The next table illustrates the categorical analyses of the QTc interval changes for both Stages 1 and 2 of the study. According to the sponsor, Stage 1 subjects (with the exception of 2 subjects at a few time points; **no data about those patients**) maintained QTc within normal limits. In the Stage 2 study, an increase in QTc was noted during the adenosine infusion. According to the Adenoscan® package insert, despite the short half-life of Adenoscan® (< 10 seconds), cardiac AE's previously reported to possibly be related to Adenoscan® (1% to 3% incidence) include ST-segment depression, 1° and 2° AV block, and arrhythmias (not specified).

TABLE 9: IMUS [redacted] – QT_C INTERVAL CATEGORIES
(% = Only Patients who exhibited ↑ QTc Interval)

TIME	STAGE 1 (N = 23): MSEC (msec *change*) (QTc)				STAGE 2 (N = 16): MSEC (msec *change*) (QTc)			
	≤ 30	31 – 60	> 60	> 500	≤ 30	31 – 60	> 60	> 500
Post-AF0150								
5 min	13 (93%)	1 (7%)	0	0	9 (75%)	2 (17%)	1 (8%)	0
15 min	13 (93%)	0	1 (7%)	0	8 (67%)	2 (17%)	2 (17%)	0
Pre-Adenosine Stress Testing								
5 min					11 (79%)	2 (14%)	1 (7%)	0
During Adenosine Stress Testing								
1 min					9 (60%)	1 (7%)	4 (27%)	1 (7%)
2 min					6 (46%)	3 (23%)	2 (15%)	2 (15%)
3 min					9 (60%)	0	5 (33%)	1 (7%)
4 min					8 (57%)	2 (14%)	2 (14%)	2 (14%)
5 min					7 (47%)	5 (33%)	2 (14%)	1 (7%)
6 min					8 (57%)	4 (27%)	2 (15%)	1 (7%)
Post-Adenosine Stress Testing								
5 min					14 (87%)	1 (7%)	0	1 (7%)
10 min					13 (81%)	2 (15%)	1 (7%)	0
15 min					13 (81%)	2 (15%)	1 (7%)	0
30 min					8 (57%)	6 (46%)	2 (15%)	0
1 hour	21 (91%)	2 (9%)	0	0	10 (62%)	3 (23%)	3 (23%)	0
24 hour	20 (95%)	1 (5%)	0	0	14 (87%)	1 (7%)	1 (7%)	0
Completion								
					0	1 (100%)	0	0

Data derived from Volume 2, p 02-098 (Appendix II.B.1): Table 5.
Normal for baseline: QTc ≤ 500 msec with a heart rate between 50 and 120 beats per minute.
Abnormal QTc: > 500 msec or increase from baseline > 30 msec

The above data submitted by the sponsor demonstrates that most patients who exhibited any kind of QTc prolongation after AF0150 administration did not exhibit "abnormal" prolongation (an increase from the baseline of > 30 msec). However, most patients in

both stages of IMUS [redacted] did exhibit prolongation post-AF0150, as the next table demonstrates.

TABLE 10: IMUS [redacted] – QT_C INTERVAL CATEGORIES
(% = All Patients Enrolled in the Stage)

TIME	STAGE 1 (N = 23); MSEC (msec *change*)			(QTc)	STAGE 2 (N = 16); MSEC (msec *change*)			(QTc)
	≤ 30	31 – 60	> 60	> 500	≤ 30	31 – 60	> 60	> 500
Post-AF0150								
5 min	13 (56%)	1 (4%)	0	0	9 (56%)	2 (12%)	1 (4%)	0
15 min	13 (56%)	0	1 (4%)	0	8 (50%)	2 (12%)	2 (12%)	0
Pre-Adenosine Stress Testing								
5 min					11 (69%)	2 (12%)	1 (4%)	0
During Adenosine Stress Testing								
1 min					9 (56%)	1 (4%)	4 (25%)	1 (4%)
2 min					6 (37%)	3 (19%)	2 (12%)	2 (12%)
3 min					9 (56%)	0	5 (31%)	1 (4%)
4 min					8 (50%)	2 (12%)	2 (12%)	2 (12%)
5 min					7 (44%)	5 (31%)	2 (12%)	1 (4%)
6 min					8 (50%)	4 (25%)	2 (12%)	1 (4%)
Post-Adenosine Stress Testing								
5 min					14 (87%)	1 (4%)	0	1 (4%)
10 min					13 (81%)	2 (12%)	1 (4%)	0
15 min					13 (81%)	2 (12%)	1 (4%)	0
30 min					8 (50%)	6 (37%)	2 (12%)	0
1 hour	21 (91%)	2 (9%)	0	0	10 (62%)	3 (19%)	3 (19%)	0
24 hour	20 (87%)	1 (4%)	0	0	14 (87%)	1 (4%)	1 (4%)	0
Completion								
					0	1 (4%)	0	0

Data derived from Volume 2, p 02-098 (Appendix II.B.1): Table 5.
Normal for baseline: QTc ≤ 500 msec with a heart rate between 50 and 120 beats per minute.
Abnormal QTc: > 500 msec or increase from baseline > 30 msec

This evaluation demonstrates that AF0150 might contribute to prolongation of the QTc; the majority of patients post-AF0150 demonstrated some QTc prolongation (albeit not clinically significant). Among the Stage 1 patients (n = 23), 14 patients (61%) demonstrated QTc prolongation at both 5 and 15 min post-AF0150; among the Stage 2 population (n = 16), 12 patients (75%) demonstrated this also. No patient exhibited QTc prolongation > 500 msec. The sponsor did not provide the data regarding the number of patients with versus without coronary artery disease or other data – especially the dosage and administration (bolus or infusion) of the AF0150 -- to determine whether other factors may play a role in the occurrence of this event.

PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD):

Changes in $Pa0_2$ ($Sa0_2$ [%]) in the COPD subgroup is presented as a mean change from baseline for AF0150 and saline with no differentiation between those with active vs. inactive COPD. In order to resolve this, the agency requested the following information in bolded italics:

1. ***The number of patients in the subgroup of 97 with COPD who had $Pa0_2$ monitored at the various specified time-points.***

According to the sponsor, arterial 0_2 saturation was measured in the COPD patients (97 patients treated with AF0150; 15 with saline) at the following time points: baseline, 5 minutes, 15 minutes, 30 minutes, 1 hour, and 24 hours following administration of the either AF0150 or saline.

2. ***Provide clinical history on these patients in terms of disease type (e.g. asthma, bronchitis, emphysema, and bronchiolitis), including the status of disease (e.g. active vs. inactive), and concomitant medications, if any.***

A total of 112 patients were noted to have COPD in the 3 studies[7] involving the investigational bolus AF0150 treatment at 0.125 mg/kg. Per study, 1 patient in IMUS-001 had COPD (active bronchitis) and that patient received saline. In IMUS-007, a total of 52 patients were recorded as having COPD (38 patients had AF0150 and 14 patients had saline); and in IMUS-008, a total of 59 patients had COPD (all had AF0150). Patients were listed as having either active or inactive COPD; in this review, active disease is also defined as diseases where medicines for COPD are being used (differing from the sponsor) during the studies ("concomitant medicines").

Among patients receiving AF0150, there were a total of 29 patients with asthma (6 with active disease), 18 patients with bronchitis (17 with active disease), 3 patients with emphysema (1 with active disease), and 49 patients with COPD otherwise unidentified (25 with active disease). Among patients receiving saline, there were a total of 4 patients with asthma (all with active disease), 5 patients with bronchitis (all with active disease), 1 patient with emphysema (active disease), and 5 patients with COPD otherwise unidentified (3 with active disease).

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7. *Note*: The safety population in the Phase 3 studies – **IMUS-007 and –008** – had higher numbers of patients to follow than the respective efficacy populations. IMUS-007's total study population (n = 294) had an efficacy population (n = 206), an AF0150 safety population (n = 213), and a saline safety population (n = 81). IMUS-008's total study population (n = 232) had only an AF0150 efficacy population (n = 203); no saline control group was evaluated for this study.

   Note: A total of 64 **"normal" volunteers** participated in **IMUS-001**; within that population, 12 volunteers received bolus AF0150 at 0.125 mg/kg, and 20 volunteers received saline boluses. All others in IMUS-001 received various doses and/or infusions of AF0150.

TABLE 11: PATIENTS WHO RECEIVED AF0150

IMUS (# pts)	Asthma		Bronchitis		Emphysema		Other COPD	
	Active	Inactive	Active	Inactive	Active	Inactive	Active	Inactive
001 n=12	0	0	0	0	0	0	0	0
007 n=213	9	3	3	1	0	0	11	11
008 n=232	13	3	14	0	1	2	14*	13*
Total	**22**	**6**	**17**	**1**	**1**	**2**	**25**	**24**

*No. of patients with bronchiectasis: active disease = 2; inactive = 1

TABLE 12: PATIENTS WHO RECEIVED SALINE*

IMUS (# pts)	Asthma		Bronchitis		Emphysema		Other COPD	
	Active	Inactive	Active	Inactive	Active	Inactive	Active	Inactive
001 n = 20	0	0	1	0	0	0	0	0
007 n = 81	4	0	4	0	1	0	3	2
008 n = 0	0	0	0	0	0	0	0	0
Total	**4**	**0**	**5**	**0**	**1**	**0**	**3**	**2**

* Only patients within IMUS-001 and –007 had saline-treated group.

3. Reanalyze for changes (baseline vs. post-contrast) in magnitude of the $Pa0_2$ (%) in decrements of 2% for all patients at all measured time-points.

Of the 112 COPD patients within the 3 trials, there were 28 patients (25%) who were recorded as having experienced ≥ 2% decrement in 0_2 saturation after either AF0150 or saline administration. Twenty-six of the 28 patients received AF0150 and 2 received saline (see the table below; the baseline values were added for ***all*** subjects). Seventeen of those 28 (61%) had active COPD, which includes those listed by the sponsor as "inactive" but taking concomitant medications for their respective COPD. There was no predilection for any specific type of COPD to experience the ≥ 2% decrement in 0_2 saturation.

Of the 28 patients, the time-point where the greatest number of patients were recorded as having experienced a ≥ 2% decrement in 0_2 saturation was within the 1st 5 minutes following infusion of test drug. A total of 18 patients (64%) had either AF0150 (= 17 patients) or saline (= 2 patients) administered with a resultant ≥ 2% decrement in 0_2 saturation. For the other time-points, other patients recorded as having a ≥ 2% decrement in 0_2 saturation are the following:

- 18 patients between baseline and 5 minutes;

- 2 patients (both in the saline group) between 5 and 15 minutes;
- 8 patients (1 of whom received saline) between 15 and 30 minutes;
- 3 patients between 30 minutes and 1 hour; and
- 1 patient between 1 hour and 24 hours.

