optimal segments than at baseline in both studies ($p \leq 0.001$ for most segments). The extent of the added benefit of Imavist™ varied with the segment. In each study and for each blinded reader, the segments that benefited the most with Imavist™ were the segments representing the lateral cardiac wall, the anterior cardiac wall, and the posterior cardiac wall. In both studies, the mean duration of useful contrast enhancement, defined as the time during which contrast enhanced images are obtained, is approximately 2.5 minutes.

Table 4: Proportion of Suboptimal LVEB delineation scores that Improved to Optimal Delineation (1)

	IMUS –007			IMUS -008		
	R1	R2	R3	R1	R2	R3
4-chamber segments						
Basal septal	0.09	0.04*	0.17	0.41	0.36	0.66
Mid septal	0.11	0.04*	0.17	0.31	0.27	0.45
Apical septal	0.46	0.11*	0.23	0.33	0.26	0.47
Apical lateral	0.47	0.34	0.24	0.38	0.31	0.59
Mid lateral	0.53	0.39	0.61	0.54	0.46	0.75
Basal lateral	0.52	0.42	0.61	0.53	0.48	0.74
2-chamber segments						
Basal inferior	0.10*	0.03*	0.19	0.36	0.49	0.35
Mid inferior	0.08	0.05*	0.11	0.25	0.22	0.24
Apical inferior	0.41	0.17*	0.16*	0.26	0.14*	0.51
Apical anterior	0.38	0.30	0.14*	0.28	0.23	0.57
Mid anterior	0.48	0.35	0.54	0.41	0.33	0.61
Basal anterior	0.50	0.39	0.55	0.41	0.39	0.68
Long axis segments						
Basal posterior	0.42	0.31	0.46	0.42	0.40	0.55
Mid posterior	0.44	0.31	0.49	0.43	0.42	0.53
Mid anterior septal	0.22	0.13*	0.32	0.25	0.26	0.40
Basal anterior septal	0.17	0.07*	0.21	0.24	0.29	0.36

1) Derived from Dr. Castillo's analysis; Proportion of all images suboptimal at baseline and optimal after Imavist

2) * p-value not significant at the 0.05 level.

5. Ejection Fraction:

In comparison to unenhanced baseline ultrasound images, Imavist enhanced images did not provide improved precision in measurement of the left ventricular ejection fraction (LVEF). For study IMUS-007, the correlation between ultrasound LVEF and radionuclide ventriculography LVEF was 0.50, 0.49, and 0.51 for Imavist and 0.53, 0.47, and 0.56 for the unenhanced baseline images for each of the three blinded readers, respectively. For study IMUS-008, the correlation between ultrasound LVEF and radionuclide ventriculography LVEF was 0.53, 0.49, and 0.53 for Imavist and 0.55, 0.50, and 0.51 for the unenhanced baseline images for each of the three blinded readers, respectively.

3. Segmental Wall motion

One of the key studies (IMUS-008) compared the segmental wall motion agreement of the baseline and Imavist assessments with gated MRI in a subset of 26 patients. A statistically significant improvement ($p < 0.0001$) was noted for all 3 readers. However, this number of patients is insufficient to support the indication. New clinical trials are needed. It is noteworthy, that in a small sample during phase 2, an improvement is wall motion was demonstrated, also. Therefore, it is possible that this functional use may be confirmed in smaller, but appropriately justified sample sizes.

Efficacy assessment: Although an improvement in LVEB was identified, it is not supported by a rigorous interpretation at end-systole and end-diastole. The EF assessments did not demonstrated improvement over baseline. However, a rigorous end-systolic and end-diastolic measurement of the LV volumes was not obtained. Thus, the data on which the EF calculations are based are not available. Also, because the core selector identified the EF region of interest, the potential for bias can not be excluded. In order to resolve these deficiencies, a repeat blinded read is needed of the LVEB and the LV volumes at end systole and end diastole. Then the EF should be calculated based on the LV volumes. If the improvement in LVEB is not consistent with improvement in wall motion, then additional studies are needed to confirm the clinical utility of the anatomic endpoints. Also, clinical utility may be confirmed with the wall motion functional endpoint.

Additionally, because of potentially close association of all the blinded readers, the letter should note that the blinded readers for the reanalysis should be independent and should not have prior involvement in Imavist protocols.

CLINICAL SAFETY:

A total of 777 patients were evaluated in the Imavist NDA. Of these safety data were initially submitted on 608 patients who received Imavist and 101 subjects who received saline. Safety data for an additional 68 patients were submitted in the 120 day safety update. Overall, these 777 there were 466 men and 278 women with an age distribution of was 503 (66%) < 65 years, 239 (31%) were between 65-80 years, and 25 (3%) were > 80 years of age. Racial and ethnic representation was Caucasian (79%), Black (14%), Asian (2%) and other (5%). The demographics were similar in participants who received Imavist or saline.

Overall, 139 (21%) of subjects who received Imavist reported at least one adverse event. Of these 5 were serious and included 1 death. All expect one serious event occurred in the patients who received higher doses of Imavist in the cardiac perfusion study IMUS -002. One event occurred in the 007 study.

The one death occurred in a 66 year old Caucasian female who was imaged 2 days after an acute MI and percutaneous transluminal coronary angioplasty. She received two doses of Imavist (0.269 and 1.194 mg/kg). Reportedly the ejection fraction was 25%. The next day the patient had a myocardial infarction and died.

Other serious events included a patient with serious chest pain, atrial fibrillation, and CHF that responded to treatment, hypotension and cardiogenic shock, and a cardiac arrest the responded to treatment. These patients are discussed in Dr. Parker's review page 81-82 and appear to have events related to the underlying disease. The one possible exception is one patient who had an event 3 hours after Imavist. Also, Dr. Parker identified one other patient in the key studies who experience angina at a unidentified time 2 days after Imavist.

Overall, for Imavist treated subjects, the most commonly reported adverse events were in the body as a whole (9%), digestive (6%), cardiovascular (5%) and urogenital (4%) body systems. The most commonly reported adverse events were headache (3%), pain (3%), hematuria (3%) and rectal hemorrhage (2%). The reports of hematuria and rectal hemorrhage were obtained in a special study of prostate cancer and occurred after manipulation and biopsy of the area. (See page 12-14 of this review for a tabulation of the adverse events for the NDA database.)

Dr. Parker's review contains a detailed assessment of the safety profile associated with Imavist and with the saline control patients. This includes an assessment of the QTc, reported arrhythmias, oxygen saturation, myocardial injury enzymes (CPK-MB) and routine laboratory. ECG parameters for the 0.125 mg/kg dose were monitored in 445 subjects at multiple time points within the first day of Imavist (baseline; 5 minutes, 1 hour, and 24 hours post- *Imavist*™). Continuous ECG monitoring during dosing was obtained. In the key clinical studies, at 5 minutes, QTc prolongations of > 30 msec were noted in 75 (17%) subjects. None of these subjects had associated malignant arrhythmias. Similar QTc prolongations were noted in 9 (11%) of the 81 subjects who received saline.

Dr. Parker concludes that although there is a suggestion of adverse events that could be associated with arterial occlusion from Imavist, these events could be associated with the underlying cardiac disease. He notes that in the key studies the percent of events is similar to that of the saline control patients. In considering this, I agree that the saline control group suggests that Imavist is reasonably safe in the population studied in phase 3 and at the recommended doses. However, since the majority of the serious adverse events were in patients who were more acutely ill and had higher doses, the safety of these doses and in these patients has yet to be determined. The safety and efficacy of these doses are under evaluation in ongoing clinical studies.

Mechanical index: In the literature, increasing mechanical index values are associated with microbubble destruction. In association with systolic triggering, ventricular arrhythmias have been reported. In the Imavist NDA, clinical studies demonstrated microsphere destruction at mechanical index values above 1.0. Systolic triggering was not comprehensively studied in humans.

The pharmacology review identified renal abnormalities in excreting electrolytes after Imavist and saline loading. Similar abnormalities were not identified in patients.

SAFETY UPDATE: The safety update was reviewed by Dr. Parker and was found to be consistent with the original NDA data.

ASSESSMENT:

Imavist is the 5th echopharmaceutical submitted for use in echocardiography. The critical issues for this class of drugs include the safety of the particle sizes and characterization of the microspheres. A more recently emerging issue is the appropriate surrogacy of the anatomic endpoints such as the left ventricular border delineation. This NDA was submitted in support of an indication that specifically links the anatomic and functional endpoints to state their relationship. Specifically, Imavist was proposed

. As discussed in the clinical section, data to support this use and to confirm the appropriate clinical relevance of the anatomic endpoints has not be provided. However, because of the method of image analysis it is possible that this deficiency may be resolved with a rigorous blinded re-read. If this is not successful, then additional studies will be needed to confirm the clinical benefit of Imavist.

In addition to these efficacy deficiencies, additional data are needed to complete the assessment of the safety of the particle size upper range; to describe the pharmacokinetics, metabolism and disposition of the intact microsphere; and to document the chemistry and manufacturing controls. Additionally, resolution of the manufacturing site deficiencies is needed.

