Phase 3 Gadavist MRA studies performed for European approval demonstrated the adequacy of a dose consistent with a standard dose for Gadavist for MRA of a single vascular territory such as the supra-aortic or renal arteries. These older studies were performed prior to the routine use of parallel imaging and some studies use one or two fixed volumes, dependent on patient weight that approximated the 0.1 mmol/kg dose. These fixed doses were used to provide adequate bolus length for these older MRA techniques. Parallel imaging has accelerated the image acquisition by a factor of 2 to 3, so it is now easier to match the arterial bolus duration to the scan duration with the weight-based dose of 0.1 mmol/kg.

The sponsor appears, in particular, to be referencing dose-response study 91878/B204, in which segment-level reader agreement with catheter angiography was found to be 71% (0.05 mmol/kg), 86% (0.15 mmol/kg), and 81% (0.25 mmol/kg) for single-station aorto-iliac MRA (see Table 5). Note the proposed dose of 0.1 mmol/kg for U.S. labeling was not tested.

Published reports, however, have suggested that Dotarem 0.2 mmol/kg compared to 0.1 mmol/kg administered at 3 ml/s for off-label supra-aortic MRA (acquired with device settings similar to those under review) is not associated with benefit, based on visual scoring of readers blinded to dose, as well as quantitative contrast-to-noise measurements (Unterweger 2005). In addition, visual scoring and signal-to-noise were higher (3.5 vs 3 on five-point scale and 55 vs 44, respectively), albeit not significantly different, when Gadavist 0.1 mmol/kg was compared to 0.05 mmol/kg administered at 3 mL/s for MRA of the carotid artery in pigs at 1.5T (Voth 2011). In contrast, for brain MR perfusion imaging, in a randomized study of Gadavist comparing five dose groups ranging from 0.1-0.5 mmol/kg, administered at a rate of 3 mL/s, the peak of the time-susceptibility curve was found to be ~0.8 vs 0.1 arbitrary units at 0.5 mmol/kg vs. 0.1 mmol/kg. In addition, there was a clear dose-response relationship with respect to visual ratings, with the maximum corresponding to a dose of 0.4 mmol/kg (Benner 2000).

Reviewer Comment: The sponsor's decision not to deviate from the established GBCA dose of 0.1 mmol/kg for Phase 3 testing of supra-aortic and renal MRA is less than ideally supported but not unreasonable. The optimum dose for off-label MR brain perfusion imaging may be higher, meaning patients may be receiving large cumulative doses in the post-market setting if they undergo head and neck MRA and MR perfusion imaging together at the same visit. For context, the pre-clinical LD50 reported for Gadavist is 30 mmol/kg and the maximum reported human investigational dose is 0.5 mmol/kg (Staks 1994).

7.1.5. Onset, Duration, and Durability of Efficacy Effects

See Section 8.4.1 for discussion of contrast kinetic issues.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

See Section 8.4.1 for discussion of contrast kinetic issues.

7.2.2. Other Relevant Benefits

In general, diagnostic imaging drugs are used more broadly than their labeled indications because controlled trials tend toward closed-ended designs (Sn/Sp for patients with disease X), whereas many diagnostic questions are open-ended (what is disease X in this patient?). Thus, were the reasonable but unfeasible hypothesis of Gadavist-over-TOF superiority tested against the broad differential diagnosis of arterial disease (eg, traumatic dissection, subclavian steal syndrome, fibromuscular dysplasia, Henoch-Schonlein purpura, Kawasaki disease, etc.), true benefit may be greater than measure.

7.3. Integrated Assessment of Effectiveness

Table 24 provides a high-level integrated summary of the primary study-level results detailed in Tables 15 and 20.

Table 24 Reviewer's integrated tabulation of outcomes relative to win criteria

Green indicates win, red indicates loss, and yellow indicates win for relative performance but not minimum performance. Source: Tables 15 and 20 (note identical structure amenable to cell-by-cell comparison).

SUPRA-AORTIC ARTERIES			
	VISUALIZATION (%)	SENSITIVITY (%)	SPECIFICITY (%)
Majority	win	win	win
1	win	win	win
2	win	win	win
3	win	win	win
Site	win	win	win
RENAL ARTERIES			
	VISUALIZATION (%)	SENSITIVITY (%)	SPECIFICITY (%)
Majority	win	win+loss	win
1	win	loss	win
2	win	win+loss	win
3	win	win+loss	win
Site	win	win	win

See also Sections 1.3, 3.1, 4, 6.1.2, 6.2.2, and 7.1.

Reviewer Comment: 1) Improved visualization largely if not exclusively drives any conclusion that Gadavist is superior to TOF MRA. 2) Given the low sensitivity of Gadavist MRA, I recommend the following language be added as a new entry in labeling Section 5 Warnings and Precautions: "The performance of Gadavist MRA for detecting arterial segments with significant stenosis has not been shown to exceed 50%. A negative MRA study alone should not be used to rule out significant stenosis."

