NDA 21-191 **April 1, 2002**
IMAVIST

COMMENTS AS DISCUSSED DURING THE TELECONFERENCE ON 4/1/02

Please note that these comments are preliminary only, and may be subjected to additions, deletions or changes at a later time.

1. Regarding related issues on pulmonary impaired patients

   Although the data from the study conducted in dog using minute ventilation technique can not appropriately replace a study on perfluorohaxane (PFH) gas elimination in humans, preliminarily it appears that data and the additional information provided on COPD patients, may resolve the need for the pre-approval PK study in pulmonary impaired patients. In order to complete the AE evaluation in COPD patients, provide the following:

a. For the COPD patients, provide collective adverse event table with all respiratory related events regardless of the body system (e.g., cough, shortness of breath, dyspnea, chest pain).

b. In the resubmission, include labeling language to reflect that the data represent one form of pulmonary disease, COPD. Also, we expect to add language that identifies what has not been studied.

c. Also, note that the PK study in healthy dogs with different ventilation rates provided very limited information on other lung disorders because of the following deficiencies
   - Inappropriate animal model, pulmonary function was normal.
   - Insufficient observation period, thus terminal PFH elimination phase was missing
   - Missing pre-injected PFH measurement for recovery calculation
   - Missing blood PFH kinetics

   Therefore, phase 4 commitments are needed. The PK evaluation should be added to the dog pulmonary embolism study. After the review of the results of this study, a trial will be designed and conducted to evaluate the safety of Imavist in patients with chronically impaired pulmonary vasculature.

2. Regarding the 26 patient MRI subset analysis

   The general proposal for the ≥2 adjacent segment analysis is appropriate except for the following:

   a. The success for the MRI agreement is stated as in the "range" of the non-contrast. The range should be defined more precisely

COMMENTS AS DISCUSSED DURING THE TELECONFERENCE ON 4/1/02

Please note that these comments are preliminary only, and may be subjected to additions, deletions or changes at a later time.

Cont.

b. The success rate is 20%. By patient, this is 5 of 26 patients. By view, this is 15 views (26 x 3 = 78 views). Is this your intent?

   If so, we recommend a higher success rate.

c. Include an electronic SAS dataset and the program used for the evaluation.

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*** TX REPORT ***
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CONNECTION ID	
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RESULT	OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: April 1, 2002

TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	Comments per Tcon of 4/1/02	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 4

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*** TX REPORT ***
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TRANSMISSION OK

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RESULT	OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: March 18, 2002

TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Imavist Submission Date: 12/13/01	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: March 18, 2002

TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Imavist Submission Date: 12/13/01	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

Comments:

Tara: I am forwarding comments from the pharm/tox reviewers for the submission above.

Thanks.

Tia

NDA 21-191 Imavist **March 18, 2002**
Submission Date: 12/13/01

COMMENTS TO THE SPONSOR

Please note that these comments are preliminary only, and may be subjected to additions, deletions or changes at a later time.

PHARMACOLOGY/TOXICOLOGY:

Safety pharm study protocol in acute PE dogs for post-market commitment in response to the first action letter of August 14, 2000 (Section II, B, page 5)

1. A dose-response curve between pulmonary circulation responses (pulmonary arterial pressure and resistance) and various doses of polystyrene beads should be generated before testing AF0150. Effects of AF0150 should be tested at two different levels of compromised pulmonary circulation.

2. AF0150 dose selection should be based on body surface area conversion, and ideally the maximal dose of AF0150 should induce certain responses of pulmonary circulation.

3. The duration of observation duration should be long enough for the animal responses to return to baselines, and animals become stable prior to receiving next dose.

4. Susceptibility of the animal model should be re-verified with additional bead injection after AF0150 and saline treatments at the end of experiment. The animals should show further pulmonary circulation responses to the re-injection with the beads. In addition, location of embolized microspheres in the pulmonary vasculature need to be evaluated with histopathology examination at the end of study.