ACTION: Approvable pending resolution of deficiencies and labeling revisions

Key items needed:

1. Clinical: Blinded re-read of LVEB, LV volumes and ejection fraction
2. Safety:
   a) Clinical clarifications to support volume weight based labeling
   b) Pharmacology microvascular studies in a chronically compromised pulmonary vascular model; and a direct arterial injection model for the assessment of coalescence, clumping, aggregation and visualization of the microspheres.
   c) CMC controls for the upper limit of the particle size
3. Chemistry
   a) Drug product, specifications, stability and methods validation issue resolution
   b) Resolution of inspection deficiencies
   c) Possible bridging studies if the testing methodologies are not sufficiently confirmed to support the relationship between the pilot and commercial lots with the investigational lots

S

Patricia Y. Love, MD, MBA
Director, Division of Medical Imaging and
Radiopharmaceutical Drug Products

Reproduced from Dr. Parker's review page110-112

TABLE 66: ISS + 120-Day Safety Update -- Demographics

Characteristics	Total (ISS) N = 608	AF0150 120-day N = 68	TOTAL N = 676	Saline TOTAL N = 101	TOTAL Enrolled N = 777
Age					
• < 65 years	393 (65%)	48 (71%)	441 (65%)	72 (71%)	513 (66%)
• 65 – 80 years	194 (32%)	19 (28%)	213 (31%)	26 (26%)	239 (31%)
• > 80 years	21 (3%)	1 (1%)	22 (3%)	3 (3%)	25 (3%)
Gender					
• Male	398 (65%)	34 (50%)	432 (64%)	73 (72%)	505 (65%)
• Female	210 (35%)	34 (50%)	244 (36%)	28 (28%)	272 (35%)
Race					
• White	498 (82%)	37 (54%)	535 (79%)	83 (82%)	618 (79%)
• Black	82 (13%)	19 (28%)	101 (15%)	9 (9%)	110 (14%)
• Asian	10 (2%)	2 (3%)	12 (2%)	1 (1%)	13 (2%)
• Other	18 (3%)	10 (14%)	28 (4%)	8 (8%)	36 (5%)

Source: Volume 51, pp 056 and 120-Day Supplement, Volume 1, p 034.

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TABLE 67(a): ISS + 120-Day Update Combined
Adverse Events Reported in ≥ 2 Subjects (≥ 0.3%) in All Studies by Treatment Group

Body System	AF0150 Treatment Group				Saline
	All Doses (N = 676)	0.125 mg/kg Single Dose (N = 457)	Other Single Doses (N = 116)	Multiple Doses (N = 103)	(N = 101)
Any	**139 (21%)**	**49 (11%)**	**50 (43%)**	**40 (39%)**	**11 (11%)**
Body as a Whole	**64 (9%)**	**18 (4%)**	**28 (24%)**	**18 (17%)**	**2 (2%)**
Headache	22 (3%)	8 (2%)	8 (7%)	6 (6%)	2 (2%)
Pain	20 (3%)	1 (0.2%)	15 (13%)	4 (4%)	0
Chest Pain	10 (1%)	1 (0.2%)	4 (3%)	5 (5%)	0
Asthenia	9 (1%)	4 (1%)	5 (4%)	0	0
Abdominal Pain	3 (0.4%)	2 (0.4%)	0	1 (1%)	0
Fever	3 (0.4%)	0	2 (2%)	1 (1%)	0
Injection Site Reax.	3 (0.4%)	1 (0.2%)	1 (1%)	1 (1%)	0
Chills	2 (0.3%)	1 (0.2%)	1 (1%)	0	0
Cardiovascular	**31 (5%)**	**15 (3%)**	**3 (3%)**	**13 (13%)**	**2 (2%)**
Hypertension	8 (1%)	5 (1%)	1 (1%)	2 (2%)	1 (1%)
Hypotension	5 (0.7%)	2 (0.4%)	0	3 (3%)	0
Atrial Fibrillation	4 (0.6%)	0	1 (1%)	3 (3%)	0
Tachycardia	3 (0.4%)	1 (0.2%)	0	2 (2%)	0
Vasodilation	3 (0.4%)	2 (0.4%)	1 (1%)	0	0
Angina pectoris	2 (0.3%)	1 (0.2%)	0	1 (1%)	0
Palpitation	2 (0.3%)	0	0	2 (2%)	0
Digestive	**38 (6%)**	**11 (2%)**	**17 (15%)**	**10 (10%)**	**1 (1%)**
Rectal hemorrhage	12 (2%)	0	12 (10%)	0	0
Nausea	10 (1%)	5 (1%)	2 (2%)	3 (3%)	0
Diarrhea	7 (1%)	4 (1%)	1 (1%)	2 (2%)	1 (1%)
Constipation	3 (0.4%)	0	0	3 (3%)	0
Flatulence	3 (0.4%)	0	1 (1%)	2 (2%)	0
Dyspepsia	2 (0.3%)	1 (0.2%)	1 (1%)	0	0
Metabolic	**16 (2%)**	**4 (1%)**	**3 (3%)**	**9 (9%)**	**2 (2%)**
CPK Increase	3 (0.4%)	3 (0.7%)	0	0	0
Hyperglycemia	3 (0.4%)	1 (0.2%)	0	2 (2%)	1 (1%)
Hypokalemia	3 (0.4%)	0	1 (1%)	2 (2%)	0
"Edema"	2 (0.3%)	0	0	2 (2%)	0
LDH Increased	2 (0.3%)	0	1 (1%)	1 (1%)	1 (1%)
Nervous	**15 (2%)**	**3 (0.7%)**	**7 (6%)**	**5 (5%)**	**0**
Insomnia	5 (0.7%)	0	4 (3%)	1 (1%)	0
Dizziness	3 (0.4%)	2 (0.4%)	1 (1%)	0	0
Paresthesia	2 (0.3%)	1 (0.2%)	1 (1%)	0	0
Respiratory	**10 (1%)**	**0**	**3 (3%)**	**7 (7%)**	**0**
Dyspnea	2 (0.3%)	0	0	2 (2%)	0
Hiccup	2 (0.3%)	0	2 (2%)	0	0
Special Senses	**6 (1%)**	**4 (1%)**	**2 (2%)**	**0**	**3 (3%)**
Taste perversion	4 (0.6%)	4 (1%)	0	0	2 (2%)
Musculoskeletal	**2 (0.3%)**	**1 (0.2%)**	**0**	**1 (1%)**	**0**
Myalgia	2 (0.3%)	1 (0.2%)	0	1 (1%)	0
Urogenital	**24 (4%)**	**1 (0.2%)**	**20 (17%)**	**3 (3%)**	**1 (1%)**
Hematuria	19 (3%)	0	18 (15%)	1 (1%)	0
Skin & Append.	**2 (0.3%)**	**0**	**1 (1%)**	**1 (1%)**	**1 (1%)**

Reproduced from Dr. Parker's review page110-112

TABLE 67(b): ISS + 120-Day Update Combined (continued)
Adverse Events Reported in < 0.3% of Subjects in All Studies by Treatment Group

Body System	AF0150 Treatment Group				Saline
	All Doses (N = 676)	0.125 mg/kg Single Dose (N = 457)	Other Single Doses (N = 116)	Multiple Doses (N = 103)	(N = 101)
Any	**139 (21%)**	**49 (11%)**	**50 (43%)**	**40 (39%)**	**11 (11%)**
Skin & Append.	**2 (0.3%)**	**0**	**1 (1%)**	**1 (1%)**	**1 (1%)**
Herpes zoster	1 (0.1%)	0	0	1 (1%)	0
Sweating	1 (0.1%)	0	1 (1%)	0	0
Special Senses	**6 (1%)**	**4 (1%)**	**2 (2%)**	**0**	**3 (3%)**
Conjunctivitis	1 (0.1%)	0	1 (1%)	0	0
Eye Pain	1 (0.1%)	0	1 (1%)	0	0
Urogenital	**24 (4%)**	**1 (0.2%)**	**20 (17%)**	**3 (3%)**	**1 (1%)**
Bladder stenosis	1 (0.1%)	0	0	1 (1%)	0
Urinary Frequency	1 (0.1%)	0	0	1 (1%)	0
Urination impaired	1 (0.1%)	0	1 (1%)	0	0

Source: Attachment #6 within "Responses To Clinical Comments" Addendum.

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MEMORANDUM OF TELECON

DATE: May 20, 2002

APPLICATION NUMBER: NDA 21-191, Imavist

BETWEEN:

Name: Tara Fields, RAC, Director, Regulatory Affairs
Phone: (858) 410-5172
Representing: Alliance Pharmaceutical Corp

AND

Name: Tia Harper-Velazquez, Pharm.D., Regulatory Project Manager, HFD-160
Division of Medical Imaging and Radiopharmaceutical Drug Products

SUBJECT: Marketing of [redacted]

DISCUSSION:

Per the request of Hye-Joo Kim. Pharm.D., I teleconferenced with Tara Fields to confirm whether or not the sponsor has plans [redacted] in the future. Ms. Fields re-confirmed that [redacted] that the sponsor does not have any plans [redacted] in the future.