TABLE 13: PATIENTS RECORDED WITH ≥ 2% DECREMENT IN 0_2 SATURATION

	Protocol	ID	COPD Type	Dz*	0_2 Saturation: Minutes ------//--Hours-----					
					Base	5	15	30	1	24
AF0150-administered patients										
1.	**IMUS-007**	02-006	COPD	I	96.0		97.0	92.0		
2.		03-040	Asthma	I	97.0	95.0				
3.		06-021	COPD	A	96.0				98.0	96.0
4.		07-003	COPD	A	94.0			96.0	94.0	
5.		08-012	COPD	I	95.0	92.0				
6.		10-035	COPD	I	94.0	91.0				
7.		13-013	COPD	A	98.0	96.0				
8.		16-002	COPD	A	89.0	87.0				
9.	**IMUS-008**	20-005	Asthma	A	94.0	92.0	100.0	93.0		
10.		20-015	Bronchitis	A	96.0		94.0	92.0		
11.		20-017	Bronchiectasis	A	93.0			99.0	90.0	
12.		22-007	Bronchitis	A	96.0	94.0				
13.		22-010	COPD	I	96.0		96.0	94.0		
14.		22-011	Asthma	A	91.0		93.0	91.0		
15.		22-025	Asthma	A	97.0	94.0				
16.		23-001	COPD	A	94.0	92.0				
17.		23-020	Asthma	I	96.0	93.0				
18.		23-022	Bronchitis	A	96.0	92.0				
19.		23-035	Bronchitis	A	98.0	94.0				
20.		25-007	Asthma	A	98.0	93.0				
21.		27-017	COPD	I	87.0	85.0				
22.		27-027	COPD	I	95.0	93.0				
23.		28-002	COPD	I	93.0	91.0				
24.		28-005	Asthma	A	94.0		97.0	94.0		
25.		30-013	Emphysema	I	97.0	93.0				
26.		30-022	COPD	A	95.0		97.0	95.0	91.0	
Saline-administered patients										
27.	**IMUS-007**	02-005	COPD	I	97.0	96.0	91.0			
28.		13-004	Bronchitis	A	96.0	94.0	92.0	88.0		

* Disease activity: A = active disease, which includes patients taking concomitant medicines; I = inactive disease.

Ten COPD subjects experienced greater (≥ 4%) decrements in 0_2 saturation and are tabulated below. The actual 0_2 saturations with such decrements are bolded in the table.

TABLE 14: PATIENTS WITH THE GREATEST DECREMENT IN 0_2 SATURATION

	Protocol	ID	COPD Type	Dz*	0_2 Saturation (minutes post-tx)					% ↓
					Base	5	15	30	60	$Pa0_2$
AF0150-administered patients										
1.	**IMUS-007**	02-006	COPD	I	96.0		**97.0**	**92.0**		**5%**
2.	**IMUS-008**	20-005	Asthma	A	94.0	92.0	**100.0**	**93.0**		**7%**
3.		20-017	Bronchiectasis	A	93.0			**99.0**	**90.0**	**9%**
4.		23-022	Bronchitis	A	**96.0**	**92.0**				**4%**
5.		23-035	Bronchitis	A	**98.0**	**94.0**				**4%**
6.		25-007	Asthma	A	**98.0**	**93.0**				**5%**
7.		30-013	Emphysema	I	**97.0**	**93.0**				**4%**
8.		30-022	COPD	A	95.0		97.0	**95.0**	**91.0**	**4%**
Saline-administered patients										
9.	**IMUS-007**	02-005	COPD	I	97.0	**96.0**	**91.0**			**5%**
10.		13-004	Bronchitis	A	96.0	94.0	**92.0**	**88.0**		**4%**

Again, although most subjects tabulated above have active disease, there does not appear to be any predilection overall for active vs. inactive COPD, or any predilection with any particular type of COPD. Additionally, none of the patients in the above table were reported to have experienced any cardiovascular or respiratory adverse events (to be discussed later).

4. Additionally, please indicate if the $Pa0_2$ changes were associated with symptoms and/or adverse events.

As mentioned above, none of the patients in Tables 3 and 4 above (subjects who experienced a ≥ 2% decrement in 0_2 saturation) were reported to have had cardio-pulmonary adverse events. Two COPD subjects, both having active disease and treated with AF0150, were reported to have experienced the following adverse events:

(1) Subject **03-054** (IMUS-007), with **active bronchitis**: hypotension at 24 hours post-AF0150 bolus; resolved within 8 minutes.
- Baseline 0_2 saturation = 97%, with no change over the time course until 24 hours post-AF0150, when the 0_2saturation decreased to 96%.

(2) Subject **27-004** (IMUS-008), with **active bronchiectasis**: vasodilation at time 0 of AF0150 injection; resolved 2 minutes later.
- Baseline 0_2 saturation = 97%, with the next (5-minute time-point) 0_2saturation increased to 99%.

Thus, it appears that no cardio-pulmonary adverse events were associated with the changes in oxygen saturation.

5. ***Please provide information on the adverse event profile for this subgroup in comparison to the study population (minus the COPD subgroup).***

The sponsor had provided all the information the agency requested. However, no information was provided regarding the evaluation of patients with restrictive lung diseases or pulmonary diseases in which the diffusion capacity was abnormal.

