CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020292

Trade Name: FerriSeltz

Generic Name: FERRIC AMMONIUM CITRATE, BROWN

Sponsor: ONCOMEMBRANE, INC.

Approval Date: 10/14/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020292

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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Medical Review(s)	X			
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Pharmacology Review(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020292

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-292

OCT 14 1997

Oncomembrane, Inc.
1201 Third Ave., Suite 3010
Seattle, WA 98101

Attention: Toshihiko Tanaka
CEO and President

Dear Mr. Tanaka:

Please refer to your new drug application dated April 11, 1997, received April 14, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FerriSeltz, (ferric ammonium citrate, brown), Powder for Oral Administration, 600 mg.

We acknowledge receipt of your submissions dated February 20, June 27, and September 11, and 19, 1997. The User Fee goal date for this application is October 14, 1997.

This new drug application provides for the use of FerriSeltz in adult patients for use with T_1-weighted magnetic resonance imaging (MRI) to enhance the delineation of the bowel to distinguish it from organs and tissues that are adjacent to the upper regions of the gastrointestinal tract.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed marked-up draft labeling, with the following expiration date provision: the data analyses submitted do not support a 36-month expiration date; however, 15-month expiration dating is supported. Should you desire to submit information which supports modifying the expiration dating to 36 months, you may do so by submitting a supplemental application as described in 21 CFR 314.70. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-292. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your Phase 4 commitment specified in your submission dated November 20, 1996. This commitment, along with any completion date agreed upon, is listed below:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitments, please submit protocol, data, and final reports to this NDA as correspondences. In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of each commitment. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you of your commitment dated November 20, 1996, to submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug, Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

**APPEARS THIS WAY
ON ORIGINAL**

If you have any questions, please contact Kim Colangelo, Consumer Safety Officer, at (301) 443-7515.

Sincerely yours,

Patricia Y. Love, M.D., M.B.A.
Director
Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 15 1996

NDA 20-292

Oncomembrane, Inc.
1201 Third Ave., Suite 3010
Seattle, WA 98101

Attention: Toshihiko Tanaka
CEO and President

Dear Mr. Tanaka:

Please refer to your November 12, 1992, new drug application (NDA) and your resubmission dated November 15, 1995, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FerriSeltz (ferric ammonium citrate, brown).

We acknowledge receipt of your amendments and correspondence dated July 15, September 15, and December 18, 1992; January 11 and 15, March 10, June 4 and 22, July 21, August 13, October 1, and November 24, 1993; January 6, February 3, March 2 and 4 (2), April 11 and 15, May 11 and 16, June 24, August 18 and 31, September 30, October 14, and December 16, 1994; January 13, March 13, and December 22, 1995; and January 11 and 19, February 5 and 28, June 24, July 10, October 17 (2), and November 12, 1996.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit the following information:

CHEMISTRY

I. Relating to the Drug Substance (DS):

A. A reference standard of ferric ammonium citrate (FAC), brown has not been presented. In its place you have proposed a sample of FAC, brown, Control No. E0360707, to be used for methods validation. Please provide the following information for this reference compound:

   a. Its synthesis and characterization studies.
   b. The set of specifications used to establish its usefulness as a reference material for FAC, brown.

B. The

II. Relating to the Drug Product (DP):

A. Manufacturing Process-Records, DP

1. The final form of the production batch record for FerriSeltz is not present in the application, according to the statement in Vol. 4.1, 410047-48. Please finalize this form and make it available in your responses.

2. The executed batch records for products with Batch #s 96021A, 96041A and 96045A, show discrepancies in the Code RM number and Receiving number for the with respect to the numbers reported in the dispensing records for the same batches. Please clarify.

3. The executed batch records for product with Batch # 96041 show discrepancies in the Code RM number and Receiving number for the Grape Micron, ZD3870 with respect to the numbers reported in the dispensing records for the same batch. Please clarify.

4. The product batch yields appear to be out of specification (98% to 100.5%) for all three record batches presented: for batches 96021A, 96041A and 96045A respectively. Therefore, the process does not appear to be in control. Please explain.

5. The complete analytical testing report at time of release for the FerriSeltz lots manufactured at AAI is not present in the application. Please submit this information to the NDA as part of the supportive production documentation.

6. The primary label used in the manufacture of AAI lots is different from the primary labels proposed in the original submission. Please explain these inconsistencies and clarify which label will be used for the commercial product.

B. Regulatory Testing and Specifications, DP

1. Sampling for ferric content uniformity in the NDA is not consistent with recommendations in the Please revise accordingly so the number of "selected" samples is not less than and the assay is of individual units rather than a composite.

2. There is inconsistency in the definition of the testing and specifications for FerriSeltz in the application. Different sets of tests and specifications have been described as the release testing in the original submission; the July 10, 1996, amendment; the "Regulatory/Shelf-life SPECS", Table 35, Vol 2.02, 020215; and in the stability specifications in protocol DPP-811-00. We request that you have ONE set of regulatory test methods and specifications. The regulatory specifications and test methods should be those that the product must meet through

its shelf-life and they should be supported by the stability and production data. Some testing such as identification may just be performed in the initial testing as part of an approved stability protocol. You may want to have a production release specification which is clearly described as such and separated from the regulatory/shelf-life requirements.

3. There is inconsistency in the specification limits for tartrate. Different specification limits for have been provided throughout the NDA. Please explain these inconsistencies. Also, please provide the justification, along with the appropriate data, to support the proposed tartrate specifications.

4. The rationale behind the proposed specifications is not included in the submission. For example, the release and regulatory specifications chosen do not seem to be based on production or stability data (e.g., Also, the for solution appears Please explain.

5. The for the reconstituted solution appears wider than the production and stability data support. Please explain.

6. The . for FerriSeltz packets and reconstituted solution changes to which represents a decrease to of the label. According to production and stability studies it appears that your product supports the Please explain what effect these changes will have on the MRI signal.

7. Aspartate testing is missing as regulatory specification. Yet, in the pre-NDA submission, an Please provide an explanation.

C. Stability, DP

Stability of the drug product has not been adequately characterized. The following issues should be addressed:

1. The stability lots and testing proposed for primary stability studies are not adequate. The first three lots were not manufactured at the commercial site, the container closure was not identical to that proposed for marketing, and these batches were not analyzed using all the final analytical methods (i.e., , and the inclusion of reconstituted studies for the solution. Therefore, these three lots represent stability supporting information; they do not provide primary stability