8 Review of Safety

8.1. Safety Review Approach

Gadavist has been marketed since 2000 outside and since 2011 inside the United States. In addition, Table 4 highlights that this will be the fourth time since our original NDA review in 2011 that the sponsor's integrated safety database has been updated and reviewed. Finally, Gadavist, like most diagnostic imaging drugs, is rarely studied within randomized, multi-armed, placebo-controlled trials, meaning many exploratory methods based on searching for differential adverse events between drug and placebo do not apply or require modification. In the interest of efficiency, I have thus omitted non-applicable sections of the of the safety review template designed for original, therapeutic NDA/BLAs. Instead, the focus of my safety review is three-fold:

- Comparison of new safety data from the supra-aortic and renal studies for consistency with known risks from investigational and post-marketing surveillance of Gadavist to date;
- Discussion of contrast kinetic uncertainty and potential for interchangeable use of Gadavist and 0.5M GBCAs in the post-market setting.
- Brief update on class-wide GBCA tissue deposition issue (TSI #1427), new compared to the last clinical efficacy supplement review of November, 2014, and oriented toward the question of Gadavist deposition.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

As of February 26, 2015, the sponsor reports that more than (b) (4) gadobutrol injections have been administered, including to 6809 subjects under investigational use of doses ranging from < 0.09 mmol/kg to 0.51 mmol/kg.

8.3. Safety Results

8.3.1. Deaths

The sponsor reports that one death occurred during the supra-aortic study over the maximum 13-day period of observation (indented text quoted from A535).

> There was one death in this study, subject 14607-18003-0127. A 69-year-old White male had a prior medical history of a stroke occurring on (b) (6), before entry into this study which was the basis for his inclusion. On (b) (6), the subject had an

> extension of the pre-existing stroke, resulting in a new cerebrovascular accident of severe intensity and death the following day, (b) (6). This serious adverse event was considered to be not related to study drug by the investigator.

The sponsor reports that no deaths occurred during the renal study.

The sponsor attributes up to 32 of 53 reports of death/fatal outcome that it has received since 1998 to anaphylactoid Gadavist reactions (indented text quoted from A362):

> Overall, the reporting rate of fatalities associated with possible anaphylactoid reactions to gadobutrol (32 in 24.1 million or 0.00013%/0.13 per 100,000 patients) falls within the range published for GBCAs and is consistent with the safety experience observed with Magnevist, the GBCA with the greatest safety experience, as well as with other GBCAs.

8.3.2. Treatment Emergent Adverse Events and Adverse Reactions

The sponsor coded adverse event terms using MedDRA version 17.0. I found no evidence that treatment emergent adverse events (TEAEs) or adverse reactions reported during the sponsor's MRA studies were any different or more frequent than those previously estimated (see Table 25):

Table 25 Sponsor's tabulation of common TEAEs

Source: A315.

Primary System Organ Class and Preferred Term	Gadobutrol Total	Gadobutrol Indication: CE-MRA
Number of subjects	**6809 (100%)**	**1548 (100%)**
Subjects with any TEAE	663 (9.7%)	135 (8.7%)
Total number of TEAEs	995	190
Gastrointestinal disorders		
Nausea	75 (1.1%)	16 (1.0%)
General disorders and administration site condition		
Feeling hot	26 (0.4%)	10 (0.6%)
Nervous system disorders		
Dizziness	34 (0.5%)	8 (0.5%)
Headache	100 (1.5%)	21 (1.4%)

The specific listings of reported adverse reactions during the supra-aortic and renal studies compared to the sponsor's overall investigational safety database are shown in Table 26.

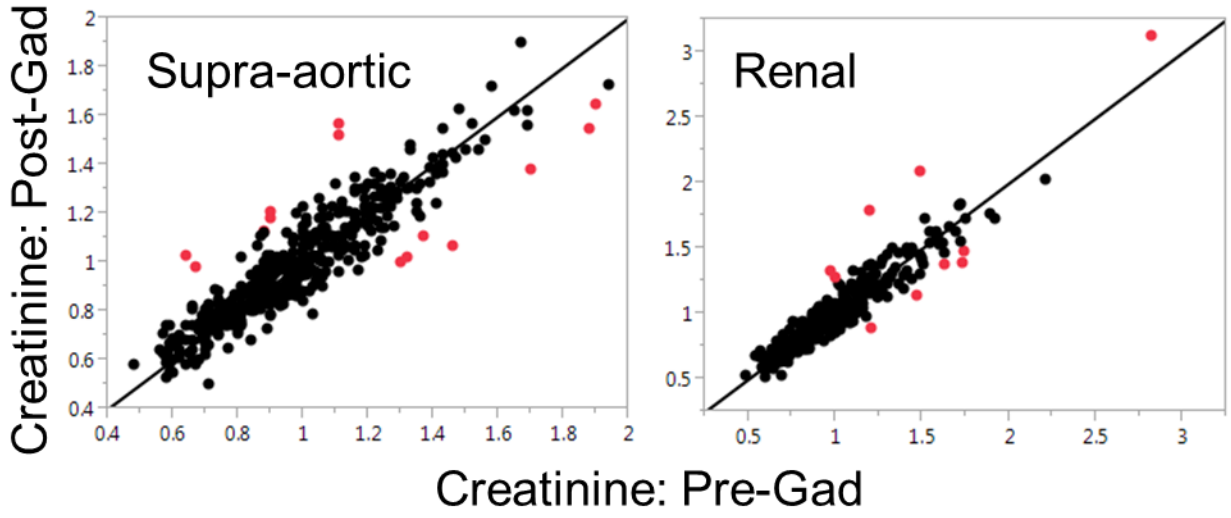
Table 26 Reviewer's tabulation of adverse drug reactions for Gadavist by study
Source: A320, A525, A1496