TABLE 15: Imavist™vs. Saline in COPD Patients

	COPD			
	AF0150 N = 97		Saline N= 15	
	N	(%)	N	(%)
Any	**17**	**(17%)**	**1**	**(7%)**
Body	**9**	**(9%)**	**0**	
• Headache	4	(4%)	0	
• Abdominal pain	2	(2%)	0	
• Asthenia	1	(1%)	0	
• Chest pain	1	(1%)	0	
• Chills	1	(1%)	0	
Cardiovascular	**2**	**(2%)**	**0**	
• Hypotension	1	(1%)	0	
• Vasodilation	1	(1%)	0	
Digestive System	**6**	**(6%)**	**0**	
• Nausea	3	(3%)	0	
• Diarrhea	1	(1%)	0	
• Dyspepsia	1	(1%)	0	
• Tongue Disorder	1	(1%)	0	
Heme-Lymphatic	**1**	**(1%)**	**0**	
• Thrombocytopenia	1	(1%)	0	
Metabolic	**1**	**(1%)**	**0**	
• Hyperglycemia	1	(1%)	0	
Special Senses	**2**	**(2%)**	**0**	
• Taste Perversion	2	(2%)	0	

The sponsor provided the following safety information regarding COPD patients, comparing AF0150 administration versus saline administration (see table in inset). This particular analysis demonstrates that AF0150 administration in COPD patients can induce significantly greater adverse effects in comparison to saline administration in the same population. None of the adverse events (AE's) reported in AF0150-"treated" COPD patients occurred in saline-"treated" COPD patients. (Of note, however, the number of saline-"treated" COPD patients [N = 15] was < 25% of the number of AF0150-"treated" COPD patients [N = 97].) AF0150-"treated" COPD patients were reported to have experienced the following AE's most prominently: headache (9%), nausea (3%), and abdominal pain (2%). Because headache is a symptom which is part of the constellation of symptoms noted in gas/air embolism, the AE result might indicate a greater chance of the syndrome of air embolism in patients with obstructive lung diseases over other patients. This is demonstrated also in the next table, where COPD patients have a greater percentage of headache reported over non-COPD patients (4% vs. 1%). However, restrictive lung disease patients were not studied. It is certainly understandable that patients with poor or abnormal diffusion capacities (DLco; normal = 20 mL/min /mmHg at rest; ≥ 60 mL/min/mmHg with exercise) due to diseases such as diffuse interstitial fibrosis, sarcoidosis and others where an alveolar-capillary block is noted. In such cases where alveolar membrane thickness is increased, leading to a low DLco , a decision cannot be made as to how such patients will do after AF0150

administration. Finally, none of the patients evaluated underwent formal pulmonary functions testing as a part of enrollment into the pivotal studies, nor was there any study where patients with pulmonary diseases in general were evaluated.

TABLE 16: Imavist Use in COPD vs. Non-COPD Pts

	AF0150			
	COPD N = 97		Others N = 360	
	N	(%)	N	(%)
Any	**17**	**(17%)**	**32**	**(9%)**
Body	**9**	**(9%)**	**9**	**(2%)**
• Headache	4	(4%)	4	(1%)
• Abdominal pain	2	(2%)	0	
• Asthenia	1	(1%)	3	(1%)
• Chest pain	1	(1%)	0	
• Chills	1	(1%)	0	
• Injection site reaction	0		1	(0%)
• Pain	0		1	(0%)
Cardiovascular	**2**	**(2%)**	**13**	**(4%)**
• Hypotension	1	(1%)	1	(0%)
• Vasodilation	1	(1%)	1	(0%)
• Hypertension	0		5	(1%)
• EKG abnormality	0		2	(1%)
• Angina pectoris	0		1	(0%)
• Supravent. Tachycardia	0		1	(0%)
• T-wave inversion	0		1	(0%)
• Tachycardia	0		1	(0%)
Digestive System	**6**	**(6%)**	**5**	**(1%)**
• Nausea	3	(3%)	2	(1%)
• Diarrhea	1	(1%)	3	(1%)
• Dyspepsia	1	(1%)	0	
• Tongue Disorder	1	(1%)	0	
Heme-Lymphatic	**1**	**(1%)**	**3**	**(1%)**
• Thrombocytopenia	1	(1%)	0	
• Leukocytosis	0		2	(1%)
• Fibrinogen Increased	0		1	(0%)
Metabolic	**1**	**(1%)**	**3**	**(1%)**
• Hyperglycemia	1	(1%)	0	
• CPK increased	0		3	(1%)
Musculo-skeletal	**0**		**1**	**(0%)**
• Myalgia	0		1	(0%)
Nervous	**0**		**3**	**(1%)**
• Dizziness	0		2	(1%)
• Paresthesia	0		1	(0%)
Special Senses	**2**	**(2%)**	**2**	**(1%)**
• Taste Perversion	2	(2%)	2	(1%)
Genito-urinary	**0**		**1**	**(0%)**
• Albuminuria	0		1	(0%)

Derived from Table 19 in the Appendix of this review.

Table 16 illustrates the comparison of COPD patients versus others, all of whom were treated with AF0150. What is noted in this particular case is the higher percentage of certain AE's in COPD which were shared with non-COPD patients, including headache (4% vs. 1%), nausea (3% vs. 1%), and taste perversion (2% vs. 1%). AE's occurring among COPD patients which were not shared with non-COPD patients include abdominal pain (2% vs. 0 patients). On the other hand, cardiac AE's not noted among COPD patients but noted among the non-COPD patients included hypertension (5 patients or 1%) and EKG abnormalities (2 patients or 1%). Other AE's reported in more non-COPD patients include diarrhea, CPK increase, leukocytosis, and dizziness. Of course, there were > 3x the number of non-COPD patients versus COPD patients.

A complete comparison of AE data is in the Appendix (Table 19).

