AF0150 administration. Despite prominent post-AF0150 elevations in IMUS-002 subjects, no correlation was made between the general characteristic / entry criterion for these subjects (patients with recent 1st-time myocardial infarcts) and the post-AF0150 elevations in fibrinogen.

TABLE 53 – INTEGRATED SAFETY

Subjects with "Potentially Clinical Significant" Values: Fibrinogen Post-dosing

Protocol	Subject	Parameter (mg/dL)	Observed Values (seconds) Baseline	1 hour	24 hour	Clinical Significance
Baseline values either normal or missing						
AF0150 0.125 mg/kg single dose						
IMUS-007-USA (N = 213)	06-020	Fibrinogen	Not available	Not available	**778***	Unknown
	14-006	Fibrinogen	377	**1***	**391**	Collection error
	16-009	Fibrinogen	271	Not available	**1***	Collection error
IMUS-008-USA (N = 232)	21-001	Fibrinogen	Not available	**667***	Not available	Subject's Disease
	30-017	Fibrinogen	Not available	**695***	Not available	Subject's Disease
	23-010	Fibrinogen	Not available	**616***	**628***	No
AF0150 multiple dose						
IMUS-002-USA	04-004	Fibrinogen	Not available	371 (30 min)	**633* (Day 7)**	No
Baseline values abnormal						
AF0150 0.125 mg/kg single dose						
IMUS-007-USA (N = 213)	08-010	Fibrinogen	524	588	**674**	Subject's Disease
	08-012	Fibrinogen	416	Not available	**4***	Subject's Disease
IMUS-008-USA (N = 232)	23-022	Fibrinogen	546	**630***	**602***	No
	26-005	Fibrinogen	539	541	**644***	No
AF0150 multiple dose						
IMUS-002-USA (N = 41)	01-004	Fibrinogen	566	**606* (20 min)**	**660* (Day 3)**	No
	04-005	Fibrinogen	571	**607* (30 min)**	491	No
	05-001	Fibrinogen	582	**768* (30 min)**	590	No
	05-002	Fibrinogen	552	522 (30 min)	**737* (Day 7)**	No
	05-006	Fibrinogen	435	492 (30 min)	**746***	No
	05-008	Fibrinogen	308	404 (30 min)	**678***	No
	05-010	Fibrinogen	591	**618* (20 min)**	**721***	No
	05-014	Fibrinogen	509	**541 (30 min)**	**615*(Day 2)**	No
	07-002	Fibrinogen	592	**558 (30 min)**	**606* (Day 2)**	No
	07-004	Fibrinogen	599	**684***	**684***	No
IMUS-003-USA (N = 47)	03-003	Fibrinogen	559	**606***	**606***	No
	03-005	Fibrinogen	599	582	582	No

Source: Volume 44, pp 208 (Table VIII.47; bolded numbers with asterisks are PCS values.

* Normal ranges: fibrinogen = low normal range of 150 – 200 mg/dL to high normal range of 330 – 500 mg/dL.

In the Phase 3 studies, 9 patients -- 3 patients in IMUS-007 and 6 patients in IMUS-008, which is 1% and 2% of the subjects, respectively -- had elevated CPK-MB levels. The CPK-MB level of elevation for all subjects was slight and there were no clinical manifestations associated with these lab data; therefore, these were not listed as adverse events. No explanation for the CPK-MB elevation was given; the medical histories of those subjects with elevated CPK-MB was not correlated with the elevated levels. Two patients (5%) enrolled in IMUS-002 had elevated CPK-MB levels, and LDH levels were also noted to be elevated in 5 subjects (12%). (No LDH isoenzymes were listed in the submission.) Because the subjects enrolled in this study had recent myocardial infarctions (1st-time MI's with documented Q-waves and elevated cardiac enzymes), a high percentage of subjects with elevated LDH is expected. Three subjects enrolled in IMUS-018

had elevated LDH levels, but since LDH isoenzymes were not recorded, those elevated levels could be related to the entry requirements of those subjects (must have focal lesions of the liver or kidney, affecting LDH_{4-5} levels and LDH_{1-2} levels, respectively).

TABLE 54 – INTEGRATED SAFETY

Subjects with "Potentially Clinical Significant" Values: Cardiac Enzymes Post-dosing

Protocol	Subject	Parameter	Observed Values (seconds)			Clinical Significance
			Baseline	1 hour	24 hour	
Baseline values either normal or missing						
AF0150 0.125 mg/kg single dose						
IMUS-007-USA (N = 213)	09-001	CPK-MB	4.6	5.1	**6.6***	No
	10-034	CPK-MB	1.1	0.9	**6.7***	Unknown
	12-007	CPK-MB	4.9	**5.2***	3.6	Not evaluated
IMUS-008-USA (N = 232)	20-003	CPK-MB	4.9	4.3	**6.0***	No
	20-010	CPK-MB	4.4	4.6	**6.4***	No
	20-018	CPK-MB	0.9	**5.8***	1.1	Unknown
	21-001	LDH	Not assessed	**597***	**585***	Subject's Disease
	22-014	LDH	195	**482***	181	No
	27-023	CPK-MB	4.5	4.1	**6.1***	No
	27-024	CPK-MB	5.0	4.2	**5.3***	No
	28-001	CPK-MB	1.3	**8.2***	1.4	Unknown; sp. Collect
AF0150 multiple dose						
IMUS-002-USA (N = 41)	03-002	CPK-MB	4.7	4.5 (30 min)	**10.9* (Day 7)**	Not stated
	03-003	CPK-MB	2.8	2.4 (30 min)	**16.8* (Day 3)**	Not stated
IMUS-003-USA (N = 47)	06-002	LDH	186	**513***	160	Not stated
	06-010	LDH	189	**487***	151	Not stated
Baseline values abnormal						
AF0150 0.125 mg/kg single dose						
IMUS-007-USA	None					
IMUS-008-USA	None					
AF0150 multiple dose						
IMUS-002-USA (N = 41)	01-002	LDH	344	**853* (15 min)**	**607***	Not stated
	02-001	LDH	316	**727* (30 min)**	287	Not stated
	03-003	LDH	410	**474* (5 min)**	296	Not stated
	05-007	LDH	399	291 (30 min)	**478* (Day 2)**	Not stated
	06-001	LDH	420	**490* (30 min)**	369	Not stated
IMUS-003-USA	04-003	LDH	430	**905* (4 hr)**	370	Not stated
IMUS-018-USA	02-011	LDH	407	**480***	431	Not stated

Source: Volume 44, pp 214 (Table VIII.50; bolded numbers with asterisks are PCS values.

* Normal ranges: CPK = low normal range of 0 – 24 IU/L to high normal range of 170 – 240 IU/L.

* Normal ranges: CPK-MB = low normal value of 0 IU/L to high normal range of 5 - 6 IU/L.

* Normal ranges: LDH = low normal range of 25 – 97 IU/L to high normal range of 125 – 250 IU/L.

Subjects who were enrolled in the single-dosed 0.125 mg/kg dose of AF0150 with **potentially clinically significant** values for ***both*** elevated cardiac enzymes and prolonged QTc are listed below, with each subject's medical history:

1. **Protocol IMUS-007-USA**
   a) **Subject 09-001**: History of being status post myocardial infarction and subsequent coronary artery bypass grafting due to history of coronary artery disease resulting from a history of hypertension.
   b) **Subject 04-021**: History of cardiac murmur

c) **Subject 08-012**: History of cardiomyopathy with resultant congestive heart failure, left atrial dilatation, and left ventricular hypertrophy; atrial fibrillation, cardiac murmurs, chronic obstructive pulmonary disease and obesity.

2. **Protocol IMUS-008-USA**

a) **Subject 20-020**: History of coronary artery disease and stable angina pectoris with subsequent coronary artery bypass grafting; history of atrio-ventricular block and right bundle branch block.

b) **Subject 22-005**: History of hypertension with resultant stable angina pectoris; history of diabetes mellitus.

c) **Subject 27-017**: History of cardiomegaly and congestive heart failure along with angina pectoris; history of atrio-ventricular block and status post pacemaker placement; history of diabetes mellitus.

ECG ABNORMALITIES (ADVERSE EVENTS / CHANGES)

A review of the ECG abnormalities viewed and recorded as adverse events are listed below as a composite from all studies. **(Please also refer to Table 50 above, illustrating the reported Cardiovascular and Pulmonary AE's.)** No clinically significant trends were noted by the sponsor. However, the view of the clinical reviewer in the Agency is that patients with recent or active cardiac disease related to either infarction or ischemia are at greater risk for arrhythmia. The risk is even greater in those subjects receiving multiple doses. This is best illustrated in the next table. The table below illustrates the fact that ECG abnormalities were most prominent in the "multiple dose" group. [Again, what needs to be emphasized is that the "multiple doses" group had subjects who had (1) recent myocardial infarctions in IMUS-002, (2) liver or kidney lesion in IMUS-003, and (3) left ventricular dysfunction with EF's between 20 and 40% in IMUS-018, as well as normal volunteers (IMUS-012).] No submission could be found regarding individual data (particularly when reviewing the pivotal Phase 3 data) to identify any possible trend toward having a "clinically significant" ECG adverse events.

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TABLE 55a: ECG (Cardiac Rhythm)
Abnormalities Reported as Adverse Events Post-Dosing

ECG Abnormalities Reported As Adverse Events	All Doses N = 608	AF0150 Single 0.125 mg/kg N = 457	Single other N = 48	Multiple doses N = 103	Saline N = 101
Atrial fibrillation	3 (0.5%)	0	0	3 (3%)	0
Atrial flutter	1 (0.2%)	0	0	1 (1%)	0
Bradycardia	1 (0.2%)	0	0	1 (1%)	0
ECG Abnormality	2 (0.3%)	2 (0.4%)	0	0	0
Extrasystoles	1 (0.2%)	0	0	1 (1%)	0
Sinus Bradycardia	1 (0.2%)	0	0	1 (1%)	0
Supravent. Tachycardia	1 (0.2%)	1 (0.2%)	0	0	0
T wave Inversion	1 (0.2%)	1 (0.2%)	0	0	0
Tachycardia (sinus?)	3 (0.5%)	1 (0.2%)	0	2 (2%)	0

Source: Volume 44, pp 246 (Table VIII.75).

The subjects who were recorded as having each of these abnormalities are as follows; again, one may refer to Table 50, where all of these subjects are listed with their respective AE (s).