Minutes Prepared By:

/S/

Tia Harper-Velazquez, Pharm.D.
Regulatory Project Manager
HFD-160

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/s/

Tia Harper-Velazquez
5/20/02 01:43:08 PM
CSO

MEMORANDUM OF TELECON

DATE: April 30, 2002

APPL. NUMBER: NDA 21-191, Imavist

BETWEEN:

Name: Howard Dittrich, M.D.
Phone: (858) 410-5680
Representing: Alliance Pharmaceutical Corp

AND

Name: Patricia Y. Love, M.D., M.B.A., Kaye Cho, Pharm.D.,
Tia Harper-Velazquez, Pharm.D., Regulatory Project Manager, HFD-160
Division of Medical Imaging and Radiopharmaceutical Drug Products

SUBJECT: Imavist (Imagent) Review Process

BACKGROUND:

In response to an email request concerning the review timeline for NDA 21-191 from Tara Fields, the sponsor was informed by Tia Harper-Velazquez, Project Manager on April 25th that the division is still working with a 3 month review timeline for the resubmission, as indicated in the industry meeting held on March 12, 2002.

DISCUSSION:

Dr. Love began the discussion by stating that the division was responding to Dr. Dittrich's email to Dr. Houn. (attached) Dr. Dittrich was assured that the division is working as quickly as possible to review the April 5, 2002, submission, and that the division is anticipating issuing a letter in early June, 2002.

In regards to the review timeline, Dr. Love stated that approximately 2 weeks were saved with the early submission of the safety information. However, because of the electronic database issues, the efficacy data required more review. Therefore, the division is working with approximately a two and a half month time frame for review. The sponsor was also informed that the Office of Drug Safety is in the process of reviewing the name change of the drug product, although they are not able to commit to a completion date at this time. Additional time must also be reserved to discuss any nomenclature issues, should there be any.

Dr. Dittrich reiterated the timing concerns to his company. In order to facilitate this, the sponsor is ready to address any questions with minimal notice. Dr. Love reminded the sponsor that the

decision whether or not an application is approved is based on the data submitted. The division is working as expeditiously as possible.

Minutes Prepared By:

(See appended signature)

S

Tia Harper-Velazquez, Pharm.D.
Regulatory Project Manager
HFD-160

EMAIL ATTACHMENT

Please let me know how you wish to respond. Flo

-----Original Message-----
From: Howard Dittrich [mailto:HCD@ALLP.COM]
Sent: Thursday, April 25, 2002 4:56 PM
To: 'hounf@cder.fda.gov'; 'lovep@cder.fda.gov'
Cc: 'harpervelazt@cder.fda.gov'; 'chok@cder.fda.gov'; Duane Roth; Tara Fields
Subject: NDA 21-191 (Imagent) Review Process

> Dear Drs Love and Houn,
>
> In reply to Tara's message to Tia asking about the progress of the review
> of the Imagent resubmission, we received the e mail below. I feel
> compelled to reply with a plea for a more expedient response. We have
> reviewed our minutes of the meeting and we believe that by providing the
> safety information directed to patients with COPD and the efficacy
> analysis plan, we had created an opportunity to reduce the review time.
> Instead, we seem to be back to a time-line initially suggested by HFD-160
> in the overheads presented at the time of the March 12th 2002 meeting.
>
> We communicated the safety information along with the analysis plan in the
> weeks prior to the resubmission on April 5th. We revised our analysis
> plan per your request, which is reflected in the resubmission. We
> provided additional information last week to answer questions raised by
> the statistician on efficacy. Given our resubmission and the focus on
> efficacy, with other areas (other than labeling) being straight forward,
> we see no reason why you will require this length of time to conclude the
> review process.
>
>
> Concluding our combined efforts by the end of May
> should not be onerous. After all, these efficacy data are not primary
> endpoints. They exist to justify a trend toward clinical utility. Your
> group understood fully what those data would be more than two weeks before
> the resubmission went in. There is nothing new in these analyses.
>
> On behalf of Alliance Pharmaceutical Corp. I implore you to act
> expeditiously to achieve closure on this process in the next several

> weeks, including labeling discussions if appropriate. We stand ready to
> address any question with minimal notice. Please respond promptly to this
> communication.
>
> Howard C Dittrich, MD
> Senior Vice President, Clinical Research and Regulatory Affairs
> Chief Medical Officer
> Alliance Pharmaceutical Corp.
> 3040 Science Park Road
> San Diego, CA 92121
> 858 410-5680
>
> -----Original Message-----
> From: Harper Velazquez, Tia M <HARPERVELAZT@cder.fda.gov>
> To: 'Tara Fields' <tkf@ALLP.COM>
> CC: Cho, Kyong A <CHOK@cder.fda.gov>
> Sent: Thu Apr 25 05:20:13 2002
> Subject: RE: I got your message
>
> Hi Tara:
>
> As far as the timeline, we are still working with a 3 month time-line, as
> was indicated in the industry meeting. We did, however, save
> approximately
> 2 weeks with the early submitting of the safety information. However
> there
> is still efficacy information that needs more review. That being the
> case,
> we are working with a 2 & 1/2 month time frame, more or less.
>
> As far as the nomenclature change, the consult has been submitted, and I'm
> sure that the office has started working on their review. I've been in
> contact with the office, and they are aware that we're working with a
> shorter than normal turnaround time, and have made the nomenclature review
> a
> priority. They cannot give me a definite date of when they'll have their
> review will be completed, but I do not anticipate this being an issue that
> would negatively effect our 2 & 1/2 month time frame.
>
> Concerning labeling negotiations, I do not anticipate this starting until
> sometime in late May. However Dr. Salazar, the chemistry reviewer, does
> have some preliminary comments concerning the label that she asked I
> forward
> to you. I will fax these to you today.
>

> Thanks.
>
> Tia

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/s/

Tia Harper-Velazquez
6/25/02 05:25:33 PM
CSO

MEMORANDUM OF TELECON

DATE: January 2, 2002

APPLICATION NUMBER: NDA 21-191, Imavist

BETWEEN:

Name: Tara Fields, RAC, Drug Regulatory Affairs
Phone: (858) 410-5272
Representing: Alliance Pharmaceuticals

AND

Name: Tia Harper-Velazquez, Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Clinical inquiry concerning COPD patients.

DISCUSSION:

This serves a documentation that I contacted Tara Fields of Alliance Pharmaceuticals by telephone at the request of Dr. Ramesh Raman, and asked if the COPD patients included in the 2 trials of the resubmission dated August 16, 2001, received pulse oximetry. Ms. Fields returned my call, and stated that this information is found in volume 44, page 251, table 8.81, which discusses FAO2 measurements, and includes changes from baseline for subjects with COPD. She said that the phase 3 study included 97 patients with COPD, (there were 14 saline patients), and that pulse oximetry was done for all of these patients. This information was relayed to Dr. Raman. If further clarification is necessary, it will be done via tcon.

Submitted by:

(See electronic signature.)

/S/

Tia Harper-Velazquez
Regulatory Project Manager

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/s/

Tia Harper-Velazquez
1/4/02 01:53:16 PM
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MEMORANDUM OF TELECON

DATE: May 7, 2001

APPLICATION NUMBER: NDA 21-191, Imavist (perflaxane lipid microsphere) for Injectable Suspension

BETWEEN:

Name: Tara Fields, Director, Regulatory Affairs
Phone: 858-410-5320
Representing: Alliance Pharmaceutical Corp.

AND

Name: Patricia A. Stewart, Regulatory Project Manager
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: The sponsor submitted a general correspondence dated February 5, 2001, addressing clinical deficiency issues outlined in the August 14, 2001, approvable letter, in particular, the issues concerning left ventricular endocardial border delineation (LVEBD) and left ventricular opacification (LVO) as surrogate markers. The sponsor asked for feedback from the Agency before resubmitting the NDA.

The sponsor was informed that after preliminary review of the general correspondence dated February 5, 2001, the Agency is favorably inclined to consider the new information for review.

/S/

Patricia A. Stewart
Regulatory Project Manager

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/s/

Patricia Stewart
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CSO

MEMORANDUM OF TELECON

DATE: April 18, 2001

APPLICATION NUMBER: NDA 21-191, Imavist™ (Perflexane-Phospholipid Microbubbles for Injection)

BETWEEN:

Name: Howard Dietrich, M.D., Vice President Regulatory Affairs
David Kline, Ph.D., Senior Vice President Pharmaceutical Development
Leo Trevino, Ph.D., Director Product research and Development
Tara Fields, Director Regulatory Affairs
Phone: 888-742-8686
Representing: Alliance Pharmaceuticals

AND

Name: Patricia A. Stewart, Regulatory Project Manager
Eldon Leutzinger, Ph.D., Chemistry Team Leader
Milagros Salazar, Ph.D., Chemistry Reviewer
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: The sponsor submitted a general correspondence dated March 7, 2001, outlining a "planned approach" for resubmission of the NDA to address the chemistry deficiencies in the approvable action letter.

A. MICROSPHERE CHARACTERIZATION:

The sponsor explained that there is no consistent evidence that there are bubbles larger than 20µm. There are a very low number of counts over a wide distribution range ( ) and the numbers of counts are inconsistent and cannot be distinguished from noise. To improve the statistics, a larger number of samples were analyzed using a tiered testing procedure. Ten samples are analyzed and if the average number of counts in the µm range is greater than 3, 20 samples will be counted. The greatest number of bubbles seen in the upper range was but that was never reproduced. The dilution factor is 10,000, so a specification was established of approximately (microbubbles) per mL are (0.0% of the total count). The chemistry reviewer asked if the numbers actually mean anything or if the counts are just noise and if so, what is the meaning of the specification.