SAFETY CONCLUSIONS:

The sponsor provided the following information, from which these safety conclusions are derived regarding Imavist™ (AF0150 for injection):

1. INTEGRATED SAFETY SUMMARY:

The sponsor submitted data from 3 additional IND's involving Imavist™ (AF0150 for injection). One IND (multi-centered) involves AF0150 administration (not similar to the dose and administration proposed for the package insert) to two groups of patients: Some normal volunteers, and others with coronary artery disease (CAD). The other 2 IND's (both physician-sponsored) involve AF0150 administration to patients with either unspecified tumor(s), or (specifically) prostate cancer.

The ongoing, multi-center CAD study evaluates stable patients with either recent transmural myocardial infarctions (Stage 1) or with ≥ 1 coronary vessel with a high-grade (> 70%) coronary stenosis who can tolerate adenosine-induced stress testing. Despite the noted low incidence of headache, vasodilation and other cardiovascular events, the sponsor did not provide specific data on individuals (whether patients had CAD or were normal volunteers) or the drug administration (dose; bolus vs. infusion). No serious AE's, study withdrawals, or deaths were reported.

Regarding the 2 physician-sponsored studies, Alliance did not provide a non-serious AE profile, but stated that no serious AE's were reported except for one of the 2 studies (prostate cancer study), where the patient experienced cardiac arrest following 2 episodes of syncope with one episode of seizure. Although that patient had a history of vaso-vagally-related syncope, AF0150 drug-effect cannot be ruled out as a factor.

2. EVALUATION OF THE QTc INTERVAL:

The sponsor provided narrative summaries on the patients enrolled in the two Phase 3 studies receiving the proposed bolus dose of Imavist™ (AF0150 for injection), to complement the QTc data which was provided by the sponsor in the original NDA submission. No factors could be easily identified that could serve as factors leading to QTc prolongation for these patients.

QTc data from ongoing multi-center study (IMUS- [redacted]) involving CAD patients was provided, which demonstrated a trend that AF0150 might contribute to prolongation of the QTc. This is because a majority of patients post-AF0150 demonstrated some QTc prolongation (albeit not clinically significant) at both 5 and 15 min post-AF0150. No patient exhibited QTc prolongation > 500 msec. No data was provided by the sponsor concerning individual patients (normal volunteer versus coronary artery disease history) or dosage and administration (bolus or infusion) of the AF0150 to determine whether other factors may play a role in the occurrence of this event.

3. SUMMARY OF PATIENTS WITH COPD:

The sponsor sent data from the Phase 3 studies (IMUS-007 and –008) regarding patients with chronic obstructive pulmonary disease. Data regarding patients with restrictive pulmonary disease were not submitted.

For the studies involving bolus Imavist™ (AF0150), a total of 457 COPD patients received bolus AF0150 at the dosage sought for approval; a total of 101 COPD patients received saline bolus. Approximately 6% of the AF0150-treated COPD patients experienced a ≥ 2% decrement in 0_2 saturation post-AF0150, with most experiencing the decrement within the 1st 5 minutes post-administration. This is comparison to the 2% of COPD patients treated with bolus saline. Within the 6% of AF0150-treated COPD patients who experienced ≥ 2% 0_2 desaturation, 31% had a ≥ 4% decrement in 0_2 saturation (versus 2% in the saline-treated COPD group). Oxygen desaturation was not related to activity of disease.

Finally, the adverse event profiles of both the COPD and non-COPD patients were submitted. Of the AF0150-treated COPD patients (n = 97), 17% had adverse events, compared with saline-treated COPD patients (n = 15), where 1% experienced adverse events, and the AF0150-treated *non*-COPD patients (n = 32), where 9% experienced adverse events. The predominant AE's in the AF0150-treated COPD group were headache (4% vs. 0% vs. 1%, respectively), which is a symptom in the "air-embolism syndrome", and nausea (3% vs. 0% vs. 1%, respectively).

4. Non-Clinical Issues

- **Chemistry Issues:** The issues regarding product stability have been addressed, reviewed and deemed acceptable by the chemistry reviewer.

- **Pharmacology/Toxicology Issues:** The issues regarding the impact of Imavist™ administration in animals with obstructive pulmonary disease have been addressed, reviewed and deemed acceptable by the pharm/tox reviewer.

- **Pharmacokinetic Issues:** The issues regarding Imavist administration in pulmonary-impaired humans and animals have been addressed, reviewed and deemed acceptable by the clinical pharmacology reviewer.

5. Pediatric Plan

6. Conclusion

Imavist™ (AF0150) administered as a bolus at 0.125 mg/kg (proposed clinical dose; PCD) appears to be safe for patients undergoing 2D-echocardiography for the determination of cardiac function. A low incidence of patients experience symptoms

related to "air-embolism syndrome", but patients with chronic obstructive pulmonary disease appear to experience a greater (albeit still low) incidence of the same symptoms. It is presently unknown as to how patients with restrictive pulmonary disease would respond; this will need to be evaluated in future submissions. Bolus administration of the PCD of Imavist™ may cause QTc prolongation, although predominantly not clinically significant, as indicated within the agency's review of the originally submitted NDA. Nevertheless, patients with cardiac disease and pulmonary disease might have a greater propensity for QTc prolongation, as well as other EKG abnormalities. Finally, the sponsor provided data from three additional studies involving Imavist™ administration, one of which involves evaluation of patients with CAD, comparing myocardial perfusion to the myocardial perfusion in normal volunteers. The adverse event profile was submitted for the multi-centered CAD protocol but not for the other 2 (physician-sponsored, non-cardiac) protocols. There was a low incidence of AE's but, because no individual data of the patient history or Imavist™ dose was provided, one cannot determine whether the AE's are Imavist™-related or not.