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TABLE 55b: ECG (Cardiac Rhythm) Abnormalities Reported as Adverse Events Post-Dosing

ECG Abnormality	Protocol	ID #	Cardiac (and Related Risk Factors) History
Atrial fibrillation	IMUS-002	01-010	**Present**: CAD, HTN, "irregular heart rhythm", NIDDM **Past**: Multiple myocardial Infarctions (7 / 80; 10 / 80; 03 /97); "irregular heart rhythm"
		05-006	**Present**: Hypertension (HTN), on Vasotec® (enalapril) & Lopressor® (metoprolol) **Past**: Anterior Myocardial Infarction (12 / 96), on nitrates
		05-009	**Present**: HTN (on Lopressor®; metoprolol) , atrial fibrillation **Past**: Inferior Myocardial Infarction (12 / 96), on nitrates
Atrial flutter	IMUS-002	05-009	See above.
Bradycardia	IMUS-002	06-001	**Present**: Coronary Artery Disease, on Lopressor® (metoprolol) & nitroglycerine and other nitrates **Past**: Inferior Myocardial Infarction (02 / 97), as above
ECG Abnormality (unspecified)	IMUS-008	28-007	**Present**: Hyperlipidemia, premature atrial contractions, aortic sclerosis, borderline cardiomegaly **Past**: As above; only receiving Plendil® (felodipine) for HTN
	IMUS-008	30-023	**Present**: Congestive heart failure(on digitoxin, furosemide, & enalapril), coronary artery disease **Past**: Myocardial infarction, hyperlipidemia (on atorvastatin -- Lipitor®), and COPD
Extrasystoles	IMUS-002	03-001	**Present**: Hyperlipidemia (1986); also supravent. tachycardia treated with esmolol **Past**: Myocardial Infarction (01 / 97); on nitrites
Sinus Bradycardia	IMUS-002	03-002	**Present**: Graves Disease, treated with I^{131} (1975) and on thyroxine; hyperlipidemia, on lovastatin **Past**: Myocardial Infarction (02 / 97), on β-blocker (Lopressor®; metoprolol)
Supravent. Tachycardia	IMUS-007	07-009	**Present**: Diabetes mellitus, HTN (on ACE-inhibitors), CAD (on nitrates and Class Ib anti-arrythmics), CHF (on digitalis), anemia (possibly related to renal Insufficiency), obesity **Past**: Tobacco Abuse
T wave inversion	IMUS-008	28-008	**Present**: Angina, trace MVP and mitral regurgitation **Past**: Sinus tachycardia, tobacco abuse (on no C-V meds!)
Tachycardia	IMUS-007	03-063	**Present**: Dilated left atrium, mild mitral regurgitation; dyspnea **Past**:Status post cardioversion → atrial fibrillation (No Meds!)
	IMUS-002	04-004	**Present**: CAD (treated with metoprolol and nitrates), hyperlipidemia (treated with Lescol®; fluvastatin), hypokalemia (treated with oral potassium supplements) **Past**: Diabetes mellitus (05 / 96) treated with glyburide
	IMUS-003	03-003	**Present**: Hypothyroidism (treated with thyroxine); anemia (related to renal cell carcinoma) **Past**: unremarkable

Sources: Volume 125 pp 055 – 079 (IMUS-002), Volume 130 pp 105 – 146 (IMUS-003), Volume 105 pp 144 – 188 (meds) & 203 – 240 (subjects' histories in IMUS-007), & Volume 121 pp 018 – 039 (meds) & 051 – 158 (subjects' histories in IMUS-008).

***Potentially Clinically Significant (PCS)* ECG Abnormalities** *(includes those reported as AE's)*
Potentially clinically significant electrocardiogram (PCS ECGs) abnormalities were also submitted. Patients recorded with ECG abnormalities in all studies were tabulated in Volume 44 pp 240 – 247 of the submission. For the Phase 3 studies, the following was noted:

1. ***IMUS-007***: Subjects recorded as having ECG changes were 9 (4% of 213) and 5 (6% of 81) safety subjects randomized to AF0150 and saline treatment, respectively. Among those individuals, 3 (AF0150 – 2 subjects; saline – 1 subject) had abnormal baseline ECGs that changed to normal after dosing. [ECG abnormalities were noted at baseline for 91 subjects (43%) of those randomized to the AF0150 arm and 38 subjects (47%) randomized to the saline arm.] An additional 6 subjects (AF0150 – 3 subjects; saline – 3 subjects) with normal baseline ECGs and subsequent abnormal post-dose readings (as read by the core laboratory) were judged by the investigators to be normal.

TABLE 56: *PCS* ECG Abnormalities Post-Dosing in IMUS-007-USA

Subject No.	Baseline	Abnormality	Time of Change
AF0150-treated			
10-015	T-wave abnormality	Normal sinus rhythm	24 hrs post-AF0150
13-013			
03-002		T-wave abnormality	5 min, 1 hr, and 24 hrs post-AF0150
05-029	AV pacemaker	Arrhythmia	24 hrs post-AF0150
05-013	LAH, Q-wave	Atrial fibrillation, Q-wave and AV conduction defects	24 hrs post-AF0150
13-012	Q-wave abnormality	ST elevation and T-wave abnormality	5 min, 1 hr, and 24 hrs post-AF0150
03-047	Normal sinus rhythm	Arrhythmia	1 hr post-AF0150
13-018		T-wave abnormality	24 hrs post-AF0150
16-003		Arrhythmia	5 min post-AF0150
Saline-treated			
06-003	Arrhythmia, AV condition, and Q-wave	Ventricular pair	24 hrs post-saline
05-019	Normal sinus rhythm	ST segment depression	5 min post-saline
06-007		T-wave abnormality	24 hrs post-saline
07-008		ST segment depression, and T-wave abnormality	1 hr post-saline

Source: Volume 44, pp 241 (Table VIII.72).

2. ***IMUS-008***: Subjects recorded as having ECG changes were 24 (10% of 232) safety subjects treated with AF0150. Among those individuals, 5 subjects had abnormal baseline ECGs that changed to normal after dosing. [ECG abnormalities were noted at baseline for 136 subjects (59%).] Eleven of the 24 subjects with ECG changes had those changes occurring at 24 hours only.

TABLE 57: *PCS* ECG Abnormalities Post-Dosing in IMUS-008-USA

Subject No.	Baseline	Abnormality	Time of Change
AF0150-treated			
24-012	Normal sinus rhythm	ST depression; T-wave abnormality	1 hr post-AF0150
20-012		T-wave abnormality	24 hrs post-AF0150
25-005		T-wave abnormality	1 hr and 24 hrs post-AF0150
27-033		T-wave abnormality	24 hrs post-AF0150
28-007		T-wave abnormality	1 hr and 24 hrs post-AF0150
28-008		Normal sinus rhythm (disagreed)	5 min post-AF0150
20-011	ST depression; T-wave abnormality	Normal sinus rhythm	24 hr post-AF0150
22-006		Left ventricular hypertrophy; ST elevation	5 min and 1 hr post-AF0150
30-016		T-wave abnormality	1 hr and 24 hrs post-AF0150
22-017	Q-wave abnormality; atrio- ventricular conduction defect; T-wave abnormality	ST-segment depression	5 min and 1 hr post-AF0150
25-003		T-wave abnormality; ST segment depression	24 hrs post-AF0150
22-023	Q-wave abnormality	T-wave abnormality	24 hrs post-AF0150
27-019		ST depression	24 hrs post-AF0150
24-024	T-wave abnormality	T-wave abnormality	24 hrs post-AF0150
29-004		Normal sinus rhythm	24 hrs post-AF0150
30-023		ST depression	5 min and 1 hr post-AF0150
23-002	Arrhythmia	LAH; laterT-wave abnormality	5 min and then 1 hr and 24 hrs post-AF0150
24-022	Arrhythmia; ectopic atrial rhythm	T-wave abnormality	24 hrs post-AF0150
30-017	Arrhythmia; pacemaker	Pacemaker only (arrhythmia gone)	5 min and 24 hrs post-AF0150
22-008	AV conduction defects	T-wave abnormality	24 hrs post-AF0150
27-004	Ventricular conduction defect; T-wave abnormality	Disappearance of T-wave inversion	1 hr post-AF0150
30-013	Left bundle branch block; AV conduction block	Normal sinus rhythm	24 hrs post-AF0150

Source: Volume 44, pp 242 (Table VIII.73).

Tabulated below is a summary of the number of subjects who had potentially clinically significant prolonged QTc intervals. The QTc interval was monitored closely due to correlation of this adverse event with the triggering of ventricular dysrrhythmias. A total of 75 subjects (17% of 445 subjects receiving AF0150) experienced QTc prolongation, most of whom had a single incident (54 subjects = 72% of the 75 subjects). Within that subgroup, most subjects had QTc prolongation to occur within 1 hour to 24 hours post-AF0150 injection (42 subjects = 78% of the 54 subjects).

TABLE 58
PHASE 3 STUDIES -- QTc PROLONGATION POST-AFO150

Phase 3 Studies Study Drug	AF0150 total	IMUS-007 AF0150	IMUS-007 Saline	IMUS-008 AF0150
Safety Population	**445**	**213**	**81**	**232**
Total w/ prolonged QTc	**75 (17%)**	**36 (17%)**	**9 (11%)**	**39 (17%)**
• 5 min* post-injection	*26 (34%)*	*16 (44%)*	*3 (33%)*	*10 (26%)*
• 1 hr* post-injection	*39 (51%)*	*16 (44%)*	*3 (33%)*	*23 (59%)*
• 24 hr* post-injection	*35 (45%)*	*19 (53%)*	*6 (67%)*	*16 (41%)*
Single incidences	**54 (12%)**	**23 (11%)**	**6 (7%)**	**31 (13%)**
• 5 min post-injection	*12 (22%)*	*6 (26%)*	*2 (33%)*	*6 (19%)*
• 1 hr post-injection	*20 (37%)*	*5 (22%)*	*1 (17%)*	*15 (48%)*
• 24 hr post-injection	*22 (41%)*	*12 (52%)*	*3 (50%)*	*10 (32%)*
Incidences noted 5 min & at 1 hr post-injection	**8 (2%)**	**6 (3%)**	**0**	**2 (1%)**
Incidences noted 1 hr & at 24 hrs post-injection	**7 (2%)**	**3 (1%)**	**2 (2%)**	**4 (2%)**
Other incidences noted twice per subject	**2 (0.4%)**	**2 (1%)**	**1 (1%)**	**0**
Incidences noted throughout 24 hr period	**4 (1%)**	**2 (1%)**	**0**	**2 (1%)**

* Within this group, there are overlapping results; some subjects are counted at > 1 time-point.

As illustrated in Table 58, most subjects with QTc prolongation were noted to have this event to occur 1 to 24 hours after dosing with either AF0150 or saline. More subjects treated with AF0150 experienced QTc prolongation that those treated with saline. Notable is a small number of patients with baseline QTc intervals ≥ 450 msec whose post-AF0150 not only was prolonged > 30 msec but also reached ≥ 500 msec in length. Thus, subjects with baseline QTc's ≥ 450 msecs should be monitored for the possibility of potential arrhythmias due to prolongation of the QTc.