Database % of 6809	Supra-aortic % of 479	Renal % of 315
Headache 1.5	Creatinine↑ 0.6	Nausea 2.2
Nausea 1.1	Nausea 0.2	Rash 1.0
Dizziness 0.5	Vomiting 0.2	Urticaria 1.0
Dysgeusia 0.4	Feeling hot 0.2	Asthenopia 0.3
Feeling hot 0.4	Insulin decreased 0.2	Eye pain 0.3
Injection site 0.4	Phosphorus↑ 0.2	Upper abdominal pain 0.3
Vomiting 0.4	Urea↑ 0.2	Oral disorder 0.3
Rash 0.3	Headache 0.2	Vomiting 0.3
Pruritus 0.2	Throat irritation 0.2	Feeling hot 0.3
Erythema 0.2		Hypothermia
Anaphylactoid 0.1		Infusion related 0.3
Dyspnea 0.1		Dysgeusia 0.3
Paresthesia 0.1		Headache 0.3
		Loss of consciousness 0.3
		Paraesthesia 0.3
		Dysphonia 0.3
		Pruritus 0.3

Warning and Precaution 5.3 in Gadavist's current label reads, "In patients with chronic renal impairment, acute kidney injury sometimes requiring dialysis has been observed with the use of some GBCAs." To explore whether Gadavist may have caused creatinine to increase in patients in the supra-aortic and renal studies, most of whom had normal renal function, I compared pre- and post-contrast values (obtained at 24 hours in the supra-aortic study and 72 hours in the renal study) in Figure 16.

Figure 16 Reviewer's data visualization of creatinine in supra-aortic and renal studies

Each dot represents one patient exposed to Gadavist (N=464 and N=305, respectively). The unity lines represents where patients would fall if no change occurred between pre- and post-Gadavist creatinine. Red dots show patients in whom the difference between pre- and post-contrast creatinine was at least 0.25 mg/dL. Asymmetry above the line would suggest that Gadavist caused creatinine to increase. The graphs suggest symmetry. Source: LB_creat1199_creat928_0vs1464.jmp and LB_creat861_creat610_0vs3305.jmp.



Reviewer Comment: Compared to the established profile for Gadavist, I detected no new safety signal specific to Gadavist MRA, based both on the sponsor's integrated report of MRA studies and the patient-level data it submitted in support of its proposed MRA indication.

8.4. Analysis of Submission-Specific Safety Issues

8.4.1. Risk of suboptimal MRA with interchangeable use of Gadavist 1.0M and 0.5M GBCAs in the post-market setting

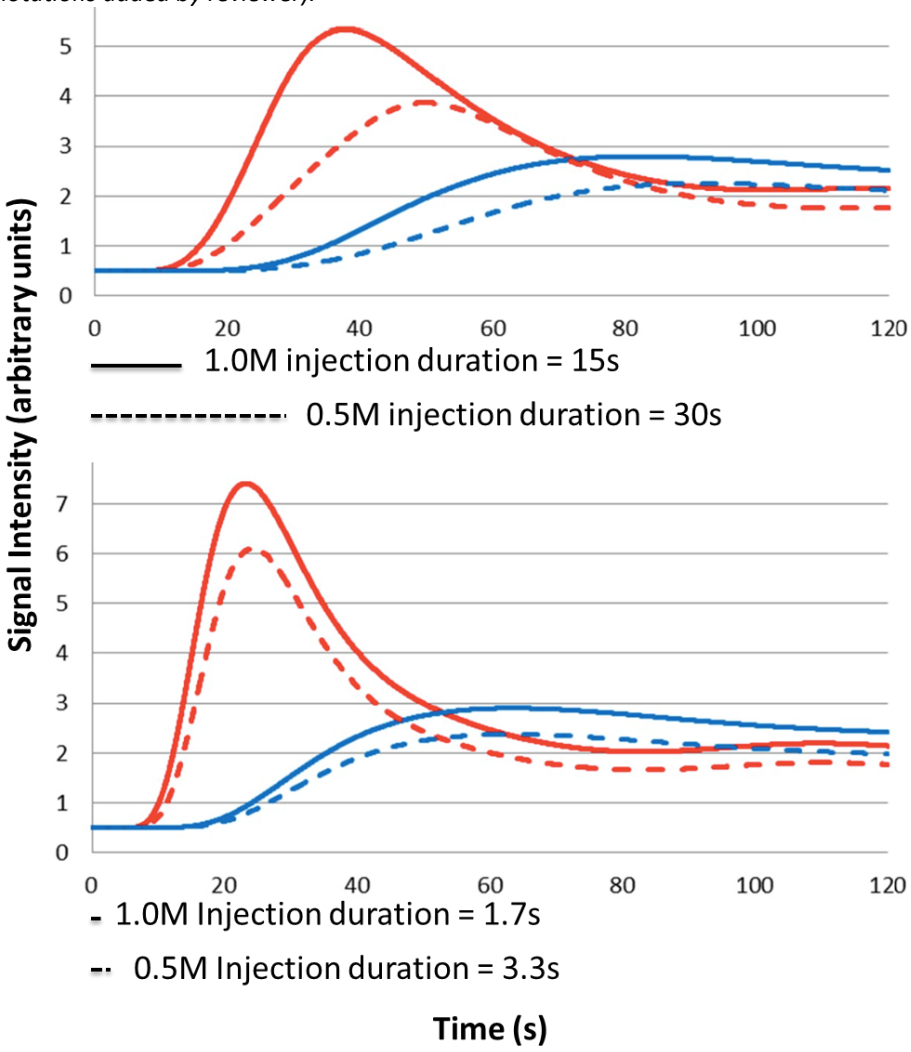
Imaging centers routinely maintain instructions so that technicians know what device software to run and in what order when providers refer patients for imaging, for example, by requesting "MRA head and neck with or without contrast." I refer to these as practice protocols (not to be confused with investigational protocols designed by study sponsors). GBCAs are not combination products, and practice protocols typically refer to GBCAs as a class (not to a particular agent). A natural question thus arises: What are the potential risks of using Gadavist and 0.5M GBCAs interchangeably for MRA in the post-market setting in the absence of contrast kinetic data for device operators to integrate into their reasoning about imaging duration?