OVERALL RECOMMENDATION:

The sponsor continues to propose a structural claim for the product. The data is not supportive of a functional claim, but a weak trend towards a functional claim upon which such a structural claim has been demonstrated. The current recommendations stand, with an additional supportive study being necessary for approval.

LABELING SECTION:

I. Proposed Insert Indication

Original proposal:

II. Issues

As mentioned previously, the studies submitted are not, in the opinion of the clinical reviewer, supportive for an approval.

Nevertheless, the package insert was reviewed and corrections and additions were provided by the clinical reviewer, with the disclaimer that an additional study is needed to provide validation of the previous study.

APPENDIX:

TABLE 17(a): IMUS-008 (N = 26); *Evaluable* Contiguous Segments % of SWM 2D-Echo Agreement with MRI: Analyses of Each Cardiac View

	READER 1				READER 2				READER 3			
Views	**Baseline**		**Contrast**		**Baseline**		**Contrast**		**Baseline**		**Contrast**	
	%	#/ total	%	#/ total	%	#/total	%	#/ total	%	#/ total	%	#/ total
Apical 4-Chamber View: 15 different contiguous combinations x 26 patients = 390 total												
Normal	73%	(8/11)	78%	(49/63)	67%	(6/9)	78%	(42/54)	64%	(9/14)	78%	(66/85)
Abnormal	20%	(1/5)	32%	(7/22)	**100%**	(1/1)	**67%**	(6/9)	**67%**	(6/9)	**54%**	(19/35)
Total	56%	(9/16)	66%	(56/85)	70%	(7/10)	76%	(48/63)	65%	(15/23)	71%	(85/120)
Apical 2-Chamber View: 15 different contiguous combinations x 26 patients = 390 total												
Normal	**80%**	(8/10)	**80%**	(32/40)	60%	(3/5)	90%	(18/20)	70%	(7/10)	100%	(47/47)
Abnormal	**60%**	(3/5)	**33%**	(3/9)	**25%**	(1/4)	**18%**	(2/11)	**60%**	(6/10)	**50%**	(17/34)
Total	**73%**	(11/15)	**71%**	(35/49)	44%	(4/9)	64%	(20/31)	65%	(13/20)	79%	(64/81)
Apical Long Axis View: 6 different contiguous combinations x 26 patients = 390 total												
Normal	60%	(6/10)	79%	(33/44)	87%	(7/8)	89%	(34/38)	62%	(10/16)	87%	(58/67)
Abnormal	0%	(0/1)	57%	(4/7)	0%	(0/0)	0%	(0/0)	0%	(0/0)	0%	(0/0)
Total	55%	(6/11)	75%	(37/49)	87%	(7/8)	89%	(34/38)	62%	(10/16)	87%	(58/67)

Data derived from Table 1.5a, labeled "Echo SWM Agreement with MRI ..."
Evaluable = all separate segments per contiguous image must each have an EBD score of either 2 or 3.

TABLE 17(b): IMUS-008 (N = 26); *All* Contiguous Segments % of SWM 2D-Echo Agreement with MRI: Analyses of Each Cardiac View

	READER 1				READER 2				READER 3			
Views	**Baseline**		**Contrast**		**Baseline**		**Contrast**		**Baseline**		**Contrast**	
	%	#/ total	%	#/ total	%	#/total	%	#/ total	%	#/ total	%	#/ total
Apical 4-Chamber View: 15 different contiguous combinations x 26 patients = 390 total												
Normal	12%	(8/66)	74%	(49/66)	10%	(6/60)	70%	(42/60)	10%	(9/90)	73%	(66/90)
Abnormal	4%	(1/23)	29%	(7/24)	8%	(1/12)	50%	(6/12)	17%	(6/36)	53%	(19/36)
Total	10%	(9/90)	62%	(56/90)	10%	(7/72)	67%	(48/72)	12%	(15/126)	67%	(85/126)
Apical 2-Chamber View: 15 different contiguous combinations x 26 patients = 390 total												
Normal	19%	(8/42)	76%	(32/42)	12%	(3/24)	75%	(18/24)	15%	(7/48)	98%	(47/48)
Abnormal	**25%**	(3/12)	**25%**	(3/12)	8%	(1/12)	17%	(2/12)	17%	(6/36)	47%	(17/36)
Total	20%	(11/54)	65%	(35/54)	11%	(4/36)	56%	(20/36)	15%	(13/84)	76%	(64/84)
Apical Long Axis View: 6 different contiguous combinations x 26 patients = 156 total												
Normal	14%	(6/44)	75%	(33/44)	16%	(7/44)	77%	(34/44)	15%	(10/68)	85%	(58/68)
Abnormal	0%	(0/8)	50%	(4/8)	**0%**	(0/0)	**0%**	(0/0)	**0%**	(0/0)	**0%**	(0/0)
Total	11%	(6/52)	71%	(37/52)	16%	(7/44)	77%	(34/44)	15%	(10/68)	85%	(58/68)

Data derived from Table 1.5a, labeled "Echo SWM Agreement with MRI ..."
Evaluable = all separate segments per contiguous image must each have an EBD score of either 2 or 3.