5. Please be aware of potential carryover effects of repeat dosing AF0150 (due to crossover experimental design). Sufficient washout period should be allowed and verified with baseline monitoring (e.g. PFH in expired air and other measurements).

6. Evaluation of PFH pharmacokinetics with this study is strongly recommended to assess effects of impaired pulmonary function on PFH kinetics. Elimination kinetics of PFH in both expired air and blood should be evaluated.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: March 7, 2002

TO: MS. TARA FIELDS (for Dr. Howard C. Dittrich)	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: Alliance Pharmceutical Corp.	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (858) 410-5320	**Fax number:** (301) 480-6036
Phone number: (858) 410-5272	**Phone number:** (301) 827-7510

Subject: NDA 21-191: Imavist

Total no. of pages including cover: 2

COMMENTS: Please find attached *preliminary* comments regarding NDA 21-191: Imavist, Meeting Package of 03/05/02. Please provide an official response to the NDA A.S.A.P., or by NOON (E.S.T.), Friday, March 8, 2002. Thank you.

****
*** TX REPORT ***
****

TRANSMISSION OK

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CONNECTION ID	
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PGS. SENT	2
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: March 7, 2002

TO: MS. TARA FIELDS (for Dr. Howard C. Dittrich)	**From:** Thuy Nguyen Regulatory Health Project Manager
Company: Alliance Pharmceutical Corp.	Division of Division of Medical Imaging and Radiopharmaceutical Drug Products
Fax number: (858) 410-5320	**Fax number:** (301) 480-6036
Phone number: (858) 410-5272	**Phone number:** (301) 827-7510

Subject: NDA 21-191: Imavist

Total no. of pages including cover: 2

COMMENTS: Please find attached *preliminary* comments regarding NDA 21-191: Imavist, Meeting Package of 03/05/02. Please provide an official response to the NDA A.S.A.P., or by NOON (E.S.T.), Friday, March 8, 2002. Thank you.

PRELIMINARY COMMENTS TO THE SPONSOR

NDA 21-191: Imavist (Submission Dated 03/05/02) **03/07/02**

Please refer to the Meeting Package of 03/05/02, for the following:

1. **Page 01.010, Paragraph 1, Sentence 2 – "As stated..."**
   Page 01.010, Paragraph 1, Sentence 4 – "Data from..."

   We assume that these two sentences refer to the 26 patients that were re-analyzed and to data already resubmitted. Please confirm.

2. **Page 01.010, Paragraph 2, Sentence 1 – "In addition,..."**

   Please specify which "internal HFD-160 memorandum" (i.e., date, author) is being referenced.

3. **Page 01.011, Paragraph 2, Sentence 1 – " One Phase 2..."**

   Please confirm that no other studies (US or foreign) were initiated besides Study IMUS-022-USA after the February 2000 safety update.

4. **Page 01.014, V. Pediatric Plan**

   Please identify which "other approved microsphere products" is being referenced.

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: October 17, 2001

TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 August 16, 2001	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 3

Comments:

Tara – I am forwarding comments from the pharmacology/toxicology reviewer for NDA 21-191. Please feel free to respond by fax, followed by an original (hard copy) via U.S. mail by Friday, October 26, 2001.

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

NDA 21,191 October 17, 2001
DRUG: IMAVIST

COMMENTS TO THE SPONSOR

Please note that these comments are preliminary only, and may be subjected to additions, deletions or changes at a later time.