In response to multiple information requests motivated by this question and an educationally oriented teleconference on February 12, 2016, the sponsor suggests potential risks are negligible. Figure 17 shows the basis for this position: time-intensity curves consistently both

taller and wider for Gadavist at full compared to half concentration, the latter representative of the concentration of other marketed GBCAs.

Figure 17 Sponsor's simulation of contrast kinetics for full vs. half-concentration Gadavist

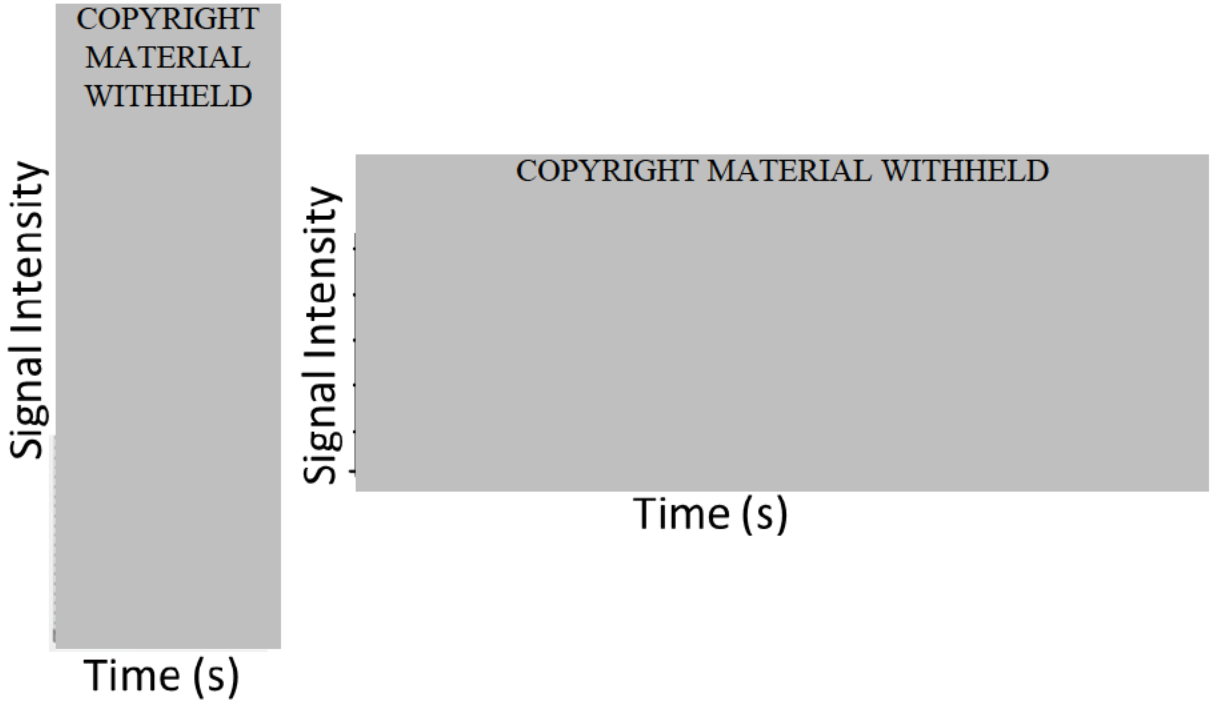
Curves represent simulated signal available for imaging in the carotid artery as a correlate of efficacy and a function of time (0=start of injection). Solid lines represent full concentration and dashed lines represent half concentration. Red lines represent arterial signal; blue lines, venous. Note that across both 0.5 mL/s (top) and 4.5 mL/s (bottom) rates of administration, the sponsor's curves suggest the following: 1) at the point of carotid imaging, the injected bolus is consistently mountain-shaped, 2) the full-concentration curve peaks at a higher signal intensity (compare heights of solid vs. dashed red curves), and 3) the duration of the full-concentration curve is longer (compare widths of solid vs. dashed red curves). Were empirical investigation to support these three hypotheses, I agree there would be negligible downside to potentially interchangeable use of Gadavist and 0.5M GBCAs for MRA in the post-market setting. Simulation parameters provided by sponsor: patient = 70-90 kg adult, intravascular volume = 6600 mL, circulation time (laminar flow) = 23-30s, cardiac output = 4.5 L/min. Source: A5497 (additional annotations added by reviewer).



