CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-191

Medical Review(s)

NOTE: A SEPARATE TEAM LEADER REVIEW WAS NOT WRITTEN. CONCURRENCE IS NOTED ON THE SIGNATURE PAGE.

Cycle #3: NDA 21-191 -- Imavist™ (AF0150 for injection) for suboptimal 2D-echocardiography
Sponsor: Alliance Pharmaceutical Corporation; San Diego, CA
Clinical Reviewer: Bernard W. Parker, MD

NDA 21-191: Imavist™
(AF0150; perflexane-phospholipid microbubbles) for injection

MANUFACTURERS: **Alliance Pharmaceutical Corporation**
San Diego, CA 92121

ABSTRACT

IMAVIST™ [AF0150 (perflexane-phospholipid microbubbles) for injection] is an intravenous ultrasound contrast agent developed by Alliance Pharmaceutical Corporation (San Diego, CA). AF0150 is a sterile, non-pyrogenic powder whose critical components include **perflexane**, a stabilizing gas diluted into N_2, and **dimyristoyl phosphatidylcholine (DMPC)**, a semi-synthetic phospholipid surfactant.

The trials were designed to demonstrate that, with improved endocardial border delineation (EBD), one may then be able to accurately determine both ejection fraction (EF; a primary endpoint) and/or the segmental wall motion (SWM; a secondary endpoint). The original overall recommendation (August 2000) was that this product might be approvable due to the significant improvement in the delineation the endocardial border in patients with stable cardiac disease [1]. Approval for EBD was contingent upon demonstration of a functional clinical utility – either improvement in the ability to accurately assess the EF and/or SWM. There was a lack of evidence of improvement in accurately determining the EF with Imavist™ in comparison to baseline 2D-echocardiograms, using radionuclide ventriculography (RVG; MUGA) as the gold standard to compare pre- and post-contrast 2D-echocardiograph (2D-echo) images. However, there was evidence of increased agreement amongst the 3 blinded readers on segmental wall assessments based on better segmental visibility. There was a suggestion of improvement in SWM assessments based on 26 patients who had MRI (gold standard) but no recommendations were made to further assess this functional endpoint. In addition, because of the small number of patients, no definitive conclusions could be drawn from the preliminary findings. Thus, efficacy for EBD as a primary endpoint had been demonstrated, but its value as a surrogate for clinical relevant information in fact was not established. A re-read of the EBD data at end-systole and at end-diastole, as well as a blinded-reader EF calculation, was requested by the Division.

The sponsor responded by proposing the indication of improving EBD alone, with the rationale that the structural indication alone (EBD) has clinical application within the realm of diagnostic cardiology due to an association with a functional aspect (SWM) as demonstrated with the small sample from the study population. The sponsor felt that the EF endpoint had not been proven and therefore EF needed to be removed from consideration as a functional corollary. The sponsor then reiterated this issue for border

[1] The patient population studied were adults (≥ 18 years of age) in normal sinus rhythm (≤ 6 ectopic beats/minute), who had suboptimal echocardiograms performed demonstrating ejection fractions ≥ 20% (without cardiac shunts or moderate-to-severe valve disease). "Suboptimal" here was defined as poor visualization of 2 to 9 segmental fields in 2-D echocardiography, using apical 4- and 2-chamber views; therefore, 12 segments (not the customary 16 segments) were viewed.

alone by referencing another microbubble contrast agent, Optison®, approved based upon EBD without a functional corollary.[2] In this context, the regulatory changes due to evolving science were not acknowledged by the sponsor. Since Imavist™ did not prospectively evaluate the appropriate patient population (those with shunts, valve disease, etc.), approval based on a structural indication (i.e. EBD alone) was not justified.

Cycle #2: Reanalysis of the data during the 2nd cycle demonstrated that comparisons of 2D-echocardiographic data with MRI had failed to demonstrate an improvement in the ability to correctly assess both for general and for specific types of abnormal segmental wall motion. There were no inter-reader analyses of the variability between segments. Additionally, there remained the issue of deleting subjects with EBD scores of either 0 (no delineation) or 1 (mild-to-fair delineation). The number of subjects tested with MRI to demonstrate a trend toward the improvement of AF0150-contrasted 2D-echo evaluation for SWM was too small, particularly since the focus was upon SWM (a secondary endpoint) instead of EF (a primary endpoint) and selected from only one site. Finally, the sponsor needed to discuss the reason and method (i.e. random) for selecting the small number of patients who underwent MRI.

The newly submitted Integrated Safety Summary (ISS) demonstrated no change in the adverse events (AE's) since completion of the 3 additional studies which were ongoing during review of the primary NDA. Each of the 3 studies involved single doses of AF0150 greater than the proposed single dose of 0.125 mg/kg. One of the 3 studies ( ) was actually discontinued; the sponsor did not address reasons for its discontinuation.

Cycle #3: Reanalysis of the data during the 3rd cycle demonstrated an improvement in the ability to correctly assess for normalcy of SWM post-contrast when (1) contiguous segments are evaluated and (2) if patients can then be grouped based upon normalcy of the post-contrast 2D-echo results. Again, the number evaluated is small to be robust enough for an approval.