Pharmacology/Toxicology:

1. Please provide the following information and data related to the microcirculation study (IM-4000):

   i. Microcirculation imaging data on CD-ROM recorded before and after intra-arterial injection of AF0150, polystyrene microparticles and saline, particularly for those images demonstrating lodging/plugging and deformation of AF0150 microbubbles in microvessels.

   ii. Specific location of catheter in aorta for injection of AF0150, polystyrene microparticles and saline.

   iii. In table III, the number of microvessels which were imaged and the number of microbubble-lodged and -plugged capillaries.

   iv. The size of lodged microbubbles and possible fraction of lodged microbubbles over injected microbubbles.

   v. In table IV, the number of microvessels plugged with polystyrene particles in all imaged microvessels. Please specify impacted microvessels (capillary, arteriole or venule).

   vi. Any change in systemic hemodynamics and clinical signs following intra-arterial injection of polystyrene microparticles.

   vii. In table A-VI, in each rat the total number of imaged capillaries and total numbers of perfused and non-perfused capillaries; and any correlation with lodged microbubbles (size and number).

   viii. Any information or observations regarding changes in arteriolar and venular diameters and blood flow in hyperlipidemic rats, as compared with in normal rats, before and after AF0150 and saline injection.

NDA 21,191 **October 17, 2001**
DRUG: IMAVIST

COMMENTS TO THE SPONSOR

Please note that these comments are preliminary only, and may be subjected to additions, deletions or changes at a later time.

Pharmacology/Toxicology:

2. Please provide a literature review to address that HES, as plasma expander, induces vacuolation in macrophage/monocytes and RES in animals and/or humans; and potential impact in function of those cells.

3. Please re-search literature to identify chronic or subacute pulmonary embolism animal models and propose a brief study plan using those animal models to further assess potential risk of AF0150 in patients with compromised pulmonary circulation.

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

/s/

Tia Harper-Velazquez
1/4/02 01:53:16 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-191

Alliance Pharmaceutical Corp.
Attention: Howard C. Dittrich, M.D.
Vice President, Regulatory Affairs
3040 Science Park Road
San Diego, CA 92121

Dear Dr. Dittrich:

We acknowledge receipt on August 20, 2001, of your August 16, 2001, resubmission to your new drug application (NDA) for Imavist™ (perflexane lipid microbubbles for injectable suspension) .

This resubmission contains additional clinical, non-clinical, and chemistry information submitted in response to our August 14, 2000, action letter.

With this amendment we have received a complete response to our August 14, 2000, action letter.

If you have any questions, call Tia Harper-Velazquez, Pharm.D., Project Manager, at (301) 827-7510.

Sincerely,

{See appended electronic signature page}

Kyong Cho, Pharm.D.
Chief, Project Management Staff
Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Kyong Cho
8/30/01 01:03:55 PM

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*** TX REPORT ***
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RESULT	OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5699 Fishers Lane, Room 18B-06
Rockville, MD 20857

DATE: June 9, 2000

To:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Clinical Comments	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 3

Comments:

Tara - The clinical comments are attached. Please respond via fax by Wednesday, June 14th. 2000 and forward hard copy via regular mail. Also, because I will be out of the [illegible] Parker, and leave him a

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5699 Fishers Lane, Room 18B-06
Rockville, MD 20857

DATE: June 9, 2000

To:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Clinical Comments	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 3

Comments:

Tara - The clinical comments are attached. Please respond via fax by Wednesday, June 14th, 2000 and forward hard copy via regular mail. Also, because I will be out of the next week, please put the fax to the attention of Dr. Bernard Parker, and leave him a voice mail so that he'll know the fax was sent.

Thanks.

Tia

NDA # 21-191 **June 9, 2000**

AFO150 ***(Imavist)***

PRELIMINARY COMMENTS TO THE SPONSOR

Please note that these comments are preliminary only, and may be subjected to additions, deletions or changes at a later time.

Clinical:

1. Please provide the following information for the serious adverse events:
   a) Amount of AFO-150 administered to each subject.
   b) Timing of AE in relationship to dose.
   c) Timing of myocardial infarction (entry criterion) and PTCA, if performed, to AFO150 dosing.

   Please provide similar dose information for those subjects who experienced **severe** and **moderate** adverse events.