Compare Figure 17, based on simulation, to the published empirical data shown in Figure 18.

Figure 18 Published contrast kinetics in relation to injection duration

Curves represent measured signal available for imaging in the lower extremity as a correlate of efficacy and function of time (0=start of injection) from two separate publications. Note how the shape of the curves change as function of injection duration. Specifically, the shape changes from mountain-shaped to box-shaped depending on whether injection duration exceeds ~25s. This concept of a temporal tipping point holds for both CT and MR contrast agents (see also Boos 2001, Bae 2003), presumably because the imaged bolus shape reflects a process of dilution from the edges (i.e., a box-shaped bolus becomes mountain-shaped when sufficient transit time has elapsed for the dilution process to reach the bolus center). In the figure on the right, where the curves are drawn on the same y-axis, also note that the area under the curves approach similarity (taller and thinner on the top vs. shorter and fatter on the bottom). Parameters. Left: Omnihance 0.1 mmol/kg, rate 3 mL/s (top), 1.5 mL/s (middle), and 0.5 mL/s (bottom). Right: Gadavist 10mL, rate 0.2 mL/s (bottom) and 0.4 mL/s top. Source: Carroll 2001 and Kramer 2007.



I highlight the following differences between the sponsor's simulated time-intensity curves (Figure 17) in comparison to measured time-intensity curves published in the literature (Figure 18) and the sponsor's marketing:

- The dependence of imaged bolus shape on injection duration is not reflected in the sponsor's simulations.
- Deviation from the reasonable hypothesis that area under the time intensity curve should be identical or nearly identical for dose-matched administrations is unexplained (see also Tombach 2003).
- Imaged bolus curves that are both taller and wider for simulated 1.0M compared to 0.5M Gadavist contradict, at the point of MRA imaging, the sponsor's current Section

12. (b) (4) abeling, “Compared to 0.5 molar gadolinium-based contrast agents, the higher concentration of Gadavist results in half the volume of administration and a more compact contrast bolus” (see Figure 19).

Expanding on the last bullet point, the sponsor’s online marketing illustrates this concept of a “more compact contrast bolus.”

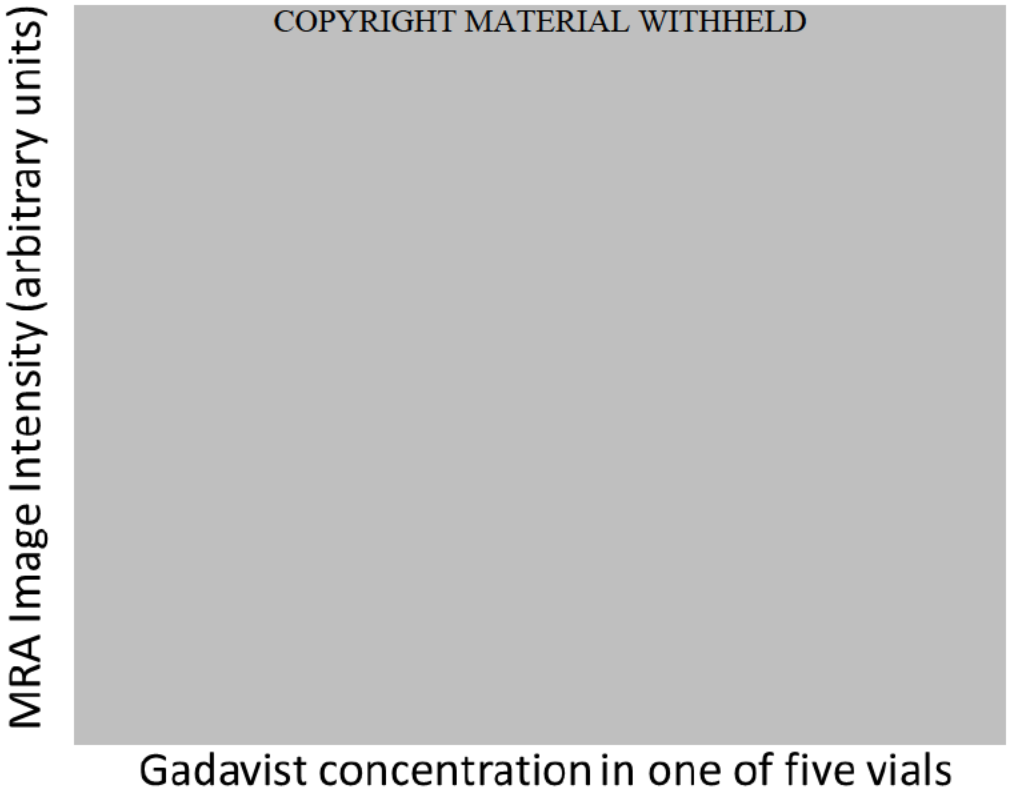
Figure 19 Sponsor’s Gadavist marketing: “double the concentration, half the volume”

Comparing this illustration to Figure 17, the upper vessel corresponds to the red solid curves and the lower vessel corresponds to the red dashed curves. Note the red solid curves are less compact (not more compact) than the dashed red curves. Source: https://www.radiologysolutions.bayer.com/products/mr/contrast/gadavist.