Table 59 illustrates the individuals noted to have had potentially clinically significant prolongation of the QTc interval.

TABLE 59: EKG Data (IMUS-007 and IMUS-008) Baseline and Post-Contrast

QTc (msec): Abnormal = (1) Increase > 30 msec from baseline , Or (2) Any QTc > 500 msec			Baseline	5 minutes		1 hour		24 hours	
IMUS-007 AF0150-tx (N = 213)	1.	02-003	406	***449***	***43 msec***	***448***	***42 msec***	***439***	***33 msec***
	2.	02-007	410	431	21 msec	417	7 msec	***441***	***31 msec***
	3.	02-014	418	435	17 msec	430	12 msec	***457***	***39 msec***
	4.	03-007	377	350	-27 msec	369	-8 msec	***424***	***47 msec***
	5.	03-016	371	359	-12 msec	358	-13 msec	***427***	***56 msec***
	6.	03-021	373	***406***	***33 msec***	370	-3 msec	401	28 msec
	7.	03-024	384	321	-63 msec	390	6 msec	***422***	***38 msec***
	8.	03-026	363	357	-6 msec	***399***	***36 msec***	378	15 msec
	9.	03-028	375	***412***	***37 msec***	***414***	***39 msec***	***420***	***45 msec***
	10.	03-044	410	424	14 msec	423	13 msec	***454***	***44 msec***
	11.	03-053	389	410	21 msec	***422***	***33 msec***	400	11 msec
	12.	03-056	402	426	24 msec	***434***	***32 msec***	***434***	***32 msec***
	13.	03-063	370	376	6 msec	***402***	***32 msec***	***408***	***38 msec***
	14.	03-064	420	***453***	***33 msec***	***465***	***45 msec***	398	-22 msec
	15.	04-002	325	351	26 msec	352	27 msec	***372***	***47 msec***
	16.	04-009	350	380	30 msec	***390***	***40 msec***	***386***	***36 msec***
	17.	04-015	342	353	11 msec	***373***	***31 msec***	369	27 msec
	18.	04-019	353	***394***	***41 msec***	***387***	***34 msec***	361	8 msec
	19.	04-021	390	***425***	***35 msec***	357	-33 msec	***428***	***38 msec***
	20.	05-005	409	***445***	***36 msec***	***445***	***36 msec***	394	-15 msec
	21.	05-010	381	381	0 msec	392	11 msec	***438***	***57 msec***
	22.	06-005	394	***430***	***36 msec***	***458***	***64 msec***	410	16 msec
	23.	08-010	430	443	13 msec	459	29 msec	***462***	***32 msec***
	24.	08-012	351	***384***	***33 msec***	369	18 msec	***399***	***48 msec***
	25.	09-001	409	421	12 msec	428	19 msec	***447***	***38 msec***
	26.	09-005	344	***375***	***31 msec***	362	18 msec	369	25 msec
	27.	10-012	370	***411***	***41 msec***	388	18 msec	395	25 msec
	28.	10-030	409	416	7 msec	***442***	***33 msec***	410	1 msec
	29.	10-031	369	***405***	***36 msec***	***414***	***45 msec***	368	-1 msec
	30.	10-034	408	***445***	***37 msec***	437	29 msec	417	9 msec
	31.	10-036	360	***399***	***39 msec***	***414***	***54 msec***	380	20 msec
	32.	12-002	422	414	-8 msec	***461***	***39 msec***	442	20 msec
	33.	12-010	390	408	18 msec	411	21 msec	***427***	***37 msec***
	34.	13-015	413	***448***	***35 msec***	411	-2 msec	423	10 msec
	35.	16-017	409	419	10 msec	408	-1 msec	***444***	***35 msec***
	36.	16-022	368	***399***	***31 msec***	387	19 msec	390	22 msec
IMUS-007 Saline-tx (N = 81)	1.	03-004	387	401	14 msec	385	-2 msec	***421***	***34 msec***
	2.	04-001	373	373	0 msec	373	0 msec	***416***	***43 msec***
	3.	05-009	389	***423***	***34 msec***	398	9 msec	380	-9 msec
	4.	06-010	406	***443***	***37 msec***	420	14 msec	***444***	***38 msec***
	5.	06-013	419	427	8 msec	***450***	***31 msec***	430	11 msec
	6.	07-004	354	348	-6 msec	***407***	***53 msec***	***442***	***88 msec***
	7.	07-010	402	***435***	***33 msec***	371	-31 msec	403	1 msec
	8.	09-004	370	397	27 msec	***411***	***41 msec***	***417***	***47 msec***
	9.	09-008	317	284	-33 msec	338	21 msec	***357***	***40 msec***

Source: Volume 75 pp 001 – 349, and Volume 76 pp 001 – 212 & *263 - 281*)
Bolded italicized numbers are the significant abnormal values.

prolongation and the arrhythmia. Additionally, there are subjects who were listed in Table 60 who were recorded as having potentially clinically significant ECG changes along with QTc prolongation; this was not noted in the saline population.

Table 60: Subjects with *both* QTc prolongation and ECG abnormalities

ID #	Electrocardiographic Results				Time of ↑ed QTc interval
	Adverse Events	Time	Poten. Clin. Significant "AE"	Time	
IMUS-007					
03-063	Tachycardia, mild (unspecified)*	22 hr post-AF0150			1 hr and 24 hr post-AF0150
IMUS-008					
28-008	T-wave inversion, mild*	6 min post-AF0150	**Baseline** of NSR; afterwards, a disagreed –upon "NSR" (vs. T-wave inversion, listed under "AEs")	5 min post-AF0150 (see "AEs" at left)	24 hrs post-AF0150
30-023	ECG Abnormality, mild* (unspecified, but probably ST-depression)	5 min post-AF0150	**Baseline** of T-wave abnormality (designated "chronic stable"); afterwards, ST depression	5 min and 1 hr post-AF0150	5 min, 1 hr, and 24 hrs post-AF0150
22-023			**Baseline** of Q-wave abnormality; afterwards, a T-wave abnormality	24 hrs post-AF0150	24 hr post-AF0150
23-002			**Baseline** of arrhythmia; LAH and later a T-wave abnormality	5 min and then 1 hr and 24 hrs post-AF0150	5 min post-AF0150
24-024			**Baseline** T-wave abnormality; afterwards, T-wave abnormality	24 hrs post – AF0150	5 min post-AF0150
25-003			**Baseline** Q- and T-wave abnormalities with AV conduction defect; afterwards, T-wave abnormality and ST-segment depression	24 hrs post-AF0150	1 hr and 24 hr post-AF0150
27-004			**Baseline,** ventricular conduction defect and T-wave abnormality; afterwards, disappearance of T-wave inversion	1 hr post-AF0150	1 hr and 24 hr post-AF0150
30-013			**Baseline** left-bundle branch block and AV conduction block; afterwards, NSR	24 hrs post-AF0150	5 min and 1 hr post-AF0150

* See Table 50 for exact timing of these ECG adverse events.

In addition, 3 patients had a significant increase in heart rate (either an increase in baseline > 15 beats per minute, or > 120 beats per minute, or a decrease from baseline > 15 and < 50 beats per minute). It remains to be determined as to whether there is a relationship with a prolonged QTc interval for these patients. Those patients were 03-024, 06-021, and 16-003 (see Vol. 76 p 282).

In conclusion, AF0150 appears to be safe for patients with stable cardiac diseases; however, there appears to be a greater risk of arrhythmias in subjects with recent ischemia and infarction of the heart. This was noted among subjects receiving multiple doses of AF0150. There is also a risk of prolongation of ventricular depolarization and subsequent repolarization, as demonstrated with prolongation of the QTc interval among subjects not receiving multiple, but rather single

doses as proposed in the package insert. Although the QTc prolongation was not clinically evident, one could anticipate a clinical adverse event to occur if AF0150 is administered even at the PCD, in patients with unstable cardiac disease. It is presently unknown whether there is a drug interaction with use of AF0150 with concomitant medicines; however, with the relatively short half-life of the gas portion of AF0150, it probably is not due to a drug-AF0150 interaction. Phase 4 commitment may help in resolving these concerns.

VITAL SIGNS (ADVERSE EVENTS/CHANGES)

In spite of statistically significant changes noted for pulse rate for all doses and administrative types of AF0150, there was no clinical relevant changes seen. The same holds true for the blood pressure, respiratory rate, and temperature. All vital sign parameters demonstrated minimal effects of AF0150 upon each parameter.

OXYGEN SATURATION (ADVERSE EVENTS/CHANGES)

There were no clinically significant 0_2 saturation changes in any of the studies; this is in spite of some statistically significant ($p = 0.05$) changes noted (see table below). Indeed, those were all increases, rather than decreases, in the oxygen saturation. Nevertheless, those changes (albeit not clinically significant) cannot at present be correlated to any changes in respiration rate.

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TABLE 61
MEAN O_2 SATURATIONS (%) FOR SUBJECTS ENROLLED IN ALL STUDIES

Time	Treatment Group									
	AF0150 Dose Group								Saline	
	Single doses 0.125 mg/kg		Other doses		Multiple Doses		All Doses			
	N = 457		N = 48		N = 103		N = 608		N = 101	
	% O_2 Sat. (n)	Δ	% O_2 Sat. (n)	Δ	% O_2 Sat. (n)	Δ	% O_2 Sat. (n)	Δ	% O_2 Sat. (n)	Δ
Baseline	96% (456)		97% (38)		96% (40)		96%(534)		97% (101)	
1 minute	99% (11)	***1.5***	99% (34)	***1.1***	96% (40)	-0.2	98% (85)	***0.5***	99% (20)	***0.9***
2 minutes	99% (11)	***1.3***	99% (32)	***1.1***	N/A		99% (43)	***1.1***	99% (20)	***0.8***
3 minutes	99% (12)	***1.4***	99% (32)	***0.9***	N/A		99% (44)	***1.1***	99% (20)	***0.8***
4 minutes	99% (12)	***1.2***	99% (32)	***0.8***	N/A		99% (44)	***0.9***	99% (20)	***0.4***
5 minutes	96% (455)	-0.1	99% (32)	***0.8***	N/A		96 % (487)	0.1	97% (100)	0.1
10 minutes	98% (12)	***0.9***	98% (33)	***0.6***	96% (40)	-0.5 (39)	97% (85)	0.2	99% (20)	***0.7***
15 minutes	96% (455)	0.0	99% (32)	***1.0***	N/A		96% (487)	0.0	97% (101)	0.0
20 minutes	N/A		94% (2)	- 3.0	96% (38)	0.1	96% (40)	0.0	N/A	
30 minutes	96% (454)	0.1	99% (32)	***0.8***	N/A		96% (486)	0.1	97% (99)	0.3
1 hour	96% (453)	***0.3***	98% (32)	0.6	N/A		96% (485)	***0.3***	97% (101)	0.3
1.5 hours	99% (12)	***1.3***	98% (32)	0.1	N/A		98% (44)	0.4	99% (19)	0.5
2 hours	98% (12)	0.8	98% (31)	***0.5***	N/A		98% (43)	***0.6***	98% (20)	0.2
2.5 hours	98% (12)	0.4	98% (32)	***0.5***	N/A		98% (44)	***0.5***	98% (20)	-0.1
3 hours	98% (12)	0.5	98% (31)	0.2	N/A		98% (43)	0.3	98% (20)	-0.1
3.5 hours	97% (12)	0.1	98% (32)	0.2	N/A		98% (44)	0.2	98% (20)	0.1
4 hours	98% (12)	0.4	98% (32)	0.3	N/A		98% (44)	0.3	98% (20)	0.1
24 hours	96% (440)	***0.2***	N/A		N/A		96% (440)	***0.2***	97% (79)	0.3

Source: Modified version (combination) Volume 44 pp 248 – 249 (Tables VIII.77 and .78)
Δ = Mean change from the baseline 02 saturation; ***bolded and italicized*** data are statistically significant at a $p \leq 0.05$.