The clinical group asked that the maximum size bubble be defined because it has safety relevance. The nature of the larger particles must be determined or proved to be only noise. To facilitate defining the maximum size, the chemistry reviewer suggested it might be more meaningful to employ a blank, as used in other methodologies. Also, if the sample is not so dilute the noise may not be so high. The sponsor explained that the samples are diluted because

otherwise the coincidence rate goes up and an error message is received. The FDA reviewer noted that a coincidence should only occur when there are actual particles. She inquired about the confidence level with this method and noted that the specification calls for using a wide channel whereas the last page of the meeting packet shows counts in smaller channels. She also asked about the blanks composition and what it showed? The sponsor said the blank is water and explained that they were trying to look at the worst case scenario and assume that everything was a bubble, but were also trying to minimize the risk of rejecting a good lots by making the specifications too stringent.

The reviewer explained that the specification numbers for maximum size and number of larger bubbles does not seem acceptable to the clinicians. It is not clear whether this methodology has demonstrated clear specifications. The reviewer recommended finding a statistically validated method with numbers that are more realistic. An analytical method is needed that shows a cap where there are no microbubbles larger than a certain size. Also, the broad range of . [redacted] μm needs to be broken down and shown to be noise. The sponsor explained that the large number was chosen to catch any possible large bubbles and that they are not certain any more can be drawn out of the technology. The reviewer suggested trying a blank that is more like the product minus the bubbles. She explained that the Agency is a data driven organization and the specifications must be based on based on hard science. The sponsor said they would consider the blank but do not have much confidence at this time in finding another method.

B. SPECIFICATION AND TEST METHODS

The sponsor asked for clarification of the specification requirements for analyzing the powder and constituted product. The only release test that involves the powder is the test for perflexane in the headspace. The other tests are done with dissolved powder using alcohol or water. The sponsor said a research study comparing the results from the two dissolution methods will be performed and if the methods are shown to be equivalent only one method will be employed. The FDA accepted use the constituted powder and agreed that one method could be eliminated if the two methods of dissolution are shown to be equivalent. The testing proposed for the powder and solution were the following:

1) HES
   a. [redacted]
   b.
2) Poloxamer 188
   a.
   b. [redacted]

The chemistry reviewer asked for clarification of what was meant by "preliminary" specifications, and that testing will be done in "at least" three commercial lots. The resubmission should not include words like "preliminary" or "at least". The NDA is expected to be in the final stage and should have "final" specifications that will regulate the methods to be used to characterize the product. A significant amount of data will need to be evaluated before deciding to eliminate any testing. More than 3 commercial lots will be needed depending on the accuracy. Any specifications that are demonstrated to be unnecessary in the future can be

revised in a NDA supplement. The sponsor said that the accuracy of the methods is good (— and the resubmission will provide final specifications.

C. STABILITY

The stability protocol for PFH content and microbubble count test samples at — and —minutes are proposed to be discontinued. The FDA reviewer noted that data has not been provided for the reconstituted product showing that those points are not meaningful. The sponsor said they would complete the stability protocol and submit the data for review. The FDA agreed they should complete the stability protocol as written and any further changes can be done by an NDA supplement.

D. METHODS VALIDATION

The proposed responses to the FDA comments seem adequate.

E LABELING

The labeling will be consistent with other products on the market (Optison is the only approved microbubble) and will list all components in the powder and constituted product based on calculations from 3 commercial lots. The product must be fully characterized in the labeling including specifying the methodology for reconstitution. The methodology must be consistent to that used when analytical testing was performed.

/S/

Patricia A. Stewart
Regulatory Project Manager

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/s/

Patricia Stewart
5/22/01 01:26:53 PM
CSO

MEMORANDUM OF TELECON

DATE: November 22, 2000

APPLICATION NUMBER: NDA 21-191, AFO150 (Imavist)

BETWEEN:

Name: [redacted]
Janice Lookabaugh, MPH, Director, Biostatistics
Kathryn Flaim, Ph.D., Vice President, Clinical
Ted Roth, President & Chief Operating Officer
Mark Walters, Project Director, Imavist
Tara Fields, RAC, Director, Regulatory Affairs
Phone: 1-888-742-8686, Conf. ID # 8257077
Representing: Alliance Pharmaceutical Corp

AND

Name: Patricia Y. Love, M.D., M.B.A., Division Director, HFD-160
Victor Raczkowski, M.D., Deputy Director, ODE 3
Sally Loewke, M.D., Acting Deputy Director, HFD-160
A. Eric Jones, M.D., Medical Team Leader, HFD-160
Bernard Parker, M.D., Medical Officer, HFD-160
Sonia Castillo, Ph.D., Statistical Reviewer, HFD-715
Tia Harper-Velazquez, Pharm.D., Regulatory Project Manager, HFD-160
Division of Medical Imaging and Radiopharmaceutical Drug Products

SUBJECT: Discussion concerning improved reproducibility and agreement for functional endpoints after the addition of contrast.

DISCUSSION:

The division stated that the sponsor acted in good faith by trying to obtain an indication when the product was initially developed with increased correlation of ejection fraction and wall motion. Within the last few months, however, new data has become available that concerns the appropriateness of EBD visualization as a surrogate endpoint. Specifically, there are unexpected inconsistencies in the clinical studies, and improved EBD is not resulting in improved measurement of the clinically useful measures of wall motion or ejection fraction. Also, there are limited literature data to support the correlation of EBD to improved assessments of EF or wall motion. It is not clear if this is due to methodology, individual drug differences, or if this is a class issue. Therefore, the division is asking all sponsors to provide additional information, since this is a critical issue.

Based on the Imavist data, the division reiterated that the product is promising, and that the wall motion data in the two centers is suggestive. The best recommendation is to do one study to get on the market, and a second study for functional claims. However, it is possible that a re-read of

the data may be able to move forward to an EBD indication with a Phase 4 commitment to confirm the functional utility; i.e., provide a trend in the functional utility data as opposed to establishing an actual claim for wall motion or ejection fraction.

For example, the ejection data should be re-read. However, if that is not possible for EF, then the images could be used for wall motion. This would involve using the ECHO data and making an assessment on regional wall motion, showing that it correlated with the RVG data. An additional study would also put the sponsor well on the way to getting an indication with a Phase 4 commitment. An additional study is needed for an EBD claim, and another successful study may lead to a claim for wall motion depending on its size.

The sponsor provided information that they cannot do the re-read of ejection fraction or wall motion because of problems in the acquisition of the images. But, they do have wall motion data in comparison to MRI on 26 patients. Because these 26 patients are in one study and one study center, there is an issue with the reproducibility of the data. The sponsor indicated that there are actually two sites, but that the point made by the division is valid.

The division stated that the size of the study for utility might not need to be as large or rigorous as one that would be required for the proposed indication. A good study can potentially increase the chance of getting the indication. In response to the sponsor's query about the use of one study to support an indication, the division noted the CDER Guidance on Establishing Effectiveness that explains the parameters for one study being sufficient to get a claim. The study sample size would have to be sufficiently large, the "P" value substantial, and demonstrate internal consistency of the overall results. The sponsor could propose the use of one study, if it is large enough to demonstrate reproducibility and reliability. The sponsor asked with respect to one trial, what size of patient population the division considered acceptable. The division responded that the data variability would need to be considered and the size should then be based on this.

The sponsor asked if the statistics show that 30 patients is enough, will a study to support utility only be sufficient. The division responded that this would need to be proposed by the sponsor, and then reviewed by the division.

The division asked for clarification on the statistical issue of zero kick-out in the original analysis package. If the blinded readers scored a 0 or 1 for EBD, then electronic case report

form automatically assigned a score of 0 for SWM. The sponsor confirmed this. The division stated that this may have an effect on MRI results. This kick-out has generated issues, and an alternative approach should be considered.

Minutes Prepared By:

/S/

Tia Harper-Velazquez, Pharm.D.
Regulatory Project Manager

PFS 5/31/01 GV
IMTS ✓

MEMORANDUM OF TELECON

DATE: November 29, 2000

NDA #: 21-191

DRUG: AFO150 (Imavist)

BETWEEN:
Name: [redacted] Tara Fields, RAC
Phone: (858) 410-5272
Representing: Alliance Pharmaceutical Corp.

AND

Name: Patricia Y. Love, M.D., M.B.A., Tia Harper-Velazquez, Pharm.D.
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Clinical Efficacy Issues

DISCUSSION:

The division had previously requested that the sponsor do a re-read of the two key studies' results at end-systole and end-diastole. This would provide information to support the clinical benefit of the endocardial border delineation. The sponsor stated that they feel that their 26 patient subset analysis in comparison to MRI is sufficient. Therefore, the sponsor felt that we are at an impasse. They are considering what approach they will take for resolution.

The division asked if the sponsor had any preliminary data to see if reads at end-systole and end-diastole would alter echocardiography results. The sponsor responded that they do not have any preliminary data, but they do have evidence that clinically there would not be a change, and they feel that a re-read of RVG will not provide any new information. Also a read of ejection fraction is not possible because of the reasons presented in an earlier meeting..

Dr. Love will speak with Dr. Raczkowski and follow-up with the sponsor.

Prepared by: 11 . 1 11

Tia M Harper-Velazquez, Pharm.D. V /
Regulatory Project Manager

DFS 3/31/01 LV
MTS ✓

MEMORANDUM OF TELECON

DATE: December 18, 2000

NDA #: 21-191

DRUG: AFO150 (Imavist)

BETWEEN:

Name: — Tara Fields, RAC
Phone: (858) 410-5272
Representing Alliance Pharmaceutical Corp.