APPENDIX (continued):

TABLE 18(a): IMUS-008 (N = 26); *Evaluable* (Separate) Segments
% of SWM 2D-Echo Agreement with MRI: Analyses of Each Cardiac View

	READER 1				READER 2				READER 3			
Views	**Baseline**		**Contrast**		**Baseline**		**Contrast**		**Baseline**		**Contrast**	
	%	#/ total	%	#/ total	%	#/total	%	#/ total	%	#/ total	%	#/ total
Apical 4-Chamber View												
Normal	56%	(10/18)	77%	(61/79)	67%	(16/24)	80%	(60/75)	72%	(13/18)	77%	(73/95)
Abnormal	20%	(2/10)	30%	(8/27)	67%	(10/15)	61%	(14/23)	43%	(6/14)	46%	(19/41)
Total	43%	(12/28)	65%	(69/106)	67%	(26/39)	75%	(74/98)	59%	(19/32)	68%	(92/136)
Apical 2-Chamber View												
Normal	68%	(19/28)	83%	(50/60)	71%	(17/24)	88%	(38/43)	72%	(26/36)	91%	(75/82)
Abnormal	**43%**	(10/23)	**34%**	(10/29)	**36%**	(4/11)	**36%**	(9/25)	**53%**	(10/19)	**46%**	(21/46)
Total	57%	(29/51)	67%	(60/89)	60%	(21/35)	69%	(47/68)	65%	(36/55)	75%	(96/128)
Apical Long Axis View												
Normal	50%	(11/22)	79%	(38/48)	69%	(11/16)	85%	(40/47)	48%	(15/31)	76%	(64/84)
Abnormal	0%	(0/1)	57%	(4/7)	**33%**	(1/3)	**17%**	(1/6)	57%	(4/7)	62%	(5/8)
Total	48%	(11/23)	76%	(42/55)	63%	(12/19)	77%	(41/53)	50%	(19/38)	75%	(69/92)

Data derived from Table 1.7a, labeled "Echo SWM Agreement with MRI ..."
Evaluable = all separate segments per contiguous image must each have an EBD score of either 2 or 3.

TABLE 18(b): IMUS-008 (N = 26); *All* (Separate) Segments
% of SWM 2D-Echo Agreement with MRI: Analyses of Each Cardiac View

	READER 1				READER 2				READER 3			
Views	**Baseline**		**Contrast**		**Baseline**		**Contrast**		**Baseline**		**Contrast**	
	%	#/ total	%	#/ total	%	#/total	%	#/ total	%	#/ total	%	#/ total
Apical 4-Chamber View: 26 patients x 6 segments = total of 156 segments												
Normal =102	10%	10	60%	61	16%	16	59%	60	13%	13	72%	73
Abnorm = 54	4%	2	15%	8	18%	10	26%	14	11%	6	35%	19
Total = 156	8%	12	44%	69	17%	26	47%	74	12%	19	59%	92
Apical 2-Chamber View: 26 patients x 6 segments = total of 156 segments												
Normal = 96	20%	19	52%	50	18%	17	40%	38	27%	26	40%	38
Abnorm = 60	**17%**	10	**17%**	10	7%	4	15%	9	**17%**	10	**15%**	9
Total = 156	19%	29	38%	60	13%	21	30%	47	23%	36	30%	47
Apical Long Axis View: 26 patients x 4 segments = total of 104 segments												
Normal = 96	11%	11	40%	38	11%	11	42%	40	16%	15	67%	64
Abnormal = 8	0%	0	50%	4	**12%**	1	**12%**	1	50%	4	62%	5
Total = 104	11%	11	40%	42	12%	12	39%	41	18%	19	66%	69

Data derived from Table 1.7a, labeled "Echo SWM Agreement with MRI ..."
Evaluable = all separate segments per contiguous image must each have an EBD score of either 2 or 3.

TABLE 19: SAFETY DATA OF COPD PATIENTS VERSUS OTHERS

	COPD				Others			
	AF0150 N = 97		Saline N= 15		AF0150 N = 360		Saline N = 86	
	N	(%)	N	(%)	N	(%)	N	(%)
Any	**17**	**(17%)**	**1**	**(7%)**	**32**	**(9%)**	**10**	**(12%)**
Body	**9**	**(9%)**	**0**		**9**	**(2%)**	**2**	**(2%)**
• Headache	4	(4%)	0		4	(1%)	2	(2%)
• Abdominal pain	2	(2%)	0		0		0	
• Asthenia	1	(1%)	0		3	(1%)	0	
• Chest pain	1	(1%)	0		0		0	
• Chills	1	(1%)	0		0		0	
• Injection site reaction	0		0		1	(0%)	0	
• Pain	0		0		1	(0%)	0	
Cardiovascular	**2**	**(2%)**	**0**		**13**	**(4%)**	**2**	**(2%)**
• Hypotension	1	(1%)	0		1	(0%)	0	
• Vasodilation	1	(1%)	0		1	(0%)	0	
• Hypertension	0		0		5	(1%)	1	(1%)
• EKG abnormality	0		0		2	(1%)	0	
• Angina pectoris	0		0		1	(0%)	0	
• Orthostatic Hypotension	0		0		0		1	(1%)
• Supravent. tachycardia	0		0		1	(0%)	0	
• T-wave inversion	0		0		1	(0%)	0	
• Tachycardia	0		0		1	(0%)	0	
Digestive System	**6**	**(6%)**	**0**		**5**	**(1%)**	**1**	**(1%)**
• Nausea	3	(3%)	0		2	(1%)	0	
• Diarrhea	1	(1%)	0		3	(1%)	1	(1%)
• Dyspepsia	1	(1%)	0		0		0	
• Tongue Disorder	1	(1%)	0		0		0	
Heme-Lymphatic	**1**	**(1%)**	**0**		**3**	**(1%)**	**0**	
• Thrombocytopenia	1	(1%)	0		0		0	
• Leukocytosis	0		0		2	(1%)	0	
• Fibrinogen Increased	0		0		1	(0%)	0	
Metabolic	**1**	**(1%)**	**0**		**3**	**(1%)**	**2**	**(2%)**
• Hyperglycemia	1	(1%)	0		0		1	(1%)
• CPK increased	0		0		3	(1%)	0	
• Bilirubinemia	0		0		0		1	(1%)
• LDH increased	0		0		0		1	(1%)
Musculo-skeletal	**0**		**0**		**1**	**(0%)**	**0**	
• Myalgia	0		0		1	(0%)	0	
Nervous	**0**		**0**		**3**	**(1%)**	**0**	
• Dizziness	0		0		2	(1%)	0	
• Paresthesia	0		0		1	(0%)	0	
Dermatoogic	**0**		**0**		**0**		**1**	**(1%)**
• Dry skin	0		0		0		1	(1%)
Special Senses	**2**	**(2%)**	**0**		**2**	**(1%)**	**3**	**(3%)**
• Taste Perversion	2	(2%)	0		2	(1%)	2	(2%)
• Parosmia	0		0		0		1	(1%)