Finally, in its response to our information request dated Feb 24, 2016, the sponsor estimated without explanation that the maximum concentration of Gadavist at the point of MRA imaging is approximately 10 mmol/L. Figure 20 shows how this number compares to the concentration above which MRA likely becomes less effective.

Figure 20 Published in-vitro concentration-intensity curve for Gadavist

Above some concentration tipping point, image intensity decreases with increasing GBCA concentration, meaning dosing/administration beyond this tipping point would only add to the risk side of the drug's risk-benefit balance. Based on use of a 1.5T, time-resolved, MRA sequence in vitro, this figure shows that the concentration tipping point for Gadavist likely occurs at an arterial concentration between 20-50 mmol/L, above the 10 mmol/L upper limit the sponsor has suggested is likely in the post-market setting. An estimate for the concentration tipping point of 3T MRA remains unclear. Source: Kramer 2007.



Reviewer Comment: Time-intensity curves for Gadavist full- vs. half-concentration should be measured to confirm or clarify the sponsor's simulations and resolve the following safety question, "What are the potential risks of using Gadavist and 0.5M GBCAs interchangeably in the post-market setting in the absence of data for device operators to integrate into their calculation of imaging duration for Gadavist?". The outcome of such studies might inform additional labeling in Section 12 (b)(4); for example (new candidate language underlined with purely hypothetical values): "Compared to 0.5 molar gadolinium-based contrast agents, the higher concentration of Gadavist results in half the volume of administration and a more compact contrast bolus. For supra-aortic MRA imaging at 1.5T, and at a fixed injection rate of 1.5 mL/s following injection of Gadavist at full compared to half concentration in healthy volunteers, the imaged bolus was more compact insofar as the width of the time-intensity curve at half maximum was 20s shorter (CI95 15-25, 40s vs 52s) and the peak was 20% higher (CI95 15-25%, 4 vs. 4.8 arbitrary units)."

8.4.2. Nephrogenic systemic fibrosis (NSF) and chronic gadolinium deposition

Starting in 2007, and as revised in 2010, the labels for Gadavist (and other GBCAs Multihance, Prohance, Eovist, Ablavar, and Dotarem associated with NSF at a relatively lower rate) carry a boxed warning quoted in the following indented text:

> WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
> Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities.
>
> - The risk for NSF appears highest among patients with:
>   - Chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2)
>   - Acute kidney injury.
> - Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.

The labels for GBCAs associated with NSF at a relatively higher rate (Omniscan, Magnevist, and Optimark, also referred to as Group 1 agents) carry the following boxed warning (difference highlighted in italics):

> WARNING: NEPHROGENIC SYSTEMIC FIBROSIS (NSF)
> Gadolinium-based contrast agents (GBCAs) increase the risk for NSF among patients with impaired elimination of the drugs. Avoid use of GBCAs in these patients unless the diagnostic information is essential and not available with non-contrasted MRI or other modalities.
>
> - *Do not administer [Omniscan/Magnevist/Optimark] to patients with*:
>   - Chronic, severe kidney disease (GFR < 30 mL/min/1.73m^2)
>   - Acute kidney injury.
> - Screen patients for acute kidney injury and other conditions that may reduce renal function. For patients at risk for chronically reduced renal function (for example, age > 60 years, hypertension or diabetes), estimate the glomerular filtration rate (GFR) through laboratory testing.

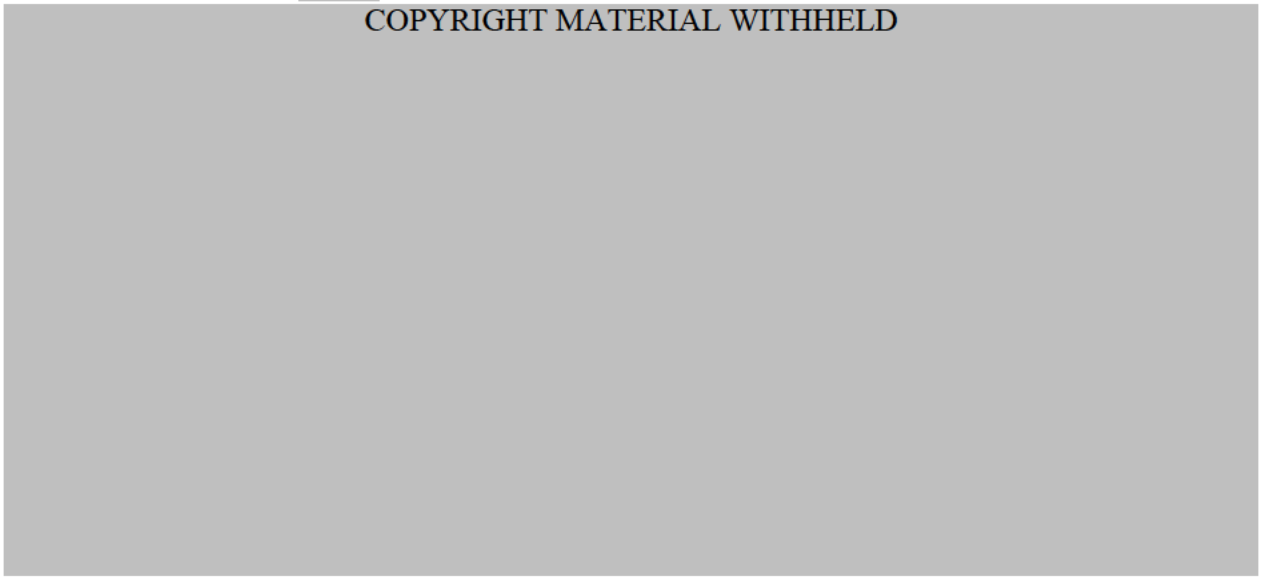
Note that in Europe, GBCAs are categorized into three groups: high-risk/group 1: Optimark, Omniscan, and Magnevist; medium-risk/group 2: Ablavar, Eovist, Multihance; and low-risk/group 3: Dotarem, ProHance, and Gadavist.