AND

Name: Patricia Y. Love, M.D., M.B.A., Tia Harper-Velazquez, Pharm.D.
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Clinical Efficacy Issues

DISCUSSION:

The division noted that the current dialogue concerning data on the 26 patients with MRI is outside the context of the action letter. Therefore, it is not possible to determine whether or not the data are sufficient to address clinical efficacy, as this is a review issue. The sponsor should resubmit on the basis of the 26 patients and augment with literature information on wall motion and ejection fraction to justify why the use of theses 26 patients is sufficient. This should include a subset analysis of the 26 patients, and comparison to the pre and post MRI ultrasound study. The sponsor should clarify the basis of their argument why a re-read or RVG or EF is not possible.

The division reiterated that a review of the full response to the action letter is needed in order to determine if the data on the 26 patients are sufficient for this purpose. This would allow for a more in-depth evaluation. Therefore, all position statements should be submitted in response to the action letter. The sponsor stated that they would like to resolve the clinical efficacy issues, and asked if this information could be submitted separate from the complete response to the action letter. The division stated that the clinical efficacy information could be submitted as a general correspondence. After an initial perusal, the division would determine the length of review time necessary. The best effort, however, is in the context of an complete official response to the action letter.

Minutes Prepared by:

S

Tia M Harper-Velazquez, PharmD
Regulatory Project Manager

Harper
DFS ✓

MEMORANDUM OF TELECON

DATE: March 9, 2000

APPLICATION NUMBER: NDA 21-191 AFO150 (*Imavist*)

BETWEEN:

Name: Tara Fields, Janice Lookabaugh, Mark Walters, Rebecca Fadulo,
Kathy Flaim, Wesley Pierson.
Phone: (858) 410-5272
Representing: Alliance Pharmaceuticals

AND

Name: Bernard Parker, M.D., Sonia Castillo, Ph.D., David Li, M.D.
Tia Harper-Velazquez, Pharm.D.
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Discussion of 1) Display of IMAGES, and 2) MRI – " Tagged" Vs "Untagged."

DISCUSSION:

Clinical:

1. In response to a question concerning amendment 2 and the addition of the confirmatory ECHO being added to the protocol, the sponsor answered that the confirmatory ECHO was added because if an outside referral was received, the information from the referral was verified.
2. FDA posed the question that out of the number of patients who were evaluable for efficacy (206 in IMUS-007 and 203 in IMUS-008) exactly how many patients completed the study, and how many withdrew? For the group of patients who withdrew, all details need to be provide, i.e., identification number, reasons for withdrawal. The sponsor responded that they will provide this information.
3. Concerning the 3 blinded reviewers, FDA asked which 3 views were actually evaluated, and how many monitors there were per viewer. The sponsor responded that there were 3 monitors per viewer. The views seen were A4-EBD, A2-EBD, and Long-EBD. All views were randomized, such that no on monitor will be purely for one type of view.
4. In response to a FDA question concerning how many tapes were made per patient, the sponsor responded that 6 tapes were made per patient. The sponsor also stated that the blinded readers called out the determined values to a technician who recorded each patent's scores.

NDA 21-191 AFO150 (*Imavist*)
Teleconference
March 9, 2000

Statistics:

1. Concerning the MRI, the sponsor stated that images described as "tagged" indicated that the image was evaluated for wall thickness, and "untagged" indicated that the image was evaluated for wall motion.
2. The sponsor will provide responses to the following questions:
   a. Please describe what was on each of the 18 echo clips per subject. Also provide a listing of the 18 echo clips.
   b. Please describe the order in which EBD, SWM, and EF were evaluated during the blinded read. For examples, when a subject's clip was being evaluated, in what order were the endpoints evaluated?
   c. Please describe where the singe end-systole and end-diastole frames used to evaluate EF were included on the clips. If the frames were not on the clips, how were the frames accessed when it came time to evaluate EF?

ACTION ITEMS:

1. The sponsor will provide answers and follow-up to outstanding clinical and statistical questions.
2. Project Manager to follow-up with sponsor for any additional clarification necessary.

/S/

Prepared by: Tia Harper-Velazquez, Pharm.D.
Regulatory Project Manager

Cc: Original NDA 21-191
HFD-160/Div. File
HFD-160/Parker/Li/Harper-Velazquez
HFD715/Castillo

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MEMORANDUM OF TELECON

DATE: February 17, 2000

APPLICATION NUMBER: NDA 21-191 AFO150 (*Imavist*)

BETWEEN:

Name: Tara Fields, Janice Lookabaugh, Mark Walters, Rebecca Fadulo,
Kathy Flaim, Wesley Pierson.
Phone: (858) 410-5272
Representing: Alliance Pharmaceuticals

AND

Name: Bernard Parker, M.D., Sonia Castillo, Ph.D.,
Tia Harper-Velazquez, Pharm.D.
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Discussion of clinical and statistical issues.

DISCUSSION:

In response to questions posed by the reviewing medical officer and reviewing statistician, the sponsored indicated that:

- The ultrasound machine settings were kept constant for baseline and post contrast image studies.
- Data sets with machine settings were only collected for baseline readings because the machine settings were kept constant.
- The case report forms contain only baseline settings since these were unchanged from post image contrast studies.
- The ejection fraction value used for analysis is based on apical 2 and 4 images. End systole and end diastole measurements were used to calculate the ejection fraction. (Reference volumes/pages 080.623, 080.280, and the Methodology Appendix 092.192.)
- As part of the addendum, it was stated MRI was not used in the determination of ejection fraction.

NDA 21-191 AFO150 (*Imavist*)
Teleconference
February 17, 2000

ACTION ITEMS:

1. The sponsor will submit data sets on baseline and post contrast machine settings, and types of machines used.
2. Project Manager to follow-up with sponsor for any additional clarification necessary.

/S/

Prepared by: Tia Harper-Velazquez, Pharm.D.
Regulatory Project Manager

Cc: Original NDA 21-191
HFD-160/Div. File
HFD-160/Parker/Harper-Velazquez
HFD715/Castillo

Filename: C/Mydocuments/AFO150/Tcon.Min.021700

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OFSV

MEMORANDUM OF TELECON

DATE: January 7, 2000

APPLICATION NUMBER: NDA 21-191 AFO150 (Imavist)

BETWEEN:

Name: Ms. Tara Fields, Janice Lookabaugh, MPH.
Phone: (858) 410-5272
Representing: Alliance Pharmaceuticals

AND

Name: Sonia Castillo, Ph.D., Tia Harper-Velazquez, Pharm.D.
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Statistical Questions

DISCUSSION: The discussion consisted of a number of questions and points of clarification needed by Dr. Castillo, followed by answers given by Ms. Lookabaugh.

The following pertain to the data set IMAGE.

1. For the variable TIMEPT, what does a value of "." mean. Also, for those patients who had a TIMEPT value equal to ".", why did they have data missing for other variables? Ans. Ms. Lookabaugh will look into this.

2. What does a value of "9" mean for the EBD variables? Ans. "9" means that the segment was not seen, and was therefore not scored.

3. Explain what is meant by the variable "AGREE." Ans. Someone at the core laboratory calculated a value for ejection fraction by drawing a line around the selected region of interest. If the blinded reader agreed with this value, the term "agree" was applied. If the reader did not agree, they determined their own region of interest from which ejection fraction was calculated.

4. Explain what is meant by the two variables "EJFRCEXP" and "EJFRCIMP" for ejection fraction. Ans. " EJFRCIMP" describes the original ejection fraction value. If the blinded reader agreed with the score, then the two values are the same. If the blinded reader did not agree, then the new ejection fraction value, as determined by the blinded reader, is represented by the variable "EJFRCEXP." If both values were the same, that value was used in the analysis. If both values differed, the value found in the variable "EJFRCEXP" was used.

5. Were there some subjects who had no EBD values seen pre or post image? Ans. Ms. Lookabaugh responded yes, but that she would double check.

The following comments pertain to the data set MRI.

1. 1. What does the variable "TAGGED" represent and how it is used in the analysis? Ans. Ms. Lookabaugh will look into this.

2. What does a value of "9" mean for the variable "WM_X?" Ans. This indicates that the segment was not viewed.

The following comments pertain to the data set RVG.

1. Is the variable "AGREE" defined the same as in the IMAGE data set? Ans. Ms. Lookabaugh responded yes.

2. Explain why there are missing values for identifier fields even though data points are present for some patients. Ans. Ms. Lookabaugh will look into this.

3. Explain why there are blank spaces for the variables "EJRCIMP" and "EJFRCEXP. Also if there is new data, it needs to be submitted. Ans. Ms. Lookabaugh will look into this.

/S/

Prepared by: Tia Harper-Velazquez, Pharm.D.

Cc: Original NDA 21-191
HFD-160/Div. File
HFD-715/Castillo
HFD-160/Harper-Velazquez

Filename: C/Mydocuments/AFO150/Tcon.stats.010700

Harper

MEMORANDUM OF TELECON

DATE: November 19, 1999

APPLICATION NUMBER: NDA 21-191 (AFO150)

BETWEEN:

Name: Ms. Tara Fields, Mr. Mark Walters, Mr. Genote Becker, Mr. Wesley Pierson, and Ms. Janice Lookabaugh
Phone: (858) 410-5272
Representing: Alliance Pharmaceutical Corp.