TABLE 19: SAFETY DATA OF COPD PATIENTS VERSUS OTHERS (CONTINUED)

	COPD				Others			
	AF0150 N = 97		Saline N= 15		AF0150 N = 360		Saline N = 86	
	N	(%)	N	(%)	N	(%)	N	(%)
Any	**17**	**(17%)**	**1**	**(7%)**	**32**	**(9%)**	**10**	**(12%)**
Genito-urinary	**0**		**1**	**(7%)**	**1**	**(0%)**	**0**	
• Abuminuria	0		0		1	(0%)	0	
• Dysuria	0		1	(7%)	0		0	

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

/s/

Bernard Parker
4/30/02 06:35:32 PM
MEDICAL OFFICER
There are two additional objects that I could not add to this, but will add separately: (1) The title page with table of contents; and (2) my review, with corrections, of the proposed package insert, with the disclaimer that this product is approvable.

Ramesh Raman
5/31/02 11:08:09 AM
MEDICAL OFFICER
Concur in essence with Dr. Parkers's review and approvable recommendation. The clinical and statistical significance of the results is curtailed by the small sample size and structural data from a single study that does not support a functional claim.

Patricia Love
5/31/02 11:13:19 AM
MEDICAL OFFICER
Approval for structural indication. See my Division Director Memo to the File dated 5/31/02 for details

NDA 21-191: IMAVIST™
(AF0150; PERFLEXAN-PHOSPHOLIPID MICROBUBBLES) FOR INJECTION

Manufacturers: [redacted] Alliance Pharmaceutical Corporation
[redacted] 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 overall recommendation in August 2000 was that this product was approvable due to the significant improvement in the delineation the endocardial border in patients with stable cardiac disease,[1] which was contingent upon demonstration of a functional clinically useful endpoint – 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. SWM was assessed at baseline and with Imavist™ and compared to MRI in a subset of 26 patients. There was a suggestion of improvement in SWM assessments in the 26 patients. Because of the small sample size, no definitive conclusions could be drawn from these preliminary findings. Thus, efficacy for EBD as a primary structural endpoint had been demonstrated, but its value as a surrogate for a clinically useful endpoint 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.

In response, the sponsor proposed a new indication for a structural claim, with the rationale that the structural indication alone (EBD) has clinical application within the realm of diagnostic cardiology. In support, the sponsor resubmitted the SWM data on the 26 patients and additionally provided literature/references. In addition, the sponsor presented inter-observer agreement data

[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

on SWM from the 2 previously identified Phase 3 pivotal studies (IMUS-007 and –008). [redacted]

[redacted]. The sponsor further reiterated this issue for a border claim alone by referring to Optison®, another agent approved for a structural EBD claim. In November 2000, all sponsors (including Alliance) were informed that an EBD claim *per se* was not a surrogate for a functional claim. This resubmission additionally included data on the issues that were raised in the action letter on chemistry, pharmacokinetics, and (pre-clinical) pharmacology/toxicology (pharm/tox), including safety.

Reanalyses of the data from the 26 patients (comparisons of 2D-echo at baseline and enhanced with MRI) 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 intra-reader analyses of the variability between segments. The number of subjects tested with Imavist™ who had the truth standard (MRI) was limited. Additionally, all patients were selected from one site, and the methods employed in the selection of these patients is debatable and questionable. Furthermore, since none of the suboptimal 2D-echos were evaluated by the blinded reader, these analyses are meaningless with respect to the sought indication. A majority of the suboptimal segments were not evaluated in these 26 patients (from the statistical data: 74.3%). Furthermore, the literature is not supportive. The inter-reader agreement data cannot be corroborated as there is no truth standard.

Regarding clinical safety:

1. No new data were included.
2. No data from the ongoing study were included.
3. No annual reports were submitted.
4. The sponsor has addressed a few of the safety concerns that were identified in relationship to pharm/tox, pharmacokinetic, and chemistry, but is proposing to completely address these post-approval.

The previous "approvable" recommendation stands and the sponsor needs to address the issues as identified and discussed in the review and follow the recommendation that follows.

2-D echocardiography, using apical 4- and 2-chamber views; therefore, 12 segments (not the customary 16 segments) were viewed.