2. Although you provided data regarding ECG adverse events, as well as data regarding **potentially clinically significant** ECG events (which **actually** concentrated upon changes in the **PR, QRS and QTc** intervals), we need to know if there were any ECG adverse events listed related to changes in the aforementioned intervals. For the phase 1 and 2 studies, do you have ECG data broken down by intervals?

3. We need to know if any "Duration of Useful Contrast Enhancement" information for subjects with > 40% EF was done and where this information is located.

4. Please direct us to the volume within the NDA where the criteria used to identify a clinically significant lab change and a clinically significant ECG interval (PR, QRS, QTc) change can be found.

NDA # 21-191 June 9, 2000

AFO150 *(Imavist)*

PRELIMINARY COMMENTS TO THE SPONSOR

Clinical (cont):

5. With regards to the gated mode image, can you please specify what the blinded reader actually saw (i.e. individual end-diastolic and end-systolic images or multiple frames of end-diastole and end-systole superimposed on one another)? Given that only one EBD score was recorded, is it safe to assume that this was a composite score of end-systole and end-diastole for both continuous and gated imaging?

6. Please provide us with an adverse event table that incorporates the new AEs reported in the safety update, as well as, those reported in the NDA. Please present this table in the format of Table VIII.14 (Vol 44 page 165) except report AEs occurring in ≥0.5% of the subjects.

Cc:

Original NDA 21-191

HFD-160/Div. File

Filename: C/Mydocuments/AFO150/Fax.Clin.comm.060900

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*** TX REPORT ***
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RESULT	OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 4/11/00

UPDATE

Center for Drug Evaluation and Research
FDA

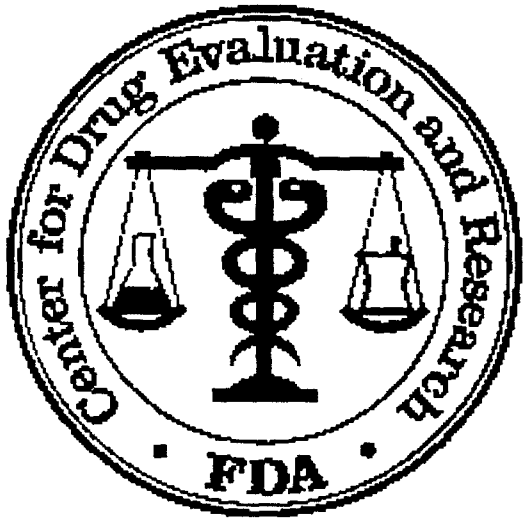
TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	Comments - Microcirculation Study Protocol	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 4/11/00

UPDATE



TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	Comments - Microcirculation Study Protocol	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

Comments:

Hello Tara:

Dr. Chen's comments on the microcirculation study protocol are attached.

Thank you.

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

NDA21,191
AF0150

April 10, 2000

COMMENTS TO THE SPONSOR

Microcirculatory Effects of AF0150 Microbubbles in the Rat Mesentery
(Study Protocol, March 31, 2000)

Comments and Suggestions to the sponsor

1. To ensure that enough microbubbles can be observed, AF0150 Dose may need to be increased to approximately 10-fold of PCD.

2. To ensure enough microbubbles are delivered into the mesenteric circulation, direct injection of AF0150 into the mesentery artery may be considered as an alternative administration route.

3. A positive control (such as solid microspheres) needs to be included to validate the assay system.

4. Coadministration or pretreatment of the animals with pharmacological stress agents is suggested to test microbubble behavior in the presence of vasoconstriction and vasodilation.

5. Please consider addressing possible effects of blood lipids and atherosclerotic lesions on microbubble behavior. In order to mimic hyperlipidemia, would it be possible to study the effects of high blood lipids by using an intravenous or intra-arterial injection of cholesterol in the proposed assay system.