AND

Name: Sally Loewke, M.D., Bernard Parker, M.D., and
Tia Harper-Velazquez, Pharm.D.
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Index issues for submission dated October 11, 1999.

DISCUSSION: The Team Leader and Medical Officer relayed to the sponsor that the index of submission dated October 11, 1999 was not sufficient. The individual study report indices for each volume are not detailed enough, and it is difficult to find the information necessary to determine whether or not the application is filable. Some specific examples of deficiencies included:

1. Volume 41 - there is no table of contents.
2. Volume 90, page 65 - table 11g cross references another section of the volume, however, the reference is not located in that section. The sponsor indicated that this is an error in the report.
3. Volume 107, page 56, table 11c is cross referenced, although there are no tables present for the cross reference.

The sponsor recognized that the indexing was confusing, and that there were some errors in the submission, and agreed to submit a new master index, as well as individual study report indexes that are more precise within the next 2 weeks.

ACTION ITEMS:

1. Project Manager to follow-up with sponsor on progress of the index.

/S/

Prepared by: Tia Harper-Velazquez, Pharm.D.

Cc: Original NDA 21-191
HFD-160/Div. File
HFD-160/Harper-Velazquez

Filename: C:Mydocuments:AFO150:Tcon.Min.Index.111999

MEMORANDUM OF MEETING MINUTES

RECORD OF TEAM MEETINGS & LABELING MEETINGS

NDA 21-191, Imagent®

MEETING TYPE: Team Meeting
MEETING DATE: April 19, 2002
TIME: 1:00pm EST
LOCATION: Parklawn, Room 18B-37
MEETING RECORDER: Tia M. Harper-Velazquez, Pharm.D., Regulatory Project Manager
FDA ATTENDEES: Bernard Parker, M.D., Eldon Leutzinger, Ph.D., Adebayo Laniyonu, Ph.D., Jin Chen, Ph.D., Young-Moon Choi, Ph.D.

DISCUSSION:

- The purpose of the meeting was clarify that there were no filing issues for the application.
- Safety issues were discussed, including the data for the COPD subgroup. It was noted that the adverse event profile for the COPD patients as compared to patients without COPD, showed an increased percentage of certain adverse events such as headache and nausea. There is also a concern with air embolism syndrome.
- The sponsor did not submit individual data for patients presently in study IMUS- [redacted] which is the ongoing study. Also other than additional information concerning adverse events, the integrated safety summary did not change from the original submission.

MEETING TYPE: Team Meeting
MEETING DATE: April 29, 2002
TIME: 12 noon EST
LOCATION: Parklawn, Room 18B-37
MEETING RECORDER: Tia M. Harper-Velazquez, Pharm.D., Regulatory Project Manager
FDA ATTENDEES: Patricia Y. Love, M.D., M.B.A., Ramesh Raman, M.D., Bernard Parker, M.D., Eldon Leutzinger, Ph.D., Adebayo Laniyonu, Ph.D., Jin Chen, Ph.D., Sonia Castillo, Ph.D., Young-Moon Choi, Ph.D.

DISCUSSION:

The purpose of the meeting was for a general team discussion of the April 5, 2002, resubmission.

MEETING TYPE:	Team Meeting
MEETING DATE:	April 29, 2002
TIME:	12 noon EST
LOCATION:	Parklawn, Room 18B-37
MEETING RECORDER:	Tia M. Harper-Velazquez, Pharm.D., Regulatory Project Manager
FDA ATTENDEES:	Patricia Y. Love, M.D., M.B.A., Eldon Leutzinger, Ph.D., Adebayo Laniyonu, Ph.D., Jin Chen, Ph.D., Sonia Castillo, Ph.D., Young-Moon Choi, Ph.D.

DISCUSSION:

- General team discussion of the April 5, 2002, resubmission.
- Some preliminary labeling issues were also discussed.

MEETING TYPE:	Labeling Meeting
MEETING DATE:	May 13, 2002
TIME:	11:30am EST
LOCATION:	Parklawn, Room 18B-37
MEETING RECORDER:	Tia M. Harper-Velazquez, Pharm.D., Regulatory Project Manager
FDA ATTENDEES:	Eldon Leutzinger, Ph.D., Adebayo Laniyonu, Ph.D., Jin Chen, Ph.D., Sonia Castillo, Ph.D., Young-Moon Choi, Ph.D.

DISCUSSION:

- The team will forward their comments on the labeling, and a draft of the division's proposed labeling will be formulated and distributed to the review team.

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/s/

Tia Harper-Velazquez
5/28/02 01:16:07 PM

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DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS

Industry Meeting (Chemistry)

SPONSOR: Alliance Pharmaceutical

PRODUCT: Imavist (AFO150)

DATE: November 2, 2000, 2:30pm ET

FDA ATTENDEES:
Patricia Y. Love, M.D., M.B.A., Division Director, HFD-160
Eldon Leutzinger, Ph.D., Chemistry Team Leader, HFD-820
Milagros Salazar-Driver, Ph.D., Chemistry Reviewer, HFD-820
Tia M. Harper-Velazquez, Pharm.D., Regulatory Project Manager, HFD-160

ALLIANCE PHARMACEUTICAL ATTENDEES:
David Klein, Ph.D., Senior Vice President, Pharmaceutical Development
Nils Olsson, Ph.D., Analytical Chemistry
[redacted]
Georg Roessling, Ph.D., Department Head, Pharmaceutical Development, Schering AG (Alliance's Co-development partner)
Mark Walters, Project Director, *Imavist*
Tara Fields, RAC, Director, Regulatory Affairs

PURPOSE: The purpose of the meeting is to discuss the chemistry portion of the Agency's approvable action letter of August 14, 2000.

DISCUSSION:

The meeting began with introductions, followed by a presentation by the sponsor (see Attachment 1). After the sponsor's presentation, the following was discussed:

1. The division asked the sponsor if the bubble is formed when the liquid is added. The sponsor responded that the active drug is formed at the end of the reconstitution procedure.
2. In response to a question from the division as to how the sponsor targeted the amount of nitrogen necessary, the sponsor responded that an actual animal efficacy model using Doppler was used. However, the control is not as "tight" as they would like.

Industry Meeting (Chemistry)
November 2, 2000, 2:30pm ET

DISCUSSION (cont.):

3. In response to a question from the division how much variability in bubble size is based on the nitrogen amount, the sponsor responded that they were not sure, however, they are in the process of developing a range. The degree of control is stringent, and both the monitor and flow are measured. Also, the sponsor felt that the pressure in the blood stream would cause the microbubbles to decrease in size. The sponsor will submit an article on nitrogen as part of the developmental portion of the resubmission.
4. In response to a question from the division, the sponsor stated that they are not sure that all of the microbubbles have pores. The division has a concern that if the sponsor cannot show that all of the microbubbles have pores, it is not possible to determine whether or not all of the microbubbles contain the drug or what the size may be.
5. The division asked how often birefrigence occurs. The sponsor responded that there is sufficient arrangement of structure to show birefringence, however, it is unclear whether or not microbubbles actually separate. The tendency would be that they do not. There currently is no evidence that the microbubbles aggregate.
6. In response to a question from the division if there are any method to determine the largest particle size, the sponsor responded that they attempted to use a [redacted] Counter for this purpose, however, experienced difficulty due to the bubble breakage.
7. The division stated that the concern from the clinical perspective is ensuring that particle size is needed because the larger particle sizes may be associated with an increased risk for pulmonary embolization in patients with pulmonary hypertension. Therefore, the upper size limit is need and should be controlled. It is not sufficient to have a specification of an even greater than 'x' size only. Also needed is the absolute number of particles greater than [redacted] um and data on each lot should be included in the resubmission.

Discussion Questions: The sponsor's discussion questions and FDA preliminary answers were presented as overheads (see Attachment 2). Also, the following points were discussed:

1. In regards to the sponsor's first discussion question, the division stated that although excipients are not active ingredients, they are a pharmaceutical component of the microsphere, and therefore do have critical function.
2. The division stated that the regulations ask for specification on all components of a drug substance, specifically injectable drugs, and in-process controls needs to be explained in the resubmission. Also, the sponsor should provide validation data of the physical properties of the microsphere to ensure that the product has the right component, and show that the drug product is reproducible.

Industry Meeting (Chemistry)
November 2, 2000, 2:30pm ET

Discussion Questions (cont.):

3. Regarding the control of the powder, all components (active and inactive/excipients), should have specification and analytical testing. If all components were controlled, then the reconstituted drug product may not need to be re-tested for each of the components, but only limited to the most relevant characteristics, such as bubble size, number, etc. (to be determined.)
4. In general, the excipients need to be quantitated. How this is done largely depends on the function performed by the excipients. The sponsor stated that osmolality was used as the surrogate because changes in the drug product will be evident in the osmolality. The division stated that for some excipients, for example, buffers, it may be more appropriate to use PTT as a surrogate.
5. The division also noted that if the components present have the potential to change during storage, therefore the question of stability should be addressed in the resubmission.
6. The division asked the sponsor to provide a justification for the use of the terminology microbubble versus microsphere. The sponsor responded that the terminology microsphere is used when referring to the powder, however the term microbubble is used in reference to the constituted product. The division asked that this justification for the terminology be included in the resubmission.
7. In response to question #4 of the submission dated October 18, 2000, the need for pH and osmolality were discussed. The division requested the validation of their proposed link between the physical properties and the amount of components.
8. Regarding the use of a filter, data are needed on how the filter effects the product.