Finally, most *potentially clinically significant* changes occurred during the 1st hour post-AF0150; the percentage of patients receiving saline (placebo) had a virtually identical change in O_2 saturation at the same time-points.

MENTAL STATUS EXAMINATION

MMSE scores did not demonstrate any consistent changes related to AF0150 administration; as the sponsor states and agreed upon by this reviewer, this was also noted in patients with a history of pulmonary disease.

CONCLUSION

AF0150 produces very few adverse events; those AE's that are part of the constellation of symptoms that ultimately can be tied together as gas embolism are generally mild and relatively sporadic. Patients with recent cardiac disease, especially related to coronary artery disease, have a greater propensity toward developing arrhythmias, which may be related to the contrast agent triggering this event. However, the relationship of the onset of arrhythmias to the underlying cardiac disease cannot be ruled out. In addition, a trend toward an increase in the QTc interval was noted in subjects receiving AF0150. However, for the pivotal Phase 3 study IMUS-007-USA, the incidence of subjects in both AF0150-treated and saline-treated groups was virtually the same; for both Phase 3 studies, the QTc interval increases were not statistically or clinically significant and therefore were not recorded as clinical adverse events. Follow-up with Phase 4 studies (post-approval) may be used to address both concerns in subjects with stable and unstable cardiac disease. It remains to be determined whether any drug-drug interaction may play a role in these cardiac and other AE's. The dosage of 0.125 mg/kg appears to be safe in the majority of patients with stable cardiac disease; there is no subpopulation of patients (i.e., gender, race, age) that can correlate with the triggering of AE's, although it appears that the different subpopulations are low in number in this study.

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VIII. Review of the 120-Day Safety Update

Submitted To NDA 21-191: February 29, 2000
Received By Agency: March 1, 2000

The 120-day safety update includes data from 3 Phase 2 clinical studies, tabulated below with summaries of study designs, doses, and number of subjects entered for each treatment within each study. Efficacy findings were not included; these studies, according to the sponsor, were conducted to evaluate AF0150 for uses other than that claimed in this application.

TABLE 62: 120-DAY SAFETY UPDATE – Studies Reviewed In This Submission

STUDY NUMBER, TITLE AND DESIGN	AF0150 DOSES	NO. SUBJECTS	PRELIMINARY SAFETY FINDINGS
IMUS-[redacted]			
Myocardial Contrast Echocardiography During Vasodilator Stress for the Assessment of Coronary Artery Disease: Relation to Coronary Flow Reserve and Radionuclide Perfusion Imaging Open-label, single center, uncontrolled Phase 2 study in subjects with known or suspected coronary artery disease with reversible perfusion defect	Infusion Therapy: Up to 4.0 mg/kg, administered up to ~ 14 minutes (20 mg/minute)	14 subjects; age range of 39 – 64 years; mean age of 53 years.	• No serious or severe adverse events. • 16 AE's reported by 50% of subjects (7 out of 14 subjects). Most common AE's included chest pain (4 subjects), insomnia (3 subjects) and pain (2 subjects). • No clinically significant abnormalities or trends in safety assessments following AF0150 administration.
IMUS-013-USA			
A Safety, Dosing and Efficacy Study of AF0150 to Improve Lesion Visualization During Ultrasonographic Evaluation of Breast Lesions Suspicious for Malignancy Open-label, multicenter, paired-comparison Phase 2 study in subjects with breast lesions on mammogram or ultrasound who are scheduled for biopsy	Bolus Treatment: Administered up to ~ 3 seconds (5.0 mL / second) • 1.0 mg/kg • 2.0 mg/kg • 4.0 mg/kg	28 subjects; age range of 40 – 74 years; mean age of 57 years. 13 subjects 1 subject 14 subjects	• No serious or severe AE's. • 4 AE's reported by 14% of subjects (4 out of 28 subjects); headache, injection site reaction, paresthesia, and breast pain (1 subject each). • No clinically significant abnormalities or trends in safety assessments following AF0150 administration.
IMUS-014-USA			
A Single-Center, Open-Label, Randomized Study to Assess the Feasibility of AF0150-Enhanced Ultrasound to Aid in the Visualization of Prostatic Lesions in Males with Elevated Prostate Specific Antigen (PSA) and/or Abnormal Digital Rectal Exam (DRE) Who are Scheduled for Transrectal Ultrasound Open-label, multicenter, randomized Phase 2 study in male subjects with elevated prostate specific antigen levels and/or abnormal digital rectal examinations who are scheduled for transrectal ultrasound with biopsy	Bolus Treatment: Administered up to ~ 15 seconds (1.0 mL / second) • 1.0 mg/kg • 2.0 mg/kg • 4.0 mg/kg Infusion Therapy: Up to 4.0 mg/kg, ~ 2 min @ 20 mg/minute, then ~ 2 min @ 35 mg/minute, then ~ 2 min @ 50 mg/minute (n = 4); up to ~ 11 min (n = 10) for 35 to 50 mg/min	26 subjects; age range of 38 – 81 years; mean age of 64 years. 4 subjects 4 subjects 4 subjects 14 subjects	• No serious or severe AE's. • 57 AE's reported by 92% of subjects (24 out of 26 subjects). Most common AE's included hematuria (18 subjects), pain (12 subjects), and rectal hemorrhage (12 subjects), all expected in patients undergoing TRUS. • No clinically significant abnormalities or trends in safety assessments following AF0150 administration.

DEMOGRAPHICS

Below is a table illustrating the characteristics of the populations enrolled in all 3 studies separately and combined. Although gender appears to be equal in terms of total subject

enrollment (IMUS-013 concentrated upon females; IMUS-014 was for males), most subjects were relatively young (< 65 years of age).

TABLE 63: 120-Day Safety Update -- Demographics

Characteristics	Protocols			Total
	IMUS [redacted] N = 14	IMUS-013-USA N = 28	IMUS-014-USA N = 26	N = 68
Age				
• < 65 years	14 (100%)	20 (71%)	14 (54%)	48 (71%)
• 65 – 80 years	0	8 (29%)	11 (42%)	19 (28%)
• > 80 years	0	[redacted]	1 (4%)	1 (1%)
Gender				
• Male	7 (50%)	1 (4%)	26 (100%)	34 (50%)
• Female	7 (50%)	27 (96%)	0	34 (50%)
Race				
• White	2 (14%)	16 (57%)	19 (73%)	37 (54%)
• Black	7 (50%)	6 (21%)	6 (23%)	19 (28%)
• Asian	1 (7%)	1 (4%)	0	2 (3%)
• Other	4 (29%)	5 (18%)	1 (4%)	10 (14%)

Source: Volume 1, pp 068 - 075

CLINICAL ADVERSE EVENTS

Because these studies are on-going, no efficacy results were submitted. This submission is to concentrate upon the safety aspects of AF0150 administration. The next table reviews the percentage of subjects for each protocol and for all together who were reported to have had treatment-emergent adverse events, sorted by body system. There were a total of 35 subjects (51%) of the 68 subjects in the 3 studies who were reported to have had adverse events. The most frequently reported were hematuria (26%, all in the prostate protocol), pain (21%), rectal hemorrhage (18%, again, all in the prostate protocol), asthenia (7%, all in the prostate protocol), chest pain and insomnia (6% each) and headache (4%). The patients in the prostate protocol (IMUS-014) were scheduled to undergo transrectal ultrasound (TRUS)-guided biopsies, and thus the hematuria, rectal hemorrhage, and asthenia were very likely not related to the study drug. Finally, all except 7 of the AE's listed were mild in severity; the 7 moderate AE's were also in the prostate protocol. Although the moderate AE's listed may be related to the TRUS-guided biopsy procedure, the descriptor "pain" was not adequately described (rectal vs. abdominal vs. chest).

TABLE 64: Safety Update – Overall Incidence of Adverse Events

Body System	Protocols				Total
	IMUS [redacted]		IMUS-013-USA	IMUS-014-USA	
	N = 14		N = 28	N = 26	N = 68
	Total	> Mild	Total	Total	> Mild	
Body as a whole						
Total No. Patients	**6 (43%)**		**2 (7%)**	**14 (54%)**	**7 (27%)**	**22 (32%)**
Asthenia				5 (19%)	2 (8%)	5 (7%)
Chest Pain	4 (29%)					4 (6%)
Chills				1 (4%)		1 (1%)
Fever				1 (4%)		1 (1%)
Headache	1 (7%)		1 (4%)	1 (4%)		3 (4%)
Inject. Site Reaction			1 (4%)			1 (1%)
Pain	2 (14%)			12 (46%)	6 (23%)	14 (21%)
Cardiovascular						
Total No. Patients	**1 (7%)**			**1 (4%)**		**2 (3%)**
Atrial fibrillation	1 (7%)					1 (1%)
Hypertension	1 (7%)					1 (1%)
Syncope				1 (4%)		1 (1%)
Digestive						
Total No. Patients	**1 (7%)**			**12 (46%)**		**13 (19%)**
Dyspepsia	1 (7%)					1 (1%)
Flatulence				1 (4%)		1 (1%)
Rectal Hemorrhage				12 (46%)		12 (18%)
Metabolic and Nutritional						
Total No. Patients	**2 (14%)**					**2 (3%)**
↑ Cholesterolemia	1 (7%)					1 (1%)
Hypokalemia	1 (7%)					1 (1%)
Nervous						
Total No. Patients	3 (21%)		1 (4%)	2 (8%)		**6 (9%)**
Insomnia	3 (21%)			1 (4%)		4 (6%)
Paresthesia			1 (4%)			1 (1%)
Urinary Retention				1 (4%)		1 (1%)
Respiratory						
Total No. Patients	1 (7%)			1 (4%)		**2 (3 %)**
Hiccup				1 (4%)		1 (1%)
Rhinitis	1 (7%)					1 (1%)
Skin and Appendages						
Total No. Patients				1 (4%)		**1 (1%)**
Sweating				1 (4%)		1 (1%)
Urogenital						
Total No. Patients			1 (4%)	19 (73%)		**20 (29%)**
Breast pain			1 (4%)			1 (1%)
Hematuria				18 (69%)		18 (26%)
Urination impaired				1 (4%)		1 (1%)

Source: Volume 1, pp 076 – 097.
All AE's > mild were moderate; there were no severe AE's. All blank areas are "0" = 0%.