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*** TX REPORT ***
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TRANSMISSION OK

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RESULT	OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 3/29/00

TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	Tcon - 3/30/00 2pm EST , 11am PST	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 3/29/00

TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	Tcon - 3/30/00 2pm EST , 11am PST	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

Comments:

Hello Tara: I have attached comments from Dr. Parker, regarding the clinical point of clarification. Dr. Parker has asked that you have vol.084 through vol.087 on hand. Dr. Chen, the pharm/tox reviewer has asked that you have on hand
vol.022 (study #IMUS-016-TOX) and vol.023(study #IMUS-035-TOX) for the Tcon.

Thanks.

Tia

COMMENTS TO THE SPONSOR

CLINICAL:

In the original and amendment of IMUS-001, it is stated that efficacy analysis would be performed. Although the study population were normal volunteers (and echo visualization played no part in the entry criteria), the sponsors left this within the plans. However, the NDA submission states that, BECAUSE the population studied did not have the same criteria as the two Phase 3 studies, the efficacy data was not included in this submission. We wish to know the efficacy data obtained.

APPEARS THIS WAY
ON ORIGINAL

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*** TX REPORT ***
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DFN

TRANSMISSION OK

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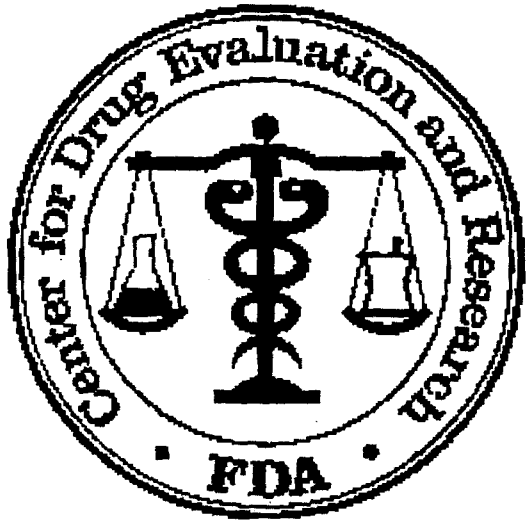
RESULT	OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 3/23/00



TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	Additional Pharm/Tox Issues	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 3/23/00

TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	Additional Pharm/Tox Issues	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

Comments:

Hello Tara: In anticipation of a Tcon next week, Dr. Chen would like you to be prepared to discuss the issues that are attached. Also, I have blocked a tentative time of Thursday, March 30, 2000 at 2:00pm EST for a Tcon. Please let me know if this day and time are good.

Thank you.

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

PHARMACOLOGY / TOXICOLOGY

TCON DISCUSSION ISSUES

Please be prepared to address the following issues for the T-con:

1. Were the QT interval data the corrected QT (QTc) in the Study "IMUS-035-TOX (Dog study)".

2. ECG summary and individual data were missing in the Study "IMUS-016-TOX (Monkey study)". We need to know the QTc in this study.

3. Please provide the ECG results (particularly QTc) from any other pharm/tox studies.

APPEARS THIS WAY
ON ORIGINAL

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	1341
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RESULT	OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 3/21/00

TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Pharm/Tox Questions	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

THIS FACSIMILE IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 3/21/00

TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Pharm/Tox Questions	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

Comments:

Hello Tara: I am forwarding pharm/tox questions that I've just received form the reviewer, Dr. Chen. If you could please respond by Friday, March 24, 2000, that would be great.

Thanks.

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

PHARMACOLOGY / TOXICOLOGY

QUESTIONS FOR THE SPONSOR

The reviewer has requested the following information:

1. ECG data in an electronic version, in the format (such as MS Excel) which can be reanalyzed, from Report# "IMUS-035-TOX (Dog study)", "IMUS-016-TOX (Monkey study)", and any other studies with ECG examination.

2. Provide summary and individual data of all ECG parameters, particularly the corrected QT (QTc), and cross species comparison of the corrected QT before and after AF0150 treatment.