Minutes Recorded By:

/S/

Tia M. Harper-Velazquez, Pharm.D.
Regulatory Project Manager
HFD-160

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DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS

INDUSTRY MEETING

NDA: 21-191

DRUG: AFO 150 (Imavist)

SPONSOR: Alliance Pharmaceutical Corp.

DATE: November 3, 2000

FDA ATTENDEES:
Patricia Y. Love, M.D., Division Director, HFD-160
Victor Raczkowski, M.D., Deputy Director, ODE III
Sally Loewke, M.D., Acting Deputy Director, HFD-160
Ramesh Raman, M.D., Clinical Team Leader, HFD-160
Bernard Parker, M.D., Medical Officer, HFD-160
Sonia Castillo, Ph.D., Statistical Reviewer, HFD-160
David Lee, Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader, HFD-870
Pat Stewart, Regulatory Project Manager, HFD-160
Tia M. Harper-Velazquez, Pharm.D., Regulatory Project Manager, HFD-160

SPONSOR ATTENDEES:

Janice Lookabaugh, MPH, Director, Biostatistics

Ted Roth, President & Chief Operating Officer
Davie Klein, Ph.D., Senior Vice President, Pharmaceutical Development
Mark Walters, Project Director, Imavist
Tara Fields, RAC, Director, Regulatory Affairs

AGENDA: The purpose of the meeting is to discuss the clinical portion of the Agency's approvable action letter of August 14, 2000.

DISCUSSION: After introductions and a presentation by the sponsor (Attachment 1), the discussion proceeded as follows:

General:

- The division asked if the sponsor's definition differentiated regional wall motion and regional wall thickening, and if wall thickening is a component of wall motion. The sponsor responded that one would expect to see wall thickening. EF calculation is load determinant, and variable, therefore the regional perspective is important.

- The division asked if the EBD scoring definitions were found in the training materials or in the original protocol. The sponsor indicated that the information was introduced to the readers prospectively. This should be clarified in the resubmission.

- The sponsor stated that it is important that the endocardium be seen at end-diastole. Clinical function cannot be assessed on a score of ≤ 1 unless the endocardium is seen and assessed throughout the cycle.

- The sponsor commented on the use of the drug for the stated indication. The use of Optison has made an impact on clinical practice as patients "rarely" go on to other procedures. The sponsor stated that approximately 5-10% of studies use rest contrast (harmonic contrast imaging), and about 20-25% use stress contrast. In response to a question by the division, the sponsor responded that whether or not contrast is used is determined by looking at two adjacent segments.

Sponsor's Discussion Questions: The sponsor's discussion questions and FDA preliminary answers were presented as overheads (see Attachment 2.) The discussion continued as follows:

Discussion Questions #1:

The division stated that there is concern with the relevance of the endpoint. In regards to the sponsor's discussion question on regional endpoints, it is not clear what question is being asked. Overall, however, it is not the key issue. At present, the clinical usefulness of EBD alone has not been determined. Therefore, we request additional information to move forward from an endocardial border delineation (EBD) claim. The data need to demonstrate systematic improvement of contrast echocardiography (c-ECHO) over non-contrast echocardiography (n-ECHO) for a clinically meaningful endpoint.

The division expressed concern that the RVG data were not collected in a uniform way. The sponsor stated that because there are not as many centers doing RVG, the quality of the images may not be uniform.

The division stated that the goal is to find enough data to support proceeding based upon an EBD claim. The division suggested a re-read of the ejection fraction data. The sponsor stated that they do not believe that a re-read will make a difference in their results.

Concerning ejection fraction, the sponsor's statistician reviewed all segments falling out (not adjacent). The sponsor stated that they got better correlation when all segments were seen at baseline. There is also a difference of opinion whether or not RVG or MRI is the gold standard for regional activity. The sponsor also stated that echocardiogram is the current clinical standard for regional activity.

In reference to the consultant's comments regarding use in trans-esophageal (T.E.E.), the division noted that when (T.E.E.) is done on pediatric patients, a sedative is needed, and asked the sponsor if the same was true for adults. The sponsor responded that Versed and other sedating agents were used. The division asked if the sponsor experienced difficulty with enrollment using T.E.E. The sponsor responded that they did not experience any difficulty, and there were not issues with the I.R.B.

The division asked if there are data that examine the effects of ventilators upon subjects undergoing echocardiography (since patients who are status post surgery or trauma tend to undergo echocardiography for cardiac evaluation). The sponsor responded that there are in-vitro studies exposing the drug product to different pressure levels. The division asked to the see the safety data in the resubmission. Also, the consultant stated that the decision to use contrast is based on ≥ 2 adjacent segments that were not available. [This is not an enrollment criteria and was not the basis of the analysis.]

Concerning the indication, the division stated that it is premature to come to a conclusion on the proposed indication change. The first agents were approved with anatomic indications. However, the current data for their NDA and other data sets under recent review suggest that this correlation between LVEBD and LVO as surrogate markers may not be appropriate. The division is looking for data strong enough to indicate a trend. Also, the data needs to show that the contrast itself is adding benefit over non-contrast.

Discussion Question #2:

Additional pharmacokinetic information is needed prior to approval. This includes:

1. Measuring the percent binding in the gas itself.
2. In regards to pulmonary impaired subjects – the sponsor needs to submit data demonstrating that the elimination mechanism is limited to minute ventilation.

Regarding the intact microbubble, the sponsor should commit to developing assay methodology in order to measure intact microbubble in vivo.

Discussion Question #3:

The division needs confirmatory evidence that DMPC follows conventional phospholipid metabolism. DMPC is semisynthetic, therefore the metabolic profile should be reviewed. The sponsor may consider exploring in-vitro metabolism.

Discussion Question #4:

The division stated that it chromatograms should be clearly labeled. Both blood and expired air samples are requested to be included in the resubmission.

Minutes Prepared By:

/S/

Tia M. Harper-Velazquez, Pharm.D.
Regulatory Project manager

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MEMORANDUM OF MEETING MINUTES

MEETING DATE:	September 18, 2001
TIME:	3:00pm EST
LOCATION:	Parklawn, Room 18B-37
APPLICATION:	NDA 21-191, Imavist® (AFO150)
TYPE OF MEETING:	Filing Meeting
MEETING RECORDER:	Tia M. Harper-Velazquez, Pharm.D., Regulatory Project Manager
FDA ATTENDEES:	Ramesh Raman, M.D., Bernard Parker, M.D., Eldon Leutzinger, Ph.D., Milagros Salazar, Ph.D., Nakissa Sadrieh, Ph.D., Jin Chen, Ph.D., Mike Welch, Ph.D., David Lee, Ph.D.
BACKGROUND:	This resubmission, dated August 16,2001, is in response to the division's approvable action letter dated August 14, 2000.

DISCUSSION POINTS (Bullet Format):

Clinical Pharmacology & Biopharmaceutics:
- Fileable

Pharmacology/Toxicology:
- Fileable

Statistics:
- Fileable

Clinical:
- Fileable

Minutes Prepared By:

(See electronic signature.)

Tia M. Harper-Velazquez, Pharm.D.
Regulatory Health Project Manager

RECORD OF PLANNING & TEAM MEETINGS

NDA 21-191, Imavist® (AFO150)

MEETING TYPE: Planning Meeting
MEETING DATE: September 20, 2001
TIME: 1:00pm EST
LOCATION: Parklawn, Room 18B-37
MEETING RECORDER: Tia M. Harper-Velazquez, Pharm.D., Regulatory Project Manager
FDA ATTENDEES: Patricia Y. Love, M.D., M.B.A., Sally Loewke, M.D., Ramesh Raman, M.D., Bernard Parker, M.D., Milagros Salazar, Ph.D., Jin Chen, Ph.D.

DISCUSSION:

- The review team was presented with the tentative 6 month timeline to review for any discrepancies or conflicts with other applications. A copy of the timeline is attached. (See Attachment 1)
- It was determined the team meetings were needed initially with chemistry, pharmacology, and clinical. Clinical team meetings, and team meetings with clinical and statistics should follow.

MEETING TYPE: Team Meeting
MEETING DATE: October 11, 2001
TIME: 2:00pm EST
LOCATION: Parklawn, Room 18B-37
MEETING RECORDER: Tia M. Harper-Velazquez, Pharm.D., Regulatory Project Manager
FDA ATTENDEES: Patricia Y. Love, M.D., M.B.A., Bernard Parker, M.D., Eldon Leutzinger, Ph.D., Milagros Salazar, Ph.D., Nakissa Sadrieh, Ph.D., Jin Chen, Ph.D.

DISCUSSION:

The purpose of the meeting was for the chemistry and pharmacology/toxicology reviewers to report their findings to the medical officer.

RECORD OF PLANNING & TEAM MEETINGS

NDA 21-191, Imavist® (AFO150)

MEETING TYPE: Team Meeting
MEETING DATE: October 15, 2001
TIME: 1:00pm EST
LOCATION: Parklawn, Room 18B-37
MEETING RECORDER: Tia M. Harper-Velazquez, Pharm.D., Regulatory Project Manager
FDA ATTENDEES: Sally Loewke, M.D., Ramesh Raman, M.D., Bernard Parker, M.D.,

DISCUSSION:
The purpose of this meeting was to discuss issues concerning safety, efficacy, and the proposed indication. The meeting included the clinical review team only.