CLINICAL LABORATORY ADVERSE EVENTS

Normal ranges for all laboratory parameters were submitted into Section N, Listing 8a (Volume 2, pp 189 – 196); the values for "potentially clinically significant" levels were also submitted in

Section N, Listing 8b (Volume 2, pp 197- 201). For identification of marked laboratory abnormalities, the "panic alert" value, or the "telephone alert" value that was used in the Phase 3 studies were also applied in these 3 studies. These "panic-alert" or "telephone-alert" values are defined as "potentially clinically significant (PCS)" values. Please refer to the Study Monitoring Section in the Integrated Efficacy part of this submission for definitions.

Two subjects, both from the Protocol IMUS- [redacted] were reported to have had laboratory abnormalities deemed as AE's.

- **Subject 01-105**: Had an elevated baseline cholesterol at 275 mg/dL (although no medical history of hyperlipidemia); one hour and 24 hours post-AF0150 dosing, the levels were still elevated at 238 mg/dL. The patient was not given any lipid-lowering agents during the study. The laboratory AE's were listed as "mild".
- **Subject 01-100**: Had a baseline serum potassium of 3.8 mEq/L, which decreased 1 hour post-AF0150 to 3.4 mEq/L ("mild" AE). The serum potassium returned to normal levels (4.9 mEq/L) at 24 hours post-AF0150.

There were no potential clinically significant values for coagulation parameters (PT and aPTT), platelet counts, or renal function values (BUN and serum creatinine).

Potentially Clinically Significant LABORATORY ADVERSE EVENTS

Below is tabulated the list of only those patients (along with the respective protocols and parameters) who were discussed in the text regarding potentially clinically significant laboratory events. Although not all data is included within this table, the data present seems to indicate that AF0150 usage might play a role in having cardiac effects in those patients with histories of cardiac ischemia. Almost all subjects tabulated below were enrolled in IMUS- [redacted] with the potentially clinically significant laboratory values noted to be elevated were cardiac enzymes – specifically LDH (without isoenzymes listed, however). Subjects enrolled in IMUS- [redacted] had known or suspected coronary artery disease, with elevated LDH levels at baseline as illustrated below. Few of those subjects had progressively increasing LDH values to occur after AF0150 dosing; most subjects had progressively decreasing (therefore, improving) LDH levels one hour and later post-AF0150. Therefore, based upon the improvement of the potentially clinically significant laboratory values noted post-AF0150 administration, AF0150 appears to be safe to administer.

TABLE 65: Patients Who Experienced Potentially Clinically Significant AE's

Protocol	Subject	Parameter (seconds)	Observed Values (seconds) Baseline	1 hour	24 hour	Clinical Significance
Baseline values either normal or missing						
AF0150 0.125 mg/kg single dose						
IMUS [redacted]	01-108	Neutrophils	84% ↑	79% ↑	91% ↑	No evid. of infection.
		LDH (IU/L)	666 ↑	663 ↑	724 ↑	
	01-113	Direct Bili.	0.4 mg/dL	1.4 mg/dL↑	0.4 mg/dL	
		LDH (IU/L)	559 ↑	1830↑	620 ↑	History of Angina
		Triglyceride	534 ↑	Not listed.	544 ↑	
	01-101	LDH (IU/L)	749 ↑	464 ↑	457 ↑	
	01-102	LDH (IU/L)	505 ↑	542 ↑	592 ↑	
	01-103	LDH (IU/L)	506 ↑	458 ↑	496 ↑	
	01-104	LDH (IU/L)	500 ↑	494 ↑	434	
	01-105	LDH (IU/L)	508 ↑	479 ↑	341	
		Urine pH	5.0	1.0 ↓	5.5	
	01-106	LDH (IU/L)	794 ↑	678 ↑	723 ↑	
	01-110	LDH (IU/L)	634 ↑	419	544 ↑	
	01-111	LDH (IU/L)	759 ↑	798 ↑	671 ↑	History of Angina
		CPK (IU/L)	830 ↑	841 ↑	771	
		CPK-MB	0.9 ng/mL	1.1 ng/mL	6.3 ↑	
	01-112	LDH (IU/L)	462 ↑	302	397	
IMUS-013	02-013	Cholesterol	393 ↑	Not listed.	377 ↑	
IMUS-014	01-024	Triglyceride	411	381	519↑	

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Source: Volume 2, pp 084 – 085, 153 – 157, and 185.

CHANGES IN 0_2 SATURATION

There were no trends or changes with oxygen saturation following use of AF0150 in IMUS-013 (patients with breast lesions) and IMUS-014 (patients with prostate lesions); however, oxygen saturation was not studied in IMUS- [redacted] (patients undergoing vasodilatory stress test for evaluation of coronary artery disease). Phase 4 follow-up studies may help to determine if the use of AF0150 will have an impact on such a patient population.

CHANGES IN VITAL SIGNS

Changes in vital signs were observed in IMUS- [redacted] . these changes may be related to the used of persantine (a vasodilatory agent) as a pharmacologic stress agent. However, one cannot completely exclude a possible drug-drug interaction with AF0150. Further studies (drug-interaction with vasodilatory agents) may be necessary.

CONCLUSION

The 120-day safety update was submitted to follow the safety data of 3 studies which were not included within the original NDA submission. The safety profile of AF0150 continues to appear to possibly have an association with potential cardiac adverse effects, as was noted with elevations of LDH and (to a lesser extent) CPK cardiac enzymes. Again, Phase 4 studies can help in answering questions regarding the impact AF0150 might have upon patients with coronary artery disease, as well as possible mechanisms.

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IX. OVERALL RECOMMENDATION

AF0150 was tested in two pivotal phase 3 studies, involving patients with stable cardiac function but poorly visualized echocardiograms. Delineation of the endocardial border (EBD) was significantly improved after use of AF0150 as a contrast agent in fundamental continuous (and also gated) 2-D echocardiography, especially in those segments with the greatest frequency of poor visualization. However, AF0150 contrast does not appear to improve the ability for the echocardiologists to accurately assess the ejection fractions (EF). Thus, the only primary endpoint that has proven efficacy is an improved EBD, with no subset demonstrating greater efficacy. Assessment of segmental wall motion (a secondary endpoint) appeared to show a statistically significant improvement when using AF0150, with a statistically significant higher percentage of segments in the AF0150-contrasted echocardiograms in agreement with MRI studies as compared with non-contrasted baseline echocardiograms' agreement with MRI studies. However, because of the small number of patients (n = 26) evaluated with MRI, the data appears testimonial (subjective) without a *universally accepted* standard of truth (objective) and therefore unreliable.

AF0150, at the proposed clinical dose of 0.125 mg/kg, produces few adverse events, even among patients with a history of cardiac or pulmonary disease; most AE's are mild and sporadic. Patients with recent complications from coronary artery disease tend to have a greater propensity toward developing arrhythmias. Preclinical studies involving cardiac evaluation after AF0150 administration had demonstrated the possibility of the ultrasound *per se* rather than the contrast agent as being the cause of arrhythmic sequelae. Follow-up with Phase 4 studies using the prescribed clinical dose of AF0150 for evaluating cardiac function (via echocardiography) in subjects who have stable recent coronary artery disease and stable (controlled) arrhythmia (arrhythmia history) may be necessary to address this concern. The dosage of 0.125 mg/kg appears to be safe in the majority of patients with stable cardiac disease; no subpopulation of patients (i.e., gender, race, age) can be distinguished as having an increased chance of AE's, due to low numbers enrolled in the studies.

The overall recommendation is that this product is approvable, in spite of the lack of evidence of improving efficacy in determining the cardiac function (EF), with and without EBD data, in patients with stable cardiac function. Because the estimation of EF did not improve after use of the contrast agent, a data base for the end-systolic (ES) and end-diastolic (ED) ventricular volumes [derived from both fundamental modes (continuous and gated) of 2-dimensional echocardiography] is needed for this determination. At this point, the Agency needs, at a

5 pages redacted from this section of the approval package consisted of draft labeling

APPENDIX A: ENDOCARDIAL BORDER DELINEATION WITH GATED MODE

IMUS-007 : Endocardial Border Delineation – Individual Segment Mean Change from Baseline Score ‡ (gated mode in 3 apical view, *N = 206*)

View	Reader 1			Reader 2			Reader 3		
(Seg.)	Baseline	AF0150	Differ.	Baseline	AF0150	Differ.	Baseline	AF0150	Differ.
View†	20.1	24.7	*4.6*	26.1	27.2	*1.1*✳	15.9	21.1	*5.2*
Apical 4-chamber segments									
View†	7.9	10.0	*2.1*	10.1	10.7	*0.6*	6.2	8.3	*2.1*
1	1.9	2.0	*0.1*✳	2.0	1.8	*-0.2*	1.7	1.6	*-0.0*✳
2	1.8	2.0	*0.2*	2.1	2.0	*-0.1*✳	1.8	1.8	*0.1*✳
3	0.8	1.3	*0.4*	0.6	1.7	*-0.0*✳	1.0	1.1	*0.2*
4	0.8	1.3	*0.5*	1.4	1.6	*0.2*	0.5	0.8	*0.4*
5	1.2	1.7	*0.5*	1.5	1.8	*0.3*	0.7	1.5	*0.8*
6	1.3	1.8	*0.4*	1.4	1.8	*0.3*	0.7	1.4	*0.8*
Apical 2-chamber segments									
View†	6.8	8.6	*1.8*	9.6	10.0	*0.4*✳	5.6	7.2	*1.6*
7	1.8	1.8	*-0.0*✳	1.9	1.8	*-0.1*	1.5	1.6	*0.1*✳
8	1.8	1.8	*0.0*✳	2.0	1.9	*-0.1*	1.7	1.8	*0.0*✳
9	0.6	1.0	*0.4*	1.6	1.5	*-0.0*✳	0.8	0.8	*0.0*✳
10	0.6	1.0	*0.5*	1.3	1.4	*0.2*	0.4	0.6	*0.2*
11	1.0	1.5	*0.5*	1.4	1.7	*0.2*	0.5	1.2	*0.7*
12	1.1	1.5	*0.4*	1.4	1.7	*0.2*	0.5	1.1	*0.6*
Apical long axis segments									
View†	5.3	6.1	*0.8*	6.4	6.5	*0.0*✳	4.1	5.6	*1.4*
13	1.3	1.5	*0.3*	1.6	1.7	*0.1*✳	1.0	1.5	*0.5*
14	1.2	1.5	*0.3*	1.6	1.7	*0.1*✳	1.0	1.5	*0.5*
15	1.3	1.5	*0.1*✳	1.6	1.6	*-0.1*✳	1.0	1.3	*0.3*
16	1.4	1.5	*0.1*✳	1.6	1.6	*-0.1*	1.1	1.3	*0.2*

Derived from Volume 90, pp 224 – 264

✳ p-value ***not*** significant at the 0.05 level.