3. Indicate how all ECG parameters were measured (manually or automatically?).

4. Submit a copy of original ECG records from all studies (prefer an electronic version).

5. Submit a summary table to indicate microbubble numbers per injection for all pharm/tox studies.

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*** TX REPORT ***
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DRSV

TRANSMISSION OK

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CONNECTION ID	
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USAGE T	00'48
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RESULT	OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 3/14/00

TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Clinical Questions	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

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Division of Medical Imaging and
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HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 3/14/00

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Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Clinical Questions	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

Comments: Tara: I am forwarding a couple of questions from Dr. Parker, I believe are left over from the Tcon last week. Could you respond (fax is okay) by Thursday, March 16, 2000.

Thank you.

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

March 14, 2000
NDA 21-191 AFO150

CLINICAL QUESTIONS

1. 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?

2. For the above referenced group of patients who withdrew, please provide all details, ie, identification number, reasons for withdrawal.

APPEARS THIS WAY
ON ORIGINAL

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*** TX REPORT ***
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TX-SV

TRANSMISSION OK

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SUBADDRESS	
CONNECTION ID	
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USAGE T	00'50
PGS. SENT	2
RESULT	OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 3/10/00

TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Stats Questions	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 3/10/00

TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Stats Questions	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

Comments: Tara: I am forwarding questions I received this morning from Dr. Castillo. She said that a written response is fine, a Tcon is not necessary. If we could received the response before Thursday, March 16, 2000 that would be great. Thank you.

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

QUESTIONS FOR THE SPONSOR

STATS:

1. Please describe what was on each of the 18 echo clips per subject. Also, provide a listing of the 18 echo clips.

2. Please describe the order in which EBD, SWM, and EF were evaluated during the blinded read. For example, when a subject's clip was being evaluated, in what order were the endpoints evaluated?

3. Please describe where the single 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?

APPEARS THIS WAY
ON ORIGINAL

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*** TX REPORT ***
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PTSV

TRANSMISSION OK

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SUBADDRESS	
CONNECTION ID	
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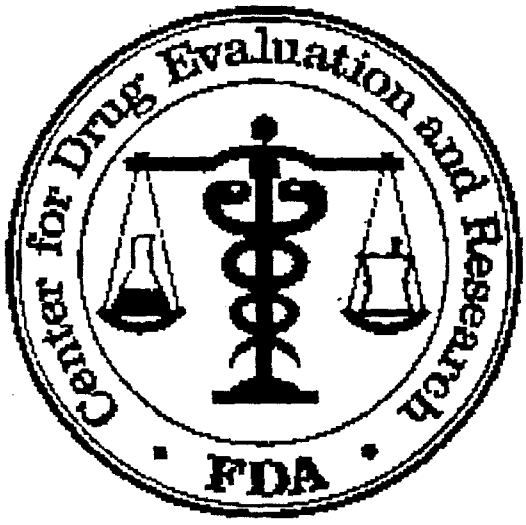
RESULT	OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products, HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 2/16/00



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Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Clinical and Statistical Comments	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

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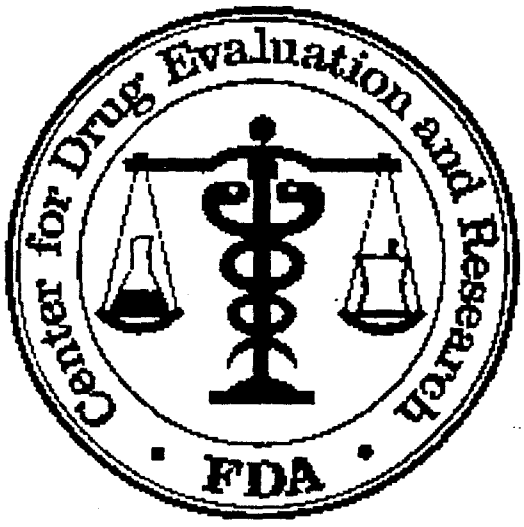
Division of Medical Imaging and
Radiopharmaceutical Drug Products, HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 2/16/00



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Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Clinical and Statistical Comments	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

Comments:

Hello Tara,

I am forwarding clinical and statistical comments received today from the reviewing medical officer and statistician. Both would like a Tcon, in order to discuss the issues. Both Dr. Castillo and Dr. Parker are available tomorrow, Thursday, 2/17 at 1pm EST. Please let me know if this times works for you as well. If not, we will set up another time.