MEETING TYPE: Team Meeting
MEETING DATE: November 9, 2001
TIME: 12:30pm EST
LOCATION: Parklawn, Room 18B-37
MEETING RECORDER: Tia M. Harper-Velazquez, Pharm.D., Regulatory Project Manager
FDA ATTENDEES: M.D., Ramesh Raman, M.D., Bernard Parker, M.D., Sonia Castillo, Ph.D.

DISCUSSION:
Clinical and statistics issues.

RECORD OF PLANNING & TEAM MEETINGS

NDA 21-191, Imavist® (AFO150)

MEETING TYPE:	Team Meeting
MEETING DATE:	November 14, 2001
TIME:	12:30pm EST
LOCATION:	Parklawn, Room 18B-37
MEETING RECORDER:	Tia M. Harper-Velazquez, Pharm.D., Regulatory Project Manager
FDA ATTENDEES:	M.D., Ramesh Raman, M.D., Bernard Parker, M.D., Sonia Castillo, Ph.D.

DISCUSSION:
Clinical by Dr. Parker. Overheads and a handout of tables are attached. (See attachments 2 and 3 respectively.)

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/s/

Tia Harper-Velazquez
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Division of Medical Imaging and Radiopharmaceutical Drug Products

End-of-Phase 2 Meeting

SPONSOR: Alliance Pharmaceutical Corp.

PRODUCT: IND [redacted] AFO150 (Perfluorohexane for Injection)

DATE: Thursday, November 13, 1997
Third Floor Conference Room M

FDA ATTENDEES:
Patricia Y. Love, MD, Division Director, HFD-160
Victor Razckowski, Deputy Director, HFD-160
Eric Jones, MD, Medical Team Leader, HFD-160
Nelson Arnstein, MD, Medical Reviewer, HFD-160
Sonia Castillo, Ph.D., Statistical Reviewer, HFD-720
David Lee, Ph.D., Biopharmaceutist Team Leader, HFD-870
Laraine Meyers, Ph.D., Pharmacology Team Leader, HFD-160
Rubynell Jordan, MPA, Consumer Safety Officer, HFD-160

ALLIANCE ATTENDEES:
D. Les Brown, Ph.D., Director, Clinical Research, Imagent
Tara Fields, Associate Director, Regulatory Affairs, Imagent
Carol L. Hopkins, R.A.C., Senior Director, Regulatory Affairs
Philip Jochelson, MD, Division Director, Clinical Research
John G. Lee, Ph.D., Senior Director, Biostatistics and Clinical Data Management
Tim Pelura, Ph.D., Vice President, Pharmaceutical Research and Development
Gordon L. Schooley, Ph.D., Vice President, Clinical Research and Regulatory Affairs
Mark D. Seefeld, Ph.D., D.A.B.T., Senior Director, Preclinical Drug Safety
Mark Walters, Project Director, Imagent
Schering AG, Alliance's Co-development Partner:
Duncan Lamb, International Project Manager
Consultant:
[redacted]

PURPOSE: To discuss the design of the Phase 3 cardiac function studies for AFO150. To provide guidance for both clinical and nonclinical sections of the IND in preparation for future filing of a NDA.

DISCUSSION: After brief introductions of all participants, the Regulatory team from Alliance then facilitated the meeting. Questions 7 and 8 were discussed first as a request from the

DISCUSSION: After brief introductions of all participants, the Regulatory team from Alliance then facilitated the meeting. Questions 7 and 8 were discussed first as a request from the Pharmacology/ToxicologyTeam Leader.

The meeting proceeded with a discussion of the questions listed by the sponsor on the attached sheets " Specific Questions for Which Sponsor Requires FDA Input"(Attachment 1) . Please refer to this sheet when noting the discussion of each of the questions. The discussion of the questions will be presented in the same order as followed at the November 13, 1997, End-of-Phase 2 meeting.

Question 7. " Is the nonclinical toxicology plan, which is presented in **Sections IV.B** and **IV.C** of the briefing document, acceptable for NDA filing?"

Discussion: The FDA indicated that the scope of the toxicology studies appear to be inclusive and adequate. The Pharmacology/Toxicology Team Leader then listed for the sponsor certain areas requiring additional consideration. Please refer to items 1-5 listed on (Attachment 2) with the Pharmacology/Toxicology primary reviewer's responses/comments under **Sponsor Question 7.**

In response to item 5 under **Sponsor Question 7**, the sponsor indicated that they could do ECG monitoring in order to determine the presence of possible arrhythmias but the animals would be anesthetized.

Question 8. "Is the nonclinical ADME plan, which is presented in Sections IV.D and IV.E of the briefing document, acceptable for NDA filing? (The sponsor requested that we refer to page 37 of the briefing document)

Discussion: The Pharmacology/Toxicology Team Leader for HFD-160 indicated that the studies seem to address the fate of the gas contained within the bubbles, but the fate of the entire bubble is not clear. Please see the Pharmacology/Toxicology primary reviewer's responses/comments under **Sponsor Question 8.** HFD-160 inquired as to when and where does the bursting of bubbles occur? The sponsor indicated that this was a difficult question to completely answer and attempted to explain the mechanism of the bubble.

The Biopharmacology/Pharmacokinetics Team Leader asked where do the bubbles go and what do they do at different body temperatures? He suggested that the sponsor consider looking at an appropriate animal model to explore this more.

There was a question from FDA as to whether bubbles grow in *vivo* or not. The sponsor indicated that bubbles do not grow in *vivo*. FDA requested that the sponsor please include this information in their drug application.

Question 1. "Will two Phase 3 studies that show a statistically significant difference in an ejection fraction primary endpoint, plus a positive trend in wall motion, be sufficient to support the above indication? "

HFD-160 asked if EF and WM were separate. The sponsor indicated that the two were separate. HFD-160 then requested that the sponsor evaluate each in their own right, as 2 primary endpoints or 1 primary and 1 secondary. The main point was that the sponsor show clinical relevance for each. The sponsor indicated that they were seeking EF and if WM happens to be okay also, then they would claim it as well. The FDA asked the sponsor if segmental visualization equals EBD in their application. The sponsor indicated that this was the case. HFD-160 indicated that this was good because the sponsor would be able to show actual technical features. Some discussion ensued about the way in which the sponsor calculated/measured EF.

Question 2. "Is the statistical method of summarizing ejection fraction data and the use of McNemar's test or binomial test for paired samples an acceptable procedure for testing the null hypothesis of the ejection fraction primary endpoint?"

Null Hypothesis: The contrast echocardiograph (ECHO) percent agreement when compared to RVG will not be significantly different than the non-contrast ECHO percent agreement with RVG.

HFD-160 inquired about the way the sponsor arrived at the 4 groups and numbers for the EF. The sponsor indicated that these were derived from classic clinical use. HFD-160 asked why 55 was used while the other groupings are well defined and have a range but not 55 and 25 (the upper and lower limits respectively).

Next the participants discussed the overhead "Primary Endpoint: Methods of Analysis" (Attachment 3)
HFD-160 asked the sponsor if there was some way to do a closer measurement to the truth without doing a correlational analysis. It was suggested that maybe the percentage of difference could be done prospectively (preset). The sponsor indicated that they have looked at a number of ways to capture the data but we need one set method for the application. According to the sponsor, so far the clinical values were the most useful .

HFD-160 asked the sponsor to think about how much agreement between contrast and noncontrast do they want to see and to please show results of readers independently, do not average reads. it is suggested that each trial have 2 independent readers and independent investigators. The sponsor indicated that this concept was understood but proposed using a third reader or tie breaker.

HFD-160 suggested that EF was objective but wall motion was more subjective. They also indicated that a prospective set of technical features was needed. HFD-160 then requested that the sponsor provide more information on the Jerrold H. Zar, "Biostatistical Analysis" reference for sample size formula.

It was requested that the sponsor determine the accuracy of their ability to assess EF with contrast versus without contrast. It was also noted that there was two parts to this, accuracy and reproducibility.

Question 3. In assessing segmental visualization, is it acceptable to use the classification consisting of visualized or non-visualized when evaluating segments?

HFD-160 requested the sponsor explain their categories for visualization of images, (partially visualized, completely visualized, not visualized, visualized), as the various ratings were not clear. The sponsor indicated that either an image is visualized and an assessment can be made or it is not visualized. They further explained that if the image is not seen well enough to make an assessment, then it is rated as not visualized(seen). HFD-160 felt that this need to be more clearly delineated in the application. Alliance agreed to clarify this issue as much as possible. Then a very lengthy discussion ensued about segments. The sponsor explained that if you can see WM of any segment it is rated as visualized and if WM is seen in more than one segment it still simply rated as visualized. HFD-160 asked that the sponsor consider doing the same segment views on all subjects when possible.

Next, HFD-160 asked that the sponsor take into consideration a number of issues when developing the Phase 3 trials, and they are as follows:

- Please determine if you need a standard of truth for WM.
- Please determine what percent of agreement you want between readers.
- Let the idea of what is truly clinically useful or meaningful guide you in the development of this drug application.
- Look at the issue of whether 2 readers agree that there is contrast or not and also at the images. The sponsor was also encouraged to look at technical features ,i.e., akinetic, hypokinetic, dyskinetic.