The safety update focused upon (1) additional data from 3 ongoing studies (whose doses were not comparable to the proposed clinical dose); (2) safety using the proposed clinical dose of Imavist™ in chronic obstructive pulmonary disease (COPD) patients enrolled in the studies; and (3) additional QTc interval data from all other ongoing and investigator studies. There appeared to be trend toward reversible QTc prolongation among patients with coronary artery disease, without concomitant cardio-respiratory adverse events or changes in oxygen saturation. COPD patients given AF0150 had a greater percentage of patients with headache and nausea than both COPD patients given saline and non-COPD patients given AF0150.

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[2] Optison® (human albumin microspheres; FS069) was approved in December 1997 for "patients with suboptimal echocardiograms to opacify the left ventricle and to improve the delineation of the left ventricular borders."

BACKGROUND (REGULATORY HISTORY)

I. Cycle #1: Review of the Original NDA

[redacted]

The sponsor decided [redacted] and has withdrawn this claim.

II. Segmental Wall Motion Assessments (from the Original NDA Review)

A secondary endpoint, assessment of segmental wall motion (SWM), appeared to show a statistically significant improvement in inter-reader agreement when using AF0150, as compared to baseline non-contrast poorly visualized echocardiograms. However, only 26 patients were evaluated with MRI. This number was considered to be too small upon which any conclusion could be drawn.

Safety issues were identified that included concerns which were non-clinical. Chemistry issues involved concerns about the particle (microbubble) size, particularly the upper range, and requests were made about CMC specification of the upper particle size limits. The toxicology issues involved suggestions of a micro-circulation study, as well as a chronic pulmonary hypertension animal model study. Finally, clinical concerns involved evaluation for QTc interval prolongation post-Imavist™ (noted in 77 patients or17%of patients enrolled in the Phase 3 studies), and an update of the integrated summary of safety, which did not include data from ongoing studies. Particularly of concern was QTc data monitoring in an ongoing Phase 2 multi-center study, detecting coronary artery disease in myocardial contrast studies.

III. Responses by Alliance

An industry meeting held Nov. 3, 2000 was a preliminary attempt by the sponsor to address the issues raised in the action letter. Four additional teleconferences were focused upon discussions on the relationships between EBD (a structural endpoint) and [redacted] and SWM (functional endpoints). Again, the sponsor did not want to pursue [redacted] but SWM data was requested by the Division with any literature support to seek for a "trend" between EBD and SWM. However, the division stated that either the action letter be followed regarding the [redacted] or a new option: Segmental wall motion may be re-assessed with radionuclide ventriculography (RVG) as the standard of truth since there were only 26 patients with MRI, in demonstrating the accuracy of the

SWM assessments with 2D-echo. The sponsor did not send any data demonstrating any relationship between 2D-echo SWM readings compared with RVG.

The division suggested that, if re-reading the [redacted] is still considered not feasible by the sponsor, then the SWM 2D-echo results could be compared with the RVG results. The sponsor stated that re-reading for [redacted] SWM would be too problematic, but that SWM could be reassessed on the 26 patients who had MRI performed.

The teleconference from Dec, 18, 2000 led to the current submission (initially sent as a correspondence on Feb. 5, 2001), consisting of previously reviewed data and newly submitted articles. Essentially, the teleconference focused upon guidelines which stated that data derived from peer-reviewed literature which can be used serve to support the approval of a product.[3] All articles are listed and discussed in the Literature Review subsection of the Efficacy Review section.

In addition, responses to clinical issues identified previously in the action letter pertaining to the following disciplines were submitted by the sponsor:

1. Chemistry, manufacturing, and controls (CMC)
2. Pharmacology (pre-clinical) and toxicology
3. Clinical pharmacology (pharmacokinetics)

IV. Cycle #2 Review

The data appeared to illustrate a trend in that an improvement in EBD scores led to improved SWM scores. However, closer analyses of the SWM data did not support that Imavist™ has the ability to improve the assessment of SWM in post-contrast 2D-echo readings.

1. EBD is visually improved with Imavist™.
2. The noted improvement in the SWM agreement is restricted by the lack of a truth standard and inferences that one can draw from the correlation data with MRI are further confounded by:
   a) Small sample size and concerns about the selection process and methodology of the 26 patients.
   b) None of the suboptimal segments were evaluated (although the package insert specifically calls for a suboptimal indication).
   c) Imavist™ identified more normals compared to baseline (unenhanced) images where truth standard indicated "normal". The clinical significance of this is yet to be established.
   d) Of concern, Imavist™ failed to identify abnormal images compared to baseline (i.e. performing inferiorly compared with baseline) when the truth standard indicated "abnormality".
   e) There was no statistical significance that was demonstrated.
3. The literature provided by the sponsor was not supportive.

[3] From "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", US DHHS, FDA, May 1998, clinical 6.

Overall, the efficacy of Imavist™ had not been established, and the agency recommended additional study(s) where a larger number of patients with a similar profile as in the pivotal studies can be evaluated for both EBD and SWM. Such a prospectively designed study could determine the ability of Imavist™-enhanced 2D-echo images to correctly assess for SWM in comparison with MRI as the truth standard. From the safety review, the agency recommended the sponsor to provide data (QTc intervals) from the ongoing study, to provide a new study for evaluating patients with high-risk pulmonary diseases, and submission of additional information regarding QTc interval monitoring in all ongoing studies.