† The "View" data is from the "No Change" Scenario; the "Worst Change" Scenario has virtually the same data.

‡ Calculated base on a scale of 0 = no delineation; 1 = mild/ fair delineation; 2 = moderate / good delineation; 3 = excellent delineation.

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IMUS-008: Endocardial Border Delineation – Individual Segment Mean Change from Baseline Score ‡ (gated mode in 3 apical view, *N = 203*)

View	Reader 1			Reader 2			Reader 3		
(Seg.)	Baseline	AF0150	Differ.	Baseline	AF0150	Differ.	Baseline	AF0150	Differ.
View†	12.1	17.4	*5.3*	10.3	18.1	*7.8*	19.6	26.3	*6.8*
Apical 4-chamber segments									
View†	4.5	6.9	*2.5*	4.5	7.4	*2.9*	7.0	10.0	*3.0*
1	1.0	1.2	*0.3*	0.8	1.2	*0.3*	1.1	1.6	*0.5*
2	1.4	1.5	*0.1*	1.1	1.4	*0.3*	1.4	1.7	*0.3*
3	0.7	1.0	*0.3*	1.0	1.2	*0.2*	1.2	1.6	*0.4*
4	0.5	0.9	*0.4*	0.7	1.1	*0.5*	1.1	1.6	*0.5*
5	0.6	1.2	*0.6*	0.5	1.2	*0.7*	1.1	1.7	*0.7*
6	0.3	1.1	*0.7*	0.4	1.2	*0.8*	1.1	1.7	*0.7*
Apical 2-chamber segments									
View†	4.6	6.3	*1.7*	3.5	6.4	*2.9*	7.3	9.8	*2.4*
7	1.1	1.3	*0.3*	0.5	1.1	*0.6*	1.4	1.8	*0.3*
8	1.4	1.5	*0.1*	1.0	1.3	*0.3*	1.5	1.8	*0.2*
9	0.7	0.8	*0.1*	0.8	1.1	*0.3*	1.1	1.5	*0.4*
10	0.4	0.7	*0.3*	0.5	0.9	*0.4*	1.1	1.5	*0.4*
11	0.6	1.0	*0.4*	0.4	1.0	*0.6*	1.1	1.6	*0.5*
12	0.4	0.9	*0.5*	0.3	1.0	*0.7*	1.1	1.6	*0.5*
Apical long axis segments									
View†	3.0	4.1	*1.1*	2.3	4.3	*2.0*	5.2	6.6	*1.3*
13	0.6	1.1	*0.5*	0.3	1.1	*0.8*	1.3	1.7	*0.4*
14	0.7	1.2	*0.5*	0.5	1.1	*0.7*	1.3	1.7	*0.4*
15	1.0	1.0	*0.0*✳	0.7	1.0	*0.3*	1.4	1.6	*0.2*
16	0.7	0.8	*0.1*✳	0.9	1.1	*0.2*	1.3	1.6	*0.3*

Derived from Volume 107, pp 214 – 252.

✳ p-value ***not*** significant at the 0.05 level.

† The "View" data actually is the sum of the scores for each of the different views in each of the (3) segment; all results are significant at a p value of 0.001.

‡ Calculated base on a scale of 0 = no delineation; 1 = mild/ fair delineation; 2 = moderate / good delineation; 3 = excellent delineation.

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APPENDIX B : TABULAR SUMMARY OF CLINICAL STUDIES USING AF0150 (Imavist™)

PROTOCOL	TITLE	STUDY DESIGN	STUDY METHODOLOGY
IMUS-001-USA	A Single-Blind, Dose-Ranging, Placebo-Controlled, Safety, and Contrast Enhancement Study in Normal Volunteers Receiving AF0150 Administered by Intravenous Injection	A single-center (Innovex, Inc., Lenexa, Kansas), single-blind, randomized, placebo-controlled, dose-ranging, 3-staged Phase 1 study investigating safety. 22 pts → Bolus AF0150 (0.125, 0.5, 2.0, or 4.0 mg/kg in 10 sec x 1 dose) 22 pts → Placebo (0.2 mL 0.9% NaCl) 4 pts → Infusion (4.0 mg/kg over 10 min)	Stage 1: 24 patients randomized to either AF0150 or placebo, followed by U/S evaluation for visual clearance of agent. Stage 2: 18 patients randomized similarly, followed by contrast imaging of the heart. Stage 3: 18 patients randomized similarly, followed by contrast imaging of the abdominal region.
IMUS-002-USA	Safety, Dosing, and Efficacy Study of AF0150 in the Contrast-Echocardiographic Assessment of Left Ventricular Function and Myocardial Perfusion in Patients Following Q-Wave Myocardial Infarct	A multicenter (all 7 centers were in the U.S.), open-label, 2-staged Phase 2 study investigating safety in such patients (see title); there is no placebo-control group. Stage 1: The "pilot stage", evaluating left-ventricular function, comparing bolus versus infusional AF0150 contrast. Stage 2: The "open stage", comparing AF0150-2D-echo results with ^{99m}Tc sestamibi-SPECT imaging results.	All subjects were to receive 2 injections of AF0150. The 1st treatment -- IV bolus of 0.25 mg/kg over 30 seconds. The 2nd treatment -- an IV infusion [redacted] of up to 80 mg AF0150 over 10 minutes. Stage 1: The "pilot stage", enrolling 10 patients referred for nuclear perfusion study prior to discharge from hospital. Stage 2: The "open stage", enrolling 30 patients but w/o regards to presence or extent of any existing myocardial perfusion abnormality.

TABULAR SUMMARY OF CLINICAL STUDIES USING AF0150 (Imavist™) *continued*:

PROTOCOL	TITLE	STUDY DESIGN	STUDY METHODOLOGY
IMUS-003-USA	Safety, Dosing, and Efficacy Study of AF0150 in the Contrast-Ultrasound Assessment of Focal Lesions of the Liver or Kidney in Patients with CT-or MRI-Confirmed Abnormalities	A multicenter (all 6 centers were in the U.S.), open-label, 2-staged Phase 2 study investigating safety in such patients (see title); there is no placebo-control group. 2° objective: efficacy using fundamental gray-scale, 2nd harmonic, and power and [redacted] Doppler ultrasound imaging.	Stage 1: The "pilot (purely safety) stage" enrolled 22 subjects; the 1st 6 patients were randomized to receive either a series of bolus doses (40 mg followed by a maximum of four 10- to 20-mg doses) or infusion. Afterwards (Amd. 3), each patient received an initial bolus followed by an infusion. Stage 2: The "open (efficacy and safety) stage" enrolled 25 subjects, who each received a bolus dose of up to 1.0 mg/kg AF0150, followed by a titrated infusion of up to 160 mg AF0150.

IMUS-007-USA	A Multicenter, Saline-Controlled Study of AF0150 in the Echocardiographic Assessment of Left Ventricular Function in Patients with Suboptimal Noncontrast Images ✳	A multicenter (all 18 centers were in the U.S.), single-blind (3 independent nuclear medicine physicians evaluate EBD, EF, and SWM), placebo- (saline-) controlled (for safety only), single-dose, randomized (for the 1st 160 patients for safety evaluation) Phase 3 pivotal, paired-comparison (comparing pre- and post-AF0150 images) study.	AF0150 IV bolus injection of 0.125 mg/kg over 10 secs.
			• 290 patients were planned to be enrolled
			  • 210 patients → AF0150 (1st 80 pts → safety)
			  • 80 patients → saline
			• 294 patients were ultimately enrolled
			  • 213 patients → AF0150 (1st 81 pts → safety)
			  • 81 patients → saline
			• 206 AF0150 patients were evaluated for efficacy
			• All patients were evaluated for safety

IMUS-008-USA	A Multicenter, Open-Label Study of AF0150 in the Echocardiographic Assessment of Left Ventricular Function in Patients with Suboptimal Noncontrast Images ✳	A multicenter (all 11 centers were in the U.S.), single-blind (3 independent nuclear medicine physicians evaluate EBD, EF, and SWM), single-dose, open-label Phase 3 supportive study	AF0150 IV bolus injection of 0.125 mg/kg over 10 secs.; 230 patients were planned for enrollment, and 232 patients were ultimately enrolled and analyzed. • 203 patients were evaluated for efficacy • All patients were studied for safety

TABULAR SUMMARY OF CLINICAL STUDIES USING AF0150 (Imavist™) *continued*:

PROTOCOL	TITLE	STUDY DESIGN	STUDY METHODOLOGY
IMUS-012-USA	An Open-label, Single-Dose Study to Assess the Pharmacokinetic Parameters and Rate of Elimination of Perfluorohexane after a 4-mg/kg Bolus Intravenous Injection of AF0150 in Healthy Adult Volunteers	A single-center (clinical site: the [redacted] single-dose, open-label, 2-staged Phase I study to evaluate the pharmacokinetics of perfluorohexane (**perflexane**, a perfluorinated alkane stabilizing gas which is diluted into N_2), an active component of AF0150	Each subject received AF0150 at 4 mg/kg IV over 25 mL/min, followed by saline flush. Pilot phase: The purpose of this is "to test the logistics of the study procedures and verify all aspects of the sample collections and analyses". Enrolled 2 subjects. Pivotal phase: Enrolled 10 subjects; pharmacokinetics, and blood & pulmonary clearances were studied.
IMUS-018-USA	An Open-Label Dose-Titration Study of 3 Doses of AF0150 in the Echocardiographic Assessment of Patients with Left Ventricular Dysfunction	A multicenter (both clinical sites were in the U.S.), open-label, dose-ranging (multi-dose, with 3 doses per subject), non-controlled (no placebo), Phase II study.	Each subject received AF0150 in the following sequence: 0.125, 0.25, and 0.5 mg/kg, injected IV over @ 10 seconds with a 10-minute interval between each dose. 1° endpt.: LV opacification (using both fundamental continuous and gated modes) 2° endpt. (using only fundamental continuous mode): (1) Duration of attenuation; (2) duration of useful contrast enhancement. Also safety assessment.