NSF is a rarely diagnosed disease (fewer than 1000 confirmed cases), indicating the presence of gadolinium deposits in the skin and body organs in association with debilitating and potentially fatal fibrosis. Interestingly, our first public health advisory on the subject in 2006 noted a linkage to off-label use for MRA in 25 patients with impaired renal function exposed to Omniscan: “The dose of gadolinium-containing contrast agent given to patients undergoing an MRA test is often higher (up to three times) than the approved dose for MRI” (FDA 2006). In our last drug safety communication on NSF in 2010, we noted, “NSF has not been reported in patients with normal kidney function” (FDA 2010).

In contrast, in 2009, in patients with normal renal function, Darrah and colleagues (2009) reported gadolinium levels up to 800 times higher in GBCA-exposed compared to unexposed post-arthroplasty bone specimens (exposure up to 8 years prior). In 2014, also in patients with normal renal function, Kanda and colleagues linked the MRI finding of dentate hyperintensity, previously misattributed to radiation or multiple sclerosis, to prior GBCA exposure (Kanda 2014). We issued a drug safety communication on the risk of brain deposits with repeated use of GBCAs on July 27, 2015 (FDA 2015). Finally, Murata and colleagues (in press) have reported on a preliminary investigation aiming to integrate across these concepts of NSF, bone deposition, and brain deposition. They have shown that microgram quantities of gadolinium are 1) higher than GBCA-unexposed control levels; 2) ~30x higher in bone compared to brain and strongly correlated; 3) likely at least an order of magnitude lower for Gadavist compared to Omniscan (a Group 1 agent; see Figure 21); and 4) potentially responsible for very rare reported cases of delayed NSF in patients whose renal failure antedated GBCA exposure.

Figure 21 Published association between Gadavist brain and bone deposition

The firgure on the left shows results from the use of inductively coupled plasma mass spectrometry (ICP-MS) in bone (rib cortex) and brain (globus pallidus shown; dentate levels highest) from 8 patients with normal renal function and a history of exposure to non-Group 1 GBCAs, including Gadavist, at autopsy. The inset on the right places the numbers shown on the y-axis of the grpah on the left in the context of Group 1 agents. In particular, the magnitude of deposition in the graph on the left is considerably smaller. (Note the comparison of Prohance to Omniscan reflects adjustment for total GBCA exposure and required retrospective comparison between unrelated autopsy studies (McDonald 2015). The temptation to rank agents in the graph on the left should be resisted given the very small convenience sample. I am confident, however, that Gadavist administration leads to more gadolinium deposition compared to unexposed controls based on convergent evidence from animal studies (for example, Robert 2015, IND (b) (4)). Source: Murata 2016.



The search for a threshold of gadolinium deposition associated with clinical meaningfulness in terms of total magnitude, chemical form, and localization is an area of active, ongoing investigation. Thus far, at this early stage of research, no specific linkage between deposition and risk has been identified, with the possible exception of a very small, theoretically increased risk of delayed NSF.

Reviewer Comment: The ideal imaging drug would be 100% excreted soon after imaging, so the growing evidence that microgram quantities of gadolinium accumulate indefinitely following GBCA administration in all patients certainly adds an unfavorable cloud of uncertainty around the use of this drug class. At present, this uncertainty is sufficient only to prompt further study and public safety communications. In the future, if gadolinium deposition is linked to a specific, clinically meaningful risk, preliminary evidence suggests the association with Gadavist will likely be greater than zero but lower compared to Group 1 agents.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was convened.

10 Labeling Recommendations

10.1. Prescribing Information

I have recommended the following changes relative to the sponsor's proposed labeling:

- Section 1.3: remove (b) (4) from indication statement, since these functions were neither tested nor supported by the sponsor's clinical development.
- Section 2.2: subdivide drug administration guidelines by indication to reflect difference in key parameters such as injection rate (see also Multihance label, A5459).
- Section 5.6: add warning and precaution for "Low Sensitivity for Significant Arterial Stenosis."
- Section 14.3: substantially rewrite MRA Clinical Studies section to focus discussion on pre-specified endpoints and post-hoc, clinically relevant findings regarding measurement variability (see A5468).

11 Risk Evaluation and Mitigation Strategies (REMS)

I have identified no need for a REMS recommendation with respect to this application.

12 Postmarketing Requirements and Commitments

For rationale, see Section 8.4.1.

I recommend that the following language be used to request a post-marketing commitment from the sponsor:

We have insufficient information to evaluate potential variation in the quality of Gadavist MRA of the supra-aortic and renal arteries in the post-market setting in which image acquisition protocols for Gadavist and other GBCAs may be used interchangeably. The prescribing information (Section 12 (b) (4)) states that: "Compared to 0.5 molar gadolinium-based contrast

agents, the higher concentration of Gadavist results in half the volume of administration and a more compact contrast bolus."
We therefore request that as a post marketing commitment you conduct a study to characterize time-intensity curves for Gadavist administered at the approved strength (1 M gadobutrol) and at half the strength (0.5 M gadobutrol) at the recommended dose of 0.1 mmol/kg and at injection rates representative of the range likely to be encountered in the post-market setting (note that for each full vs. half-strength comparison, the injection rate should be identical).

Please provide the following:

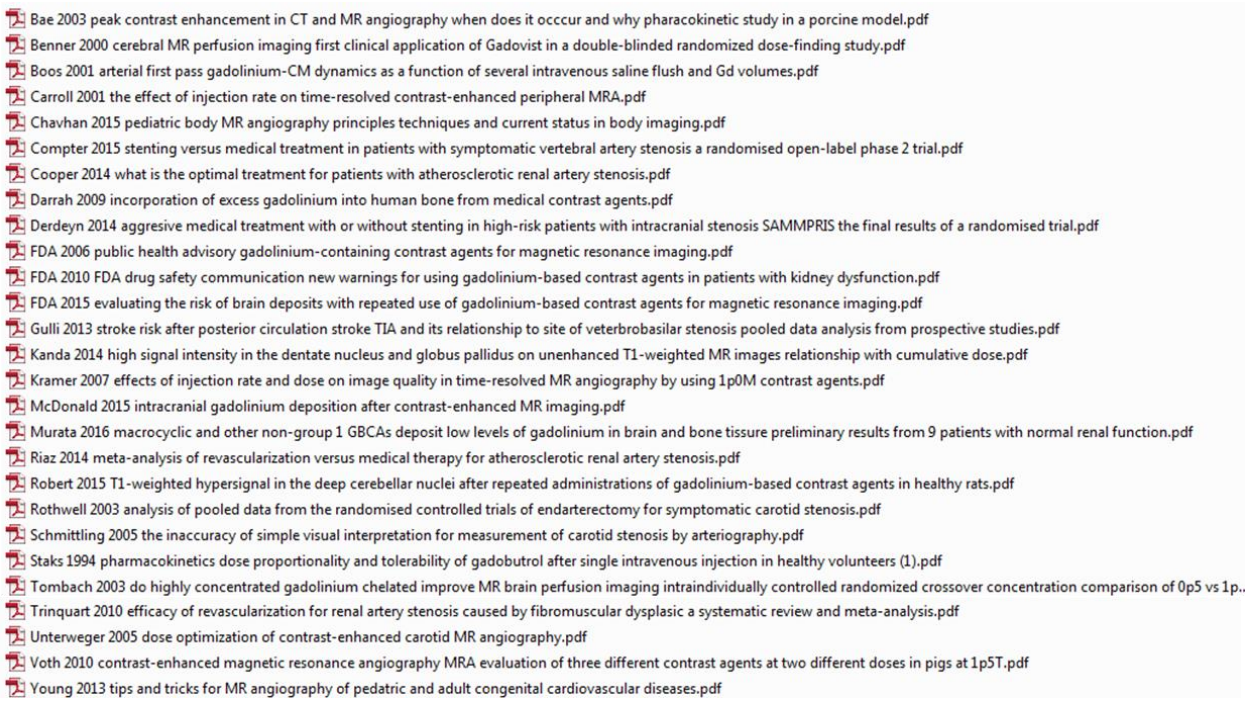
1. A protocol outline that includes the following comparisons of time-intensity curves for Gadavist full vs. half-strength.
   A. Difference in first-pass arterial time-intensity curve maximums.
   B. Difference in first-pass arterial time-intensity curve widths-at-half-maximum.
   C. Difference in first-pass arterial time-intensity curve widths-at-baseline.
   D. Difference in areas under the first-pass arterial time-intensity curve.

2. Estimate of number of subjects required to summarize the central tendency and spread of endpoints A-D. We refer you to the study by Tombach et al. 2003, in which time-intensity curves for Gadavist full vs half strength were compared for cerebral perfusion imaging.

3. Justification for extrapolating measurements in the internal carotid artery to the main renal artery or vice-versa or proposal for separate studies for each vascular territory.

13 Appendices

13.1. References



13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): GEMSAV and GRAMS

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 111		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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

/s/

ANTHONY F FOTENOS
03/24/2016
On leave starting 3/24@3:00p, back 3/29@6:30a

LIBERO L MARZELLA
03/28/2016
I concur with Dr. Fotenos' analyses and interpretation of the safety and efficacy data.