V. Responses by Alliance

The sponsor responded with the following hard-copy files –

Document ID	Correspondence Date	Date of Receipt	Description
N-000-B2	12-Feb-2002	14-Feb-2002	Discussion of key points noted within the approvable action letter.
N-000-MR	05-Mar-2002	06-Mar-2002	Briefing document for March 12, 2002 industry meeting with Alliance.
N-000-C	07-Mar-2002	11-Mar-2002	Response by Alliance to the FDA's response to the briefing document.
N-00-BZ*	15-Mar-2002	19-Mar-2002	Response by Alliance to the FDA's request for information regarding a proposed pediatric plan and analyses of patients with obstructive pulmonary disease and pharmacokinetics.
N-000-BM*	19-Mar-2002	21-Mar-2002	Post-industry meeting response by Alliance to the FDA's requests – specifically focusing upon the new efficacy analyses proposed by Alliance.
N-000-BM*	02-Apr-2002	14-Apr-2002	An update of the plans for efficacy analyses proposed by Alliance.

* The information in these submissions were repeated in this NDA's Cycle 3 submission.

This review cycle of NDA 21-191 focuses upon reviewing the data from the 26 patients in a similar way as a previously approved microbubble agent: By evaluating segments as adjacent or contiguous segments in order to demonstrate the correct assessment for SWM. Additional data included in this submission are chemistry, manufacturing and controls (CMC), a preclinical toxicology study, and a proposed pediatric study.

EFFICACY REVIEW

The sponsor has re-analyzed the Phase 3 studies for segmental wall motion (SWM) in order to comply with the Agency's request to demonstrate the clinical utility of Imavist™ (AF0150) as an ultrasound microbubble contrast agent for two-dimensional echocardiography (2D-echo). The analysis that will be focused upon by the Agency will be the demonstration of an improvement in the ability to correctly assess SWM in subjects who had suboptimal 2D-echo and therefore differentiate patients with normal SWM from those with any evidence of SWM abnormalities. "Suboptimal" was defined within the original NDA as having 2 - 9 segments poorly visualized in the apical 4- and 2-chamber views of a baseline 2D-echo. These patients also had to have ≥ 1 segment visualized in both views for an estimate of the ejection fraction to be made.

For this Cycle #3 of the NDA, in order to demonstrate improvement in the correct assessment of SWM, there are 2 criteria that must be fulfilled:

1. There must be ≥ 2 ***adjacent*** (or contiguous) segments considered suboptimal. The sponsor agreed to demonstrate the conversion of non-evaluable views (defined as ≥ 2 adjacent suboptimal segments per view) into evaluable views.
2. Magnetic resonance imaging must serve as the standard of truth to compare with the non-contrast (baseline) and contrast (AF0150) 2D-echo readings.

The methodology proposed by the sponsor would help to demonstrate an improvement both by cardiac view and by subject (patient).

CARDIAC VIEW ANALYSES

Method:

The MRI subgroup was evaluated for AF0150-conversion from non-evaluable to evaluable.[4] Afterwards, that evaluable group and the whole MRI subgroup were investigated separately to determine accuracy of SWM diagnosis in comparison to MRI. The sponsor stated that the criterion for success for this analysis would be a ≥ 30% conversion of cardiac views from non-evaluable to evaluable. Afterwards, for all segments of the post-AF0150 within both (1) the "converted" images and (2) all images of the contiguous segments, concordance with MRI for SWM is to be "within the range"[5] of that for the evaluable segments in the non-contrast (baseline) views.

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[4] A "non-evaluable" cardiac view was defined as the presence of ≥ 2 adjacent segments considered suboptimal (an endocardial border delineation [EBD] score of either 0 or 1). An "evaluable" cardiac view was defined as no adjacent suboptimal segments within a cardiac view; thus, each segment constituting a part of an image of contiguous (or adjacent) segments must have an EBD score of 2 or 3; see Table 1 below for EBD scoring.

[5] Defined as % SWM agreement between MRI and post-AF0150 2D-echo for all segments being greater than (or, if not, then within 10% below) the same between MRI and baseline for at least 2 out of 3 blinded readers.

There are 36 different combinations of "adjacent segments" possible for evaluation for this protocol (see Table 2). The sponsor also subdivided the subjects into "normal" and "abnormal" populations based upon finding either normal (SWM score of 1) or any wall motion abnormality (SWM score 2 to 5) in the MRI examination. See Table 1 below with the previous and new definitions proposed by the sponsor for this cycle.) The analyses suggested by the sponsor were devised to distinguish normal cardiac views from abnormal cardiac views.