Thank you.
Tia M. Harper-Velazquez, Pharm.D.

NDA 21-191 *AFO150* (Imavist) Date: February 16, 2000

CLINICAL AND STATISTICAL QUESTIONS AND COMMENTS

1. Were the ultrasound machine settings the same for the baseline and post-contrast images? That is, kept constant for the baseline and post-contrast images?

2. According to the protocol, the blinded readers evaluated and end-systolic and end-diastolic frame for the baseline and post-contrast images for each of the three cardiac views to determine ejection fraction (see citation below). In the dataset IMAGE, the ejection fraction value EJFRCEXP is based on which of the three cardiac views?

(Volume 168, pages 33 to 34)
Section 9.5.1 EFFICACY AND SAFETY MEASUREMENTS ASSESSED AND FLOW CHART
Echocardiograms

A selector, who was an independent cardiologist with expertise in the interpretation of echocardiograms, was to review all baseline noncontrast and contrast apical 4- and 2-chamber views in both fundamental continuous and fundamental gated modes. For each view, a single cardiac cycle that was free from artifact and arrhythmia, and that allowed the endocardium to be most fully delineated was chosen and the end-diastolic and end-systolic frames identified. This selector was not to be involved in any other reading of any other study images (i.e., RVG). ...

Each blinded reviewer was to evaluate the digitized still frames (end-diastolic and end-systolic) identified by the selector for the baseline noncontrast and contrast EF, for both continuous and gated modes. Continuous loops of noncontrast and contrast images of the 4- and 2-chamber views were linked via the computer to be viewed on the screen simultaneously with the selected still frames. Together these were to serve as the data for blinded review of EF.

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*** TX REPORT ***
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TRANSMISSION OK

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CONNECTION ID	
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RESULT	OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and
Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 2/3/00

TO:	Alliance Pharmaceuticals	FROM:	Food and Drug Administration
Name:	**Ms. Tara Fields**	Name:	**Tia M. Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Comments	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) =

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Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Comments	Location:	FDA, Div. of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) =

Comments: Hello Tara:
Dr. Castillo needs two important pieces of information (see comments attached.) Could you look in to this, and respond if possible by next Monday, February 7, 2000. If the information is not in the current material, we may need to set up a Tcon so that Dr. Castillo can specify what she needs.
Thank you.
Tia M. Harper-Velazquez, Pharm.D.

NDA 21-191
AFO150 (Imavist)

February 3, 2000

COMMENTS TO THE SPONSOR

Statistical:

1. Indicate where in the submission the SAS output from the primary analyses can be found.
2. Indicate what variables were included in the final ANOVA model used for the primary efficacy analyses on EBD.

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ON ORIGINAL

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*** TX REPORT ***
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DFB

TRANSMISSION OK

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SUBADDRESS	
CONNECTION ID	
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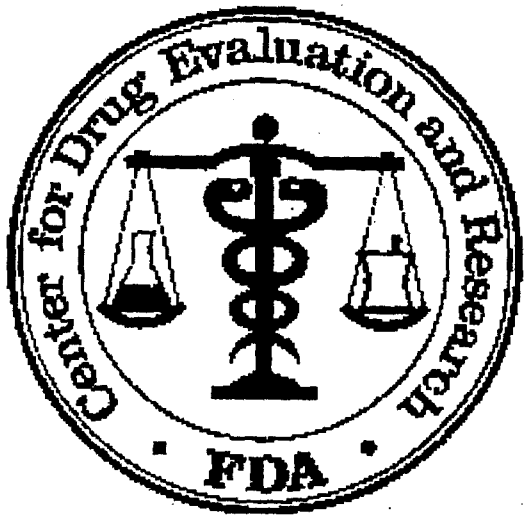
PGS. SENT	2
RESULT	OK