* EBD = endocardial border delineation; EF = left ventricular ejection fraction; SWM = segmental wall motion; RVG = gated radionuclide ventriculography (the "standard of truth" evaluation for EF).
* Fundamental continuous (real-time) mode → EBD (1° endpoint), EF (1° endpoint), and SWM (2° endpoint); fundamental gated (end-diastolic and end-systolic) mode → EBD (2° endpoint) and EF (2° endpoint)

APPENDIX C – SITES OF PHASE 3 PIVOTAL PROTOCOLS

Protocol No. IMUS-007-USA (Volume 90)

Site	Center	Location	Investigator	No. of Subjects		
				Total (n = 294)	AF0150 (n = 213)	Saline (n = 81)
1	New Jersey VA Medical Center	East Orange, NJ	Jerald Cohen, MD	1	0	1
2	San Diego Cardiology Associates	San Diego, CA	Harold Copans, MD	15	9	6
3	Kramer and Crouse Cardiology	Kansas City, MO	Linda Crouse, MD	65	48	17
4	Mount Sinai Medical Center	New York, NY	Martin Goldman, MD	25	17	8
5	San Diego Cardiovascular Associates	La Jolla, CA	Dennis Goodman, MD	34	24	10
6	Allegheny General Hospital	Pittsburgh, PA	Sunil Mankad, MD	21	13	8
7	Duke University Medical Center	Durham, NC	Thomas Ryan, MD	11	6	5
8	Krannert Institute of Cardiology	Indianapolis, IN	Douglas Segar, MD	11	7	4
9	University of Pittsburgh Medical Center	Pittsburgh, PA	Flordeliza Santos Villanueva, MD	11	7	4
10	University of Texas Medical Branch	Galveston, TX	Massood Ahmad, MD	35	29	6
11	Baylor College of Medicine	Houston, TX	William Zoghbi, MD	6	3	3
12	Montefiore Medical Center	Bronx, NY	Jamshid Shirani, MD	10	7	3
13	Louisville Cardiology	Louisville, KY	Michael Imburgia, MD	20	14	6
14	New England Medical and Radiology	Boston, MA	Natesa Pandian, MD	6	6	0
15	Medical College of Wisconsin	Milwaukee, WI	Kiran Sagar, MD	---	---	---
16	Western Baptist Hospital	Paducah, KY	Kenneth Ford, MD	23	23	0
17	Grossmont Hospital	La Mesa, CA	Martin McGreevy, MD	---	---	---
18	Florida West Coast Clinical Research Group	Tampa, FL	Carlos Marinelli, MD	---	---	---

* Shaded areas are those centers which were evaluated by the Agency's inspection team.

Site	Center	Location	Investigator	No. of Subjects AF0150 (n = 232)
20	University of Massachucetts Medical Center	Worcestor, MA	Gerard Aurigemma, MD	22
21	Vanderbilt University Medical Center	Nashville, TN	Benjamin Byrd, MD	3
22	University of Texas Southwestern Medical Center	Dallas, TX	Paul Grayburn, MD	24
23	Bowman Gray School of Medicine	Winston-Salem, NC	Dalane Kitzman, MD	45
24	University of Alabama at Birmingham	Birmingham, AL	Navin Nanda, MD	33
25	Washington University	St. Louis, MO	Julio Perez, MD	14
26	Johns Hopkins Bayview Medical Center	Baltimore, MD	Edward Shapiro, MD	7
27	San Diego Cardiovascular Associates	Encinitas, CA	David Hill, MD	37
28	Scripps Clinic and Research Foundation	La Jolla, CA	David Rubenson, MD	9
29	Hartford Hospital	Hartford, CT	Linda Gillam, MD	8
30	Southpoint Cardiology Associates	Jacksonville, FL	Stephen A. Stowers, MD	30

* Shaded areas are those centers which were evaluated by the Agency's inspection team.

APPENDIX D: TABULAR SUMMARY OF THE INTEGRATED SAFETY DATA USING AF0150 (Imavist™)

INTEGRATED SAFETY SUMMARY: Phase 1 & 2 Studies
Number and Percentage of Subjects with Treatment-Emergent Adverse Events Sorted By Body System and Severity

Body System (Preferred Term)	IMUS-001 (n = 64) AF0150 (n = 44) Mild	IMUS-001 (n = 64) AF0150 (n = 44) Moderate	IMUS-001 (n = 64) Saline Mild	IMUS-002 (n = 41) Mild	IMUS-002 (n = 41) Moderate	IMUS-002 (n = 41) Severe	IMUS-003 (n = 47) Mild	IMUS-003 (n = 47) Moderate	IMUS-003 (n = 47) Unknown	IMUS-012 (n = 13) Mild	IMUS-018 (n = 18) Mild	IMUS-018 (n = 18) Moderate	Total AF0150 (n = 163)
Body as a whole													
Fever	1 (2%)	0	0				1 (2%)	0	0				2 (1%)
Headache	3 (11%)	1 (2%)	1 (5%)	1 (2%)	0	0	3 (6%)	2 (4%)	0	1 (8%)			12 (7%)
Pain	1 (2%)	0	0	1 (2%)	1 (2%)	0	1 (2%)	0	0				4 (2%)
• Nasal										1 (8%)			1 (0.6%)
• Abdominal				1 (2%)	0	0							1 (0.6%)
• Chest				1 (2%)	0	1 (2%)	1 (2%)	1 (2%)	1 (2%)				5 (3%)
Malaise							1 (2%)	0	0				1 (0.6%)
Hypersensitivity (Injection Site)							1 (2%)	0	0				1 (0.6%)
Reaction (Site of Injection)							1 (2%)	0	0				1 (0.6%)
Cardiovascular													
Postural Hypotension	0	0	1 (5%)										1 (0.6%)
Vasodilation	0	1 (2%)	0				1 (2%)	0	0				2 (1%)
Angina				1 (2%)	0	0							1 (0.6%)
Atrial Fibrillation				0	2 (5%)	1 (2%)							3 (2%)
Atrial Flutter				1 (2%)	0	0							1 (0.6%)
Bradycardia (sinus)				1 (2%)	0	0							1 (0.6%)
Heart Failure				0	1 (2%)	0							1 (0.6%)
Extrasystoles				1 (2%)	0	0							1 (0.6%)
Cardiac Arrest/Shock				0	0	1 (2%)							1 (0.6%)
Hypertension				2 (5%)	0	0							2 (1%)
Hypotension				2 (5%)	1 (2%)	0							3 (2%)
Myocardial Infarction				0	0	1 (2%)							1 (0.6%)
Palpitations				1 (2%)	0	0	1 (2%)	0	0				2 (1%)
Tachycardia				1 (2%)	0	0	0	1 (2%)	0				2 (1%)

INTEGRATED SAFETY SUMMARY: Phase 1 & 2 Studies (continued)

Number and Percentage of Subjects with Treatment-Emergent Adverse Events Sorted By Body System and Severity

Body System (Preferred Term)	IMUS-001 (n = 64) AF0150 (n = 44) Mild	AF0150 (n = 44) Moderate	Saline Mild	IMUS-002 (n = 41) Mild	Moderate	Severe	IMUS-003 (n = 47) Mild	Moderate	Unknown	IMUS-012 (n = 13) Mild	IMUS-018 (n = 18) Mild	Moderate	Total AF0150 (n = 163)
Digestive													
Diarrhea	0	0	1 (5%)	1 (2%)	0	0	2 (4%)	0	0				4 (2%)
Nausea	1 (2%)	0	0	0	1 (2%)	0	3 (6%)	0	0				5 (3%)
Vomiting							1 (2%)	0	0				1 (0.6%)
Constipation				1 (2%)	1 (2%)	0	1 (2%)	0	0				3 (2%)
Anorexia							1 (2%)	0	0				1 (0.6%)
Flatulence							2 (4%)	0	0				2 (1%)
Respiratory													
Hiccup	1 (2%)	0	0										1 (0.6%)
Aspiration Pneumonia				0	1 (2%)	0							1 (0.6%)
Asthma				1 (2%)	0	0							1 (0.6%)
Dyspnea				0	0	1 (2%)	0	1 (2%)	0				2 (1%)
Epistaxis				1 (2%)	0	0							1 (0.6%)
Pulmonary Edema				0	1 (2%)	0							1 (0.6%)
Pneumonia (other)				1 (2%)	0	0							1 (0.6%)
Hypoxia							1 (2%)	0	0				1 (0.6%)
Nervous													
Dizziness	1 (2%)	0	0										1 (0.6%)
Confusion				0	1 (2%)	0							1 (0.6%)
Hallucinations				0	1 (2%)	0							1 (0.6%)
Torticollis				1 (2%)	0	0							1 (0.6%)
Dry Mouth							1 (2%)	0	0				1 (0.6%)
Insomnia							1 (2%)	0	0				1 (0.6%)

INTEGRATED SAFETY SUMMARY: Phase 1 & 2 Studies (continued)

Number and Percentage of Subjects with Treatment-Emergent Adverse Events Sorted By Body System and Severity

Body System (Preferred Term)	IMUS-001 (n = 64) AF0150 (n = 44) Mild	IMUS-001 (n = 64) AF0150 (n = 44) Moderate	IMUS-001 (n = 64) Saline Mild	IMUS-002 (n = 41) Mild	IMUS-002 (n = 41) Moderate	IMUS-002 (n = 41) Severe	IMUS-003 (n = 47) Mild	IMUS-003 (n = 47) Moderate	IMUS-003 (n = 47) Unknown	IMUS-012 (n = 13) Mild	IMUS-018 (n = 18) Mild	IMUS-018 (n = 18) Moderate	Total AF0150 (n = 163)
Metabolic													
Hypokalemia				0	1 (2%)	0					0	1 (6%)	2 (1%)
LDH Increase							1 (2%)	0	0		0	1 (6%)	2 (1%)
LFT Anomalies							1 (2%)	0	0				1 (0.6%)
SGOT Increase							1 (2%)	0	0				1 (0.6%)
Hyperglycemia				0	1 (2%)	0	1 (2%)	0	0				2 (1%)
"Edema"				0	1 (2%)	0	1 (2%)	0	0				2 (1%)
Hyperlipidemia							0	1 (2%)	0				1 (0.6%)
Hypophosphate							0	1 (2%)	0				1 (0.6%)
Bilirubinemia							1 (2%)	0	0				1 (0.6%)
Skin and Appendages													
Dry Skin	0	0	1 (5%)										1 (0.6%)
Herpes Zoster				1 (2%)	0	0							1 (0.6%)
Special Senses													
Conjunctivitis	0	1 (2%)	0										1 (0.6%)
Parosmia	0	0	1 (5%)										1 (0.6%)
Taste Perversion	1 (2%)	0	2 (10%)										3 (2%)
Eye Pain							1 (2%)	0	0				1 (0.6%)
Musculoskeletal													
Myalgia				1 (2%)	0	0							1 (0.6%)
Urogenital													
Bladder Stenosis				1 (2%)	0	0							1 (0.6%)
↑Urine Frequency				1 (2%)	0	0							1 (0.6%)
Hematuria							0	1 (2%)	0				1 (0.6%)