TABLE 1
PHASE 3 PROTOCOLS – SEGMENTAL WALL MOTION DEFINITIONS‡

Segmental Wall Motion (SWM)			Endocardial Border Delineation (EBD)	
Old Definition	**New Definition**	**Score**	**Score**	**Definition**
SUBOPTIMAL				
Not visualized	Cannot assess for cardiac function	**0**	**0 to 1**	No or mild-to-fair delineation (inadequate to assess function)
OPTIMAL				
"Normal"			**2 to 3**	Moderate-to-good or excellent delineation (able to assess function)
• **Normal**	Normal function	**1**		
"Abnormal"				
• **Hypokinesis**	Mild or moderately impaired function	**2**		
• **Akinesis**		**3**		
• **Dyskinesis**	Severely impaired cardiac function	**4**		
• **Aneurysmal**		**5**		
OTHER				
Cardiac view was unavailable		**N**	**N**	No view for the segment

‡ The definitions are based upon the recommendations by the American Society of Echocardiography for assessing regional cardiac function using 2D-echo; the greater the deviation from the score of 1, the worse the regional contraction abnormality. [Katz AS et al; "Chapter 27: Echocardiographic Assessment of Ventricular Systolic Function", pp 297 – 324. In **Marcus Cardiac Imaging, 2nd Edition** (1996), ed. Skorton, DJ.]

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TABLE 2: The Possible Combinations of Adjacent Segments

APICAL 4-CHAMBER: Total Combinations = 15 per patient				
1,2	1,2,3	1,2,3,4	1,2,3,4,5	1,2,3,4,5,6
	2,3	2,3,4	2,3,4,5	2,3,4,5,6
		3,4	3,4,5	3,4,5,6
			4,5	4,5,6
				5,6
APICAL 2-CHAMBER: Total Combinations = 15 per patient				
7,8	7,8,9	7,8,9,10	7,8,9,10,11	7,8,9,10,11,12
	8,9	8,9,10	8,9,10,11	8,9,10,11,12
		9,10	9,10,11	9,10,11,12
			10,11	10,11,12
				11,12
APICAL LONG AXIS: Total Combinations = 6 per patient				
13,14	13,14,15	13,14,15,16		
	14,15	14,15,16		
		15,16		

Results:

1. Conversion from Non-evaluable status to Evaluable (Improved EBD)

First, the sponsor focused upon improving from non-evaluable to evaluable images. "*Evaluable*" was stringently defined as all segments – contiguous or separate – having an EBD score of 2 or 3. This analysis is analogous to the demonstration of an improvement in EBD in previous cycles of this NDA. The sponsor provided tabulated results, FAX'ed April 18, 2002 (after the submission of Cycle #3), of the percentage of ***adjacent*** segments which converted from non-evaluable to evaluable.

TABLE 3(a): IMUS-008 (N = 26)
% of Cardiac View Conversion From Non-evaluable to Evaluable

	READER 1		READER 2		READER 3	
Views	**% converted**	**n of N**	**% converted**	**n of N**	**% converted**	**n of N**
Apical 4-Chamber View						
Normal	69%	11 of 16	67%	10 of 15	94%	15 of 16
Abnormal	44%	4 of 9	25%	2 of 8	67%	6 of 9
Total	60%	15 of 25	52%	12 of 23	84%	21 of 25
Apical 2-Chamber View						
Normal	50%	7 of 14	31%	4 of 13	61%	8 of 13
Abnormal	22%	2 of 9	20%	2 of 10	60%	6 of 10
Total	39%	9 of 23	26%	6 of 23	61%	14 of 23
Apical Long Axis View						
Normal	48%	11 of 23	46%	11 of 24	77%	17 of 22
Abnormal	100%	2 of 2	0%	0 of 1	0%	0 of 0
Total	52%	13 of 25	44%	11 of 25	77%	17 of 22

Data from Table 1.1a, labeled "Fraction of Cardiac Views for which EBD converted ..."

The most improvement in visualizing the adjacent segments was noted in the apical 4-chamber view for all 3 readers. Also, there was a greater "EBD" improvement in normal adjacent segments compared with the abnormal adjacent segments. For the abnormal contiguous segments, the increase in the number of evaluable contiguous segments was further assessed. Of note, the least improvement post-contrast was noted in the apical 2-chamber view, particularly segments 10 – 12, which visualizes the anterior wall, vascularized by the left anterior descending (LAD) coronary artery. Thus, patients with coronary artery disease involving this main coronary artery who have poorly visualized 2D-echo's at baseline may not have an improvement in the ability to assess that wall with AF0150.

Tables 3(a) and 3(b) demonstrate Reader 2 and Reader 3 having (respectively) the least and best improvement in the percentage of adjacent segments converting to the "evaluable" status. As mentioned in the agency's original clinical review of NDA 21-191, this may represent either biasness or overzealousness on the part of Reader 3.

TABLE 3(b): IMUS-008
All Cardiac Views Converted From Non-evaluable to Evaluable

	Reader 1		Reader 2		Reader 3	
View	**% converted**	**n of N**	**% converted**	**n of N**	**% converted**	**n of N**
Normal	55%	29 of 53	48%	25 of 52	78%	40 of 53
Abnormal	40%	8 of 20	21%	4 of 19	63%	12 of 19
Total	51%	37 of 73	41%	29 of 71	74%	52 of 70

Data from Table 1.1a, labeled "Fraction of Cardiac Views for which EBD converted ..."

2. SWM Analyses of Contiguous and Separate Evaluable Segment vs MRI standard
The sponsor provided data to demonstrate an improvement in the ability to correctly assess for SWM to distinguish normal from abnormal motion based upon the cardiac views, and also distinguishing patients who may have normal regional cardiac function versus those who do not have normal regional cardiac function. After review of the data by the sponsor, the agency's statistical reviewer developed a second analysis which could descriptively determine the significance of the results.

Tables 4(a) and 4(b) summarizes all the data provided by the sponsor in a FAX'ed message dated April 18, 2002, which was sent in response to the agency statistician who stated that the data provided in the submission did not adequately address the agency concerns. These tables were made to demonstrate the percentage of images, whether of ***contiguous*** (Table 4[a]) or of ***single*** (Table 4[b]) segments, which agree with the MRI results; the data was subdivided to evaluate normal versus abnormal images (but ***not*** further defining ***the type*** of abnormality). Each table actually demonstrates 2 subanalyses – (1) an analysis of *evaluable* images, and (2) an analysis of *all* images. These tables provide all-inclusive data based upon analyses of each of the 3 separate cardiac views, provided in the Appendix of this review.

What is observed in each table is an overall increase in the number of evaluable images, both contiguously and separately. Along with this is an increase in the number of correctly-assessed evaluable images of contiguous and separate segments. However, the highlighted numbers in both tables demonstrate instances where, despite an overall increase in the ***number*** of correctly-assessed contiguous images, there was an overall **decrease** (one was no change) in the ***percentage*** of correctly-assessed images (note Reader 2 and Reader 3). Additionally, in the sub-analysis evaluating only the ***evaluable*** images of *contiguous segments*, the percentage increase of correctly-assessed images post-AF0150 is considerably lesser than all of the other sub-analyses. Finally, the percentage of correctly-assessed abnormal (i.e. having at least one abnormal segment) images for either contiguous or single segments was much lower than that for normal. Nevertheless, **there was an overall improvement for post-AF0150 images in correctly distinguishing normal from abnormal SWM by cardiac view for both contiguous and separate segmental imaging.**

TABLE 4(a): IMUS-008 (N = 26); Contiguous Segmental Images
% Agreement of SWM 2D-Echo versus MRI Results, All Cardiac Views Combined*

	Reader 1				Reader 2				Reader 3			
Views	**Baseline**		**Contrast**		**Baseline**		**Contrast**		**Baseline**		**Contrast**	
	%	#/ total	%	#/ total	%	#/total	%	#/ total	%	#/ total	%	#/ total
All *Evaluable* Contiguous Segmental Images												
Normal	71%	22/31	79%	114/145	73%	16/22	84%	94/112	65%	26/40	86%	171/199
Abnormal	36%	4/11	37%	14/38	**40%**	2/5	**40%**	8/20	**63%**	12/19	**52%**	36/69
Total	62%	26/42	70%	128/183	67%	18/27	77%	102/132	64%	38/59	77%	207/268
All Contiguous Segmental Images												
Normal	14%	22/152	75%	114/152	12%	16/128	73%	94/128	13%	26/206	83%	171/206
Abnormal	9%	4/44	32%	14/44	8%	2/24	33%	8/24	17%	12/72	50%	36/72
Total	13%	26/196	65%	128/196	12%	18/152	67%	102/152	14%	38/278	74%	207/278

* See Appendix: Tables 17(a) and (b) - "% Agreement of SWM ..." for analyses of specific cardiac views.

TABLE 4(b): IMUS-008 (N = 26); Separate Segments
% Agreement of SWM 2D-Echo versus MRI Results, All Cardiac Views Combined*

	Reader 1				Reader 2				Reader 3			
Views	**Baseline**		**Contrast**		**Baseline**		**Contrast**		**Baseline**		**Contrast**	
	%	#/ total	%	#/ total	%	#/total	%	#/ total	%	#/ total	%	#/ total
Evaluable (Separate) Segments												
Normal	59%	40/68	80%	149/187	69%	44/64	84%	138/165	63%	54/85	81%	212/261
Abnormal	35%	12/34	35%	22/63	**52%**	15/29	**44%**	24/54	**50%**	20/40	**47%**	45/95
Total	51%	52/102	68%	171/250	63%	59/93	74%	162/219	59%	74/125	72%	257/356
All (Separate) Segments												
Nml= 294	14%	40	51%	149	15%	44	47%	138	18%	54	72%	232
Abn= 122	10%	12	18%	22	12%	15	20%	24	16%	20	37%	45
Tot.= 416	12%	52	41%	171	14%	59	39%	162	18%	74	62%	257

* See Appendix: Tables 18(a) and (b) - "% Agreement of SWM ..." for analyses of specific cardiac views.

SUBJECT (PATIENT) ANALYSES

Method:

The MRI patients were determined to either have normal regional cardiac function (and therefore labeled as "normal") based upon no SWM abnormalities noted by MRI, or otherwise having abnormal cardiac function (patients labeled as "abnormal"). After review of the baseline and post-AF0150 images of these subjects, the subjects were then labeled as either non-evaluable or evaluable.[6] Alliance discussed in text that this section would be successfully demonstrated by having a conversion of ≥ 40% of subjects converting from a "non-evaluable" status to an "evaluable" status.

The reviewers (clinical and statistical) then reviewed the data to determine whether AF0150 use was beneficial or detrimental as an ultrasound contrast agent for subjects with suboptimal baseline 2D-echo images in determining whether a patient is correctly diagnosed as being labeled as having either "normal" or "abnormal" SWM. This determination was compared with the determination of "normal" vs. "abnormal" using the non-contrast, suboptimal baseline images, with MRI as the standard of truth. Images not visualized (EBD scores of 0 to 1) were not assessed for SWM.

Results:

1. Conversion from Non-evaluable status to Evaluable (Improved EBD)

The next table, provided by the submission, illustrates the percentage of patients who converted from "not evaluable" status to "evaluable" in order to proceed with the final analysis of correct identification of normal patients.

TABLE 5: IMUS-008 (N = 26)
Subject (Patient) Conversion From Non-evaluable to Evaluable

	READER 1		READER 2		READER 3	
	# converted	% of N	# converted	% of N	# converted	% of N
Normal	6	54% of 11	6	60% of 10	10	91% of 11
Abnormal	7	50% of 14	4	31% of 13	9	69% of 13
Total	13	52% of 25	10	43% of 23	19	79% of 24

Data from Vol. 1, p 01-042: Table 1.2, labeled "Fraction of *Subjects* for which EBD converted ..."

The consistency in data here is that, again, Readers #2 and #3 have, respectfully, the least and most favorable results. Reader #2 has the lowest (43%) percentage of patients who converted into evaluable, which stems from the low percentage (31%) of patients who

[6] A "non-evaluable" patient was defined as a patient who had ≥ 2 (out of 3) cardiac views considered non-evaluable. The sponsor has agreed to determine the number of such "non-evaluable" subjects who convert into an "evaluable" status. An "evaluable" status was defined as having ≤ 1 (out of 3) cardiac views considered as non-evaluable. Such a definition was considered by the sponsor to be acceptable because "it would allow representative assessment of all the coronary territories typically examined in a cardiac wall motion study".

were diagnosed as having abnormal MRI results. The other 2 readers also experienced a lowering of the total percentage of evaluble patients post-contrast due to the low percentage conversion to evaluable among the abnormal patients.

2. Correct Identification of Subjects with Normal 2D-echo Results

The statistical reviewer of the agency provided the following data to descriptively analyze the accuracy of distinguishing patients with normal cardiac function from patients with any abnormality, as imaged post-contrast and confirmed by MRI. Each reviewer will have a separate analysis. Within the table below, the final analysis will be upon the results of all the views combined (separate view results also provided in the table below).

TABLE 6: IMUS-008 (N = 26)
No. of Correctly Diagnosed (vs. Incorrectly Diagnosed) Patients by Cardiac View

		Reader 1		Reader 2		Reader 3	
		Baseline (Non-Contrast)					
	Views	Correct	Wrong	Correct	Wrong	Correct	Wrong
Post-Contrast (Imavist™)	**Apical 4-Chamber View**						
	Correct	2	**9**	3	**4**	6	**6**
	Wrong	*1*	14	*2*	17	*1*	13
	Apical 2-Chamber View						
	Correct	6	**6**	4	**1**	6	**11**
	Wrong	*1*	13	*1*	20	*0*	9
	Apical Long Axis View						
	Correct	1	**8**	1	**6**	2	**12**
	Wrong	*0*	17	*0*	18	*0*	12
	★All Views Combined★						
	Correct	7	**6**	5	**1**	8	**5**
	Wrong	*2*	10	*3*	17	*1*	11

Data is derived from the statistical reviewer. Read text below for explanations of bolded and italicized numbers.

Bolded numbers above represent the number of patients who clearly benefited from AF0150 use, with a conversion from a wrong diagnosis at baseline (non-contrast) to a correct diagnosis post-AF0150 (using MRI as the standard of truth). Italicized numbers

represent the number of patients where AF0150 use proved to be detrimental by incorrectly diagnosing patients with normal and abnormal SWM, in comparison to diagnosing using the "suboptimal" baseline images.

Under the "All Views Combined" subsection tabulated above, Readers 1, 2 and 3 experienced 23% (6 patients), 8% (= 1 patient) and 19% (5 patients) increases, respectively, in correctly evaluating patients post-AF0150 with 2D-echo as having either normal or abnormal SWM. However, for each respective reader, there was an 8% (2 patients), 11% (3 patients), and 4 % (1 patient) incorrect interpretation by 2D-echo after AF0150 usage, in comparison to the baseline 2D-echo. The results from Reader #2 demonstrates the greatest problem in the demonstration of efficacy with 8% of patients benefiting from AF0150 use, when also considering its 11% of patients experiencing detrimental results following use of AF0150. This is to say that the same 11% of patients were correctly identified as having either normal or abnormal SWM with the suboptimal baseline images -- without contrast. When considering canceling the percentage of subjects who similarly experienced a disadvantage from AF0150 use by each of the other readers, approximately 15% of all 26 subjects demonstrated a benefit from AF0150 use for Readers #1 and #3.

EFFICACY CONCLUSION:

1. CARDIAC VIEW ANALYSES:

An overall increase in the number of evaluable images (contiguous and separate) and an increase in the number of correctly-assessed evaluable images of contiguous and separate segments had been demonstrated. Thus, **AF0150 led to an overall improvement in correctly distinguishing normal from abnormal SWM by cardiac view for both contiguous and separate segmental imaging.** However, specific areas where AF0150 use may not make a difference in improving the ability to correctly assess for SWM are as follows:

- Certain cardiac views (specifically, the apical 2-chamber view), despite an overall increase in the ***number*** of correctly-assessed contiguous images, demonstrated an overall **decrease** (one was no change) in the ***percentage*** of correctly-assessed images (note Reader 2 and Reader 3) was noted. It must be noted that the apical 2-chamber view had at baseline the greatest percentage of poorly evaluable, and the wall with the poorest visibility at baseline within that view was the **anterior wall**, vascularized by the left anterior descending coronary artery. **There is the chance that patients with chronic coronary artery disease involving the anterior wall may not benefit from use of this ultrasound contrast agent.**
- The sub-analysis evaluating only the ***evaluable*** images of *contiguous segments* demonstrated lesser of a percentage increase of correctly-assessed images post-AF0150 than all of the other sub-analyses.
- The percentage of correctly-assessed abnormal (i.e. having at least one abnormal segment) images for either contiguous or single segments was much lower than that for normal.

There was stringency in the original protocol (and review) in not simply identifying abnormal from normal, but also in identifying differing types of abnormalities. Thus, there is the greater challenge of correctly matching with MRI (and therefore correctly diagnosing) the ***type*** of wall motion abnormality.

2. SUBJECT (PATIENT) ANALYSES:

Overall, two of the three blinded readers demonstrated an improvement in correctly distinguishing patients post-AF0150 with 2D-echo as having either normal or abnormal SWM. However, all 3 readers also experienced some decremental results, with correct interpretation of patients using suboptimal baseline images to incorrect interpretations by 2D-echo after AF0150 usage. One blinded reader (Reader #2) actually did not benefit at all with AF0150 usage. Patients with suboptimal (baseline) 2D-echo images might benefit from use of AF0150 for identification if the patients have no regional wall motion abnormalities.

3. CONCLUSION:

The clinical reviewer believes that efficacy has been shown, as the data provided demonstrates an improvement in distinguishing normal cardiac views from abnormal views, as well as distinguishing patients with normal regional wall function from patients with any abnormalities noted in segmental wall motion. However, the data is derived from one study (IMUS-008), the patients evaluated came from one study site, and the number of patients evaluated for efficacy against the standard of truth (MRI) was small (n = 26). Thus, it must be emphasized that the analyses can only be considered as descriptive and that this study could not be evaluated for statistical significance.

SAFETY REVIEW

INTEGRATED SAFETY SUMMARY (ISS; UPDATED TO INCLUDE NEW STUDY):

The sponsor stated data from any ongoing studies would not be included into the ISS because those data are incomplete and partially verified. Therefore, the ISS data from the original (Cycle #1) review will stand apart from the additional safety data provided by the sponsor in this submission.

1. IND [redacted] IMUS [redacted] (ongoing study) --

This is a multi-center, open-label evaluation of myocardial contrast echocardiography with AF0150 in the detection of coronary artery disease. The study is being conducted in two stages. Stage 1 is the device/dose optimization (Phase 1); stage 2 is dose-optimization under rest and stress conditions. Each stage of the study has 2 sub-populations as follows:

- Stage 1: Two groups of males, (*a*) those with normal coronary perfusion and (*b*) those who are clinically stable with a "recent" history (between 6 weeks and 6 months previously) of transmural infarction.
- Stage 2: Subjects (male and female) with (*a*) normal perfusion and (*b*) subjects with at least one coronary vessel with a high-grade (> 70%) stenosis but can tolerate stress-testing with Adenoscan® (adenosine, intravenous infusion at 140 µg/kg/min for 6 min = 0.84 mg/kg).

TABLE 7: IMUS- [redacted] Adverse Event Profile

	IMUS [redacted]			
	Stage 1 N = 15		Stage 2 N = 14	
	N	(%)	N	(%)
Any	**3**	**(20%)**	**10**	**(71%)**
	INCIDENCE (NO. PATIENT NO.)			
Body				
• Headache	1	(7%)	2	(14%)
• Asthenia	0		1	(7%)
• Pain	0		2	(14%)
Cardiovascular				
• Hypotension	0		1	(7%)
• Vasodilation	0		4	(29%)
• Hypertension	1	(7%)	0	
• First degree AV block	1	(7%)	0	
• Sinus bradycardia	1	(7%)	0	
• Tachycardia	0		1	(7%)
Digestive System				
• Dry Mouth	0		1	(7%)
Metabolic				
• CPK increased	0		1	(7%)
Respiratory				
• Dyspnea	0		1	(7%)
• Rhinitis	0		1	(7%)
Nervous				
• Dizziness	0		2	(14%)
• Paresthesia	0		1	(7%)

Data derived from Volume 2, p 02-151: Table 17

Table 7 (at the left) illustrates both the number of subjects who experienced any adverse event (AE), and also the incidence of AE's thus far reported in this study.

Thus far, there have been no study discontinuations or withdrawals, deaths, or serious adverse events reported. **Of note, the number of patients in both stages in this part of the safety review differs from the number in both stages later in this review (see the QTc interval changes below) which has not been explained by the sponsor.**

- Stage 1 (15 subjects): There were 4 adverse events reported in 3 subjects.

- Stage 2 (14 subjects): There were 18 adverse events reported in 10 subjects. Five of the subjects had events to occur 1 – 5 minutes after the start of adenosine infusion; all had resolved near or at the end of the adenosine infusion.

2. IND [redacted] (physician-sponsored) –
This protocol involves use of AF0150 in combination with wide-band harmonic ultrasound imaging to allow visualization of tumor neovascularity on gray-scale imaging. Alliance provided only information regarding serious adverse events from this protocol (sponsored by Robert Mattrey, MD; University of California, San Diego, submitted June 19, 1998). Alliance stated that no serious adverse events were reported; however, data regarding ***non***-serious adverse events were not provided by Alliance.

3. IND [redacted] (physician-sponsored) –
This protocol involves use of AF0150 in intermittent ultrasound to improve detection of prostate cancer. Again, Alliance provided only information regarding serious (not any ***non***-serious) adverse events from this protocol (sponsored by Ethan Halpern, MD; Thomas Jefferson University Hospital, Philadelphia, PA, submitted Feb. 14, 2001). Alliance stated that one serious adverse event was reported; it involved patient #040, a 49 year old male with a history of prostate cancer and vaso-vagally-related syncopal episodes after venipuncture procedures.

Briefly, the patient experienced dysguisia for less than a minute during the AF0150 infusion (13.9 cc over 16 minutes). After the AF0150 infusion was completed, the patient underwent the sextant prostate biopsy. During the biopsy no. 4 of the sextant biopsy of the prostate, the patient experienced **vasodilation** ("warmth"), followed by **dizziness** with **bradycardia** (BPM < 50), followed by the 1st **syncopal episode**. Ten to 15 seconds after syncope first occurred, the patient experienced a 10 – 15 second episode of **seizure** ("wildly flailing his arms and his legs"). Patient management included Trendelenburg positioning, IV hydration, oxygen, CT scan of the head (no abnormalities) and further evaluation in the emergency room. However, the patient experienced a **2nd syncopal episode** while awaiting CT scanning, and later the same day **cardiac arrest (asystole** occurring after bradycardia) occurred, necessitating CPR; this episode **resolved** within 1 minute. A temporary pacemaker was placed and the patient was hospitalized from 03-26-02 through 03-01-02. Ultimately the patient was discharged in good condition with the pacemaker removed.

In this case, although the patient has a history of post-procedural syncopal episodes (e.g. another syncopal episode occurred 1 day after a breast biopsy performed years previously on the patient), one cannot rule out the possibility that AF0150 may be the cause.

EVALUATION OF THE QT_C INTERVAL:

The sponsor repeated the QT_c-interval information provided in the original NDA for the Phase 3 studies. In addition, the sponsor provided narrative summaries of patients in the Phase 3 studies (IMUS-007 and –008) who were reported to have had QTc prolongation. A review of the narrative summaries does not demonstrate any additional factors which could serve as reasons for the recorded potentially clinically significant QTc prolongation in the patients.

No narrative summaries were provided of individual patients enrolled in the ongoing Phase 2 study (IMUS- ▬▬), who were reported to have had QTc prolongation. However, the sponsor stated that the QTc intervals were being monitored in the ongoing Phase 2 study (IMUS- ▬▬). It must also be noted that AF0150 administration in IMUS- ▬▬ is different from the dosage and administration proposed presently for approval.

Regarding IMUS- ▬▬, **no data regarding individual patients enrolled in the protocol was provided.** However, scatter plots were provided to help in determining if there is a trend toward QTc prolongation at specific times post-AF0150 and post-stress testing. Tabulated below is a count of patients who had either normal and prolonged QTc intervals during the post-AF0150 period and the subsequent post-stress period.

TABLE 8: IMUS- ▬▬

NO. OF PATIENTS WITH QTC MEASUREMENTS (FROM SCATTER PLOTS)

	Stage 1 (n = 23)			Stage 2 (n = 16)		
	WNL*	PCS*	Overlap	WNL*	PCS*	Overlap
Post-AF0150						
• 5 minutes	11	3	9			
• 15 minutes	12	2	9	3	9	4
Post-Adenoscan® Stress						
• 2 minutes				11	2	3
• 6 minutes				4	11	1
• 10 minutes				7	9	0
• 1 hour	18	5	0	4	11	0
• 24 hour	16	5	0	9	7	0

*WNL = Within normal limits; PCS = Potentially clinically significant prolongation

The data from the scatter plots cannot be interpreted very well due to what appears to be an overlap of some patients, and areas of overlap have not be identified by the sponsor. Additionally, without any narratives submitted for these patients, additional factors which may be related to the QTc prolongations are unknown. This is particularly important for each stage of this protocol, since it involves both normal volunteers and patients with coronary artery disease. Nevertheless, the data seems to indicate (in the Stage 2 patients) a (potentially clinically) significant increase in the QTc interval notably post-Adenoscan®.