FOOD AND DRUG ADMINISTRATION
Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

DATE: 11/19/99



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Division of Medical Imaging and Radiopharmaceutical Drug Products
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Name:	**Ms. Tara Fields**	Name:	**Tia Harper-Velazquez, Pharm.D.**
Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Comments	Location:	FDA, Division of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

Comments:

Hello Tara: As you know Dr. Castillo, our statistician, will not be able to make our Tcon today. She provided comments that I am forwarding to you.

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

NDA 21-191
Imavist (AFO150) **November 19, 1999**
Submission Date: October 14, 1999

COMMENTS

Specific information needed by statistician:

A data set with the primary efficacy data and, in the same data set, a flag for those data points that were imputed due to missing data.

The following is a list of changes that need to be made by the sponsor to their submission volume table of contents:

1. Volume 1.1 needs a comprehensive, master table of contents listing all sections, data listings, tables, and figures with page and volume numbers.

2. In the ISS and ISE Report (Vol. 1.131)
   - A list of In-Text Tables is needed.
   - More detail is needed for sections VIII and IX.
   - A listing of what is Volumes 133 to 137 (part of section VIII) and Volumes 157 to 166 (part of section IX) are needed.
   - Each of the above request need to include the corresponding volume and page numbers.

3. The following changes are for the volumes of both study IMUS-007 and IMUS-008. I will use the volumes for study IMUS-007 as an example.
   Volume 1.168 - Volume numbers are needed for the entire table of contents.
   Volume 1.170 - Volume numbers are needed.
   Volume 1.171 to 1.1.175 and 1.184 - A table of contents is needed (there are none at the beginning of all these volumes).

4. In general, each individual volume needs a table of contents listing all sections, data listings, tables, and figures with associated page and volume numbers at the beginning of the volume.

5. In general, all volumes with study reports need a comprehensive table of contents listing all sections, data listings, tables, and figures with associated page and volume numbers at the beginning of the volume.

****
*** TX REPORT ***
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DFS ✓

TRANSMISSION OK

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PGS. SENT	2
RESULT	OK

FOOD AND DRUG ADMINISTRATION DATE: 11/18/99
Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160
5600 Fishers Lane, Room 18B-06
Rockville, Maryland 20857

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Fax No:	(858) 410-5320	Fax No:	(301) 480-6036
Phone No:	(858) 410-5272	Phone No:	(301) 827-7510
Re:	NDA 21-191 Comments	Location:	FDA, Division of Medical Imaging and Radiopharmaceutical Drug Products

 # PAGES (Including Cover Sheet) = 2

Comments:

Ms. Fields: I am enclosing comments from the reviewers for the above referenced NDA. We would like a response by Wednesday, November 24, 1999, so that we can proceed with the filing procedures. Also, the medical officer and statistician would like to set up a brief teleconference to discuss issues concerning the index. I will try to arrange this with you for early next week. Thank-you.

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

NDA 21-191
Imavist (AFO150)

November 18, 1999

COMMENTS TO THE SPONSOR

Microbiology:

- Please provide an example of the kit ("vented dispensing pin) referenced in Volume 1, p.15, and p. 41-44.

Pharmacology/Toxicology:

- The sponsor needs to refer to the pre-NDA meeting comments (July 29, 1999) to generate an overall summary table. Although it is not a deficiency for filing this NDA, the table will greatly enhance our review efficiency.

Statistics:

- Indicate which data set has the primary efficacy data.
  -The primary efficacy data set should have a flag indicating which missing data points were imputed.

Clinical: Please provide the following:

- New master index and individual index.
- Indices for each individual study, as well as all studies
- Analysis of adverse events, infusion vs bolus.
- Pediatric studies information.
- Duration of contrast enhancement.
- Segmental analysis needed.