Appendix E: ISS Data – Severe and Moderate Adverse Events

Study	ID #	AF0150 Injection Dose	AF0150 Injection Date	AF0150 Injection Time	Adverse Event Date	Adverse Event Time	Adverse Event Type	Severity
AF0150, single bolus, 0.125 mg/kg IV (prescribed clinical dose)								
IMUS-007	1. **09-009**	0.1252	12/02/98	11:14	12/02/98	11:22	↑ed CPK-MB fraction	Moderate
	2. **13-003**	0.1259	11/02/98	10:56	11/02/98	*Not listed.*	*Unstable angina*	*Severe*
	3. 13-010	0.1267	11/18/98	10:30	11/18/98	11:00	Nausea	Moderate
IMUS-008	4. **21-001**	0.1279	05/15/98	12:55	05/15/98	13:00	Chest pain	Moderate
					05/16/98	09:00	Nausea	Moderate
	5. **23-010**	0.1254	09/15/98	10:47	09/17/98	14:15	↑ed hypertension	Moderate
	6. 27-021	0.1266	10/15/98	15:30	10/15/98	16:45	Chills	Moderate
AF0150, single bolus, ≥ 0.125 mg/kg IV								
IMUS-001	1. 01-017	1.9734	04/16/96	11:59	04/19/96	11:00	Frontal headache	Moderate
	2. 01-026	0.4984	*04/30/96*	*09:09*	*04/30/96*	*04:30*	*Nasal congestion*	*Moderate*
	3. 01-043	4.0525	05/14/96	10:20	05/16/96	10:00	"Hot flashes"	Moderate
					05/16/96	11:30	"Hot flashes"	Moderate
					05/16/96	21:00	"Hot flashes"	Moderate
					05/17/96	08:30	"Hot flashes"	Moderate
	4. 01-052	0.5128	05/21/96	11:29	05/25/96	09:00	Conjunctivitis, bilateral	Moderate
IMUS-003	5. 01-001	0.9581	*01/06/97*	*10:54*	*12/31/96*	*Not listed.*	*Productive cough*	*Moderate*
	6. 03-001	0.9281	12/17/96	12:46	*Not listed.*	*Not listed.*	*Headache (life-long history)*	*Moderate*
					12/17/96	14:00	↑ed triglycerides	Moderate
					12/17/96	14:00	Pain due to kidney stones	Moderate
					12/19/96	16:00	↑ed triglycerides	Moderate
	7. 05-002	0.4410	*01/07/97*	*13:19*	*01/06/97*	*06:00*	*Nasal congestion*	*Moderate*
					Not listed.	*Not listed.*	*(Nothing listed.)*	*Moderate*

Bolded ID#'s are subjects narrated in the text; *Italicized text* = AE's that are either (1) not related to AF0150 treatment based upon timing of AE, or (2) without AE timing or AE type.

* Narratives provided in the text, under "Serious AE's" and "Severe and Moderate AE's" sections.

ISS Data: Severe and Moderate Adverse Events [continued]

Study	ID #	AF0150 Injection Dose	AF0150 Injection Date	AF0150 Injection Time	Adverse Event Date	Adverse Event Time	Adverse Event Type	Severity
AF0150 multiple dosing								
IMUS-003	1. 03-003	#1 – 1.0056 #2 – 1.7877	05/06/97	#1 – 13:20 #2 – 13:40	05/09/97	12:10	Tachycardia	Moderate
					05/13/97	Not listed.	Sore throat	Moderate
	2. 01-004	#1 – 0.9974 #2 – 2.0460	*11/04/97*	*#1 – 11:07* *#2 – 12:07*	*10/31/97*	*Not listed.*	*Headache*	*Moderate*
					11/04/97	16:00	Chest pain	Moderate
					11/04/97	16:00	Shortness of breath	Moderate
	3. 02-001	#1 – 1.0071 #2 – 1.7773	06/17/97	#1 – 11:23 #2 – 11:47	06/17/97	16:05	↑ed hematuria	Moderate
	4. 03-004	#1 – 0.9929 #2 – 2.8369	05/12/97	#1 – 12:06 #2 – 12:24	05/15/97	*Not listed.*	*Sinus headache*	*Moderate*
	5. 03-009	#1 – 1.0091 #2 – 2.0699	10/28/97	#1 – 10:54 #2 – 11:25	10/28/97	15:31	↓ed phosphorus	Moderate
	6. 04-005	#1 – 0.5094 #2 – 1.5094	06/09/97	#1 – 09:00 #2 – 09:37	06/09/97	12:30	Headache	Moderate
	7. 05-003	#1 – 0.1451 #2 – 2.3222	04/11/97	#1 – 13:15 #2 – 13:16	*Not listed.*	*Not listed.*	*Spastic colon*	*Moderate*
IMUS-002	8. **01-010**	#1 – 0.2464 #2 – 1.0374	03/12/97	#1 – 16:29 #2 – 16:58	03/12/97	20:00	Chest pain	Severe
					03/12/97	20:00	Shortness of breath	Severe
					03/12/97	20:00	Atrial fibrillation	Severe
					03/12/97	20:00	Cardiac failure	Severe
	9. 03-001	#1 – 0.2533 #2 – 0.8000	02/04/97	#1 – 16:15 #2 – 16:54	02/06/97	18:30	Constipation	Moderate
						18:30	Nothing listed.	Moderate
	10. 03-003	#1 – 0.2500 #2 – 1.1765	03/04/97	#1 – 10:03 #2 – 10:24	*03/09/97*	*10:00*	*Post-CABG incisional pain*	*Moderate*

Bolded ID#'s are subjects narrated in the text; *Italicized text* = AE's that are either (1) not related to AF0150 treatment based upon timing of AE, or (2) without AE timing or AE type.

* Narratives provided in the text, under "Serious AE's" and "Severe and Moderate AE's" sections.

ISS Data: Severe and Moderate Adverse Events [continued]

Study	ID #	AF0150 Injection Dose	AF0150 Injection Date	AF0150 Injection Time	Adverse Event Date	Adverse Event Time	Adverse Event Type	Adverse Event Severity
AF0150 multiple dosing (continued)								
IMUS-002 (cont.)	24. 04-004	#1 – 0.2500 #2 – 1.0526	01/13/97	#1 – 14:30 #2 – 15:10	*Not listed.*	*Not listed.*	*Multivessel coronary artery disease*	*Moderate*
					Not listed.	*Not listed.*	*PTCA performed (? AE procedure?)*	*Moderate*
	25. 05-006	#1 – 0.2636 #2 – 0.7455	12/20/96	#1 – 11:57 #2 – 12:26	12/20/96	15:00	Atrial fibrillation	Moderate
					12/21/96	19:00	Cardiogenic shock	Severe
					12/21/96	Not listed.	Congestive heart failure	Moderate
					12/21/96	Not listed.	Pulmonary edema	Moderate
					12/21/96	23:00	Hypotension	Moderate
					12/21/96	23:00	Nothing listed.	Moderate
					12/22/96	Not listed.	Hyperglycemia	Moderate
					12/22/96	Not listed.	Aspiration	Moderate
					12/22/96	Not listed.	Nothing listed.	Moderate
					12/22/96	Not listed.	Nothing listed.	Moderate
	26. 05-007	#1 – 0.2756 #2 – 0.8820	12/23/96	#1 – 16:09 #2 – 16:50	12/26/96	Not listed.	Nausea	Moderate
					12/26/96	Not listed.	Edema (peripheral)	Moderate
					12/26/96	Not listed.	Hypokalemia	Moderate
	27. **05-009**	#1 – 0.2668 #2 – 0.9281	*12/24/96*	*#1 – 15:22* *#2 – 15:36*	*12/24/96*	*01:05*	*Atrial fibrillation*	*Moderate*
					12/24/96	*01:05*	*Atrial fibrillation*	*Moderate*
					12/25/96	01:44	Asystole x 2 episodes	Severe
	28. **05-010**	#1 – 0.2687 #2 – 1.1940	12/30/96	#1 – 15:04 #2 – 15:23	01/01/97	20:00	Acute myocardial infarction	Severe

Bolded ID#'s are subjects narrated in the text; *Italicized text* = AE's that are either (1) not related to AF0150 treatment based upon timing of AE, or (2) without AE timing or AE type.

* Narratives provided in the text, under "Serious AE's" and "Severe and Moderate AE's" sections.

ISS Data: Severe and Moderate Adverse Events [continued]

Study	ID #	AF0150 Injection Dose	AF0150 Injection Date	AF0150 Injection Time	Adverse Event Date	Adverse Event Time	Adverse Event Type	Adverse Event Severity
AF0150 multiple dosing (continued)								
IMUS-002 (cont.)	24. 06-003	#1 – 0.2546 #2 – 0.8208	03/05/97	#1 – 15:41 #2 – 16:08	*02/25/97*	*Not listed.*	*Headache*	*Severe*
					02/25/97	*Not listed.*	*Nothing listed.*	*Severe*
					02/25/97	*Not listed.*	*Nothing listed.*	*Moderate*
					03/05/97	*Not listed.*	*Nothing listed.*	*Moderate*
					03/05/97	*Not listed.*	*Nothing listed.*	*Moderate*
					03/06/97	17:30	Confusion	Moderate
					03/06/97	17:30	Hallucinations	Moderate
					03/06/97	17:30	Hallucinations	Moderate
					03/06/97	*17:30*	*Nothing listed.*	*Moderate*
					03/12/97	*Not listed.*	*Nothing listed.*	*Moderate*
	25. 07-003	#1 – 0.2700 #2 – 0.7381	02/06/97	#1 – 16:35 #2 – 16:56	*02/02/97*	*Not listed.*	*Headache.*	*Moderate*
IMUS-018	26. 02-001	#1 – 0.1251 #2 – 0.2502 #3 – 0.5025	08/11/98	#1 – 09:54 #2 – 10:04 #3 – 10:14	08/11/98	10:58	↓ed serum potassium	Moderate
	27. 02-009	#1 – 0.1245 #2 – 0.2491 #3 – 0.4981	09/01/98	#1 – 14:25 #2 – 14:35 #3 – 14:45	09/02/98	14:33	↑ed lactate dehydrogenase	Moderate

Bolded ID#'s are subjects narrated in the text; *Italicized text* = AE's that are either (1) not related to AF0150 treatment based upon timing of AE, or (2) without AE timing or AE type.

* Narratives provided in the text, under "Serious AE's" and "Severe and Moderate AE's" sections.

CYCLE 3

SEE PAGE 15 OF MEDICAL OFFICER'S REVIEW (SIGNED BY MEDICAL OFFICER ON 4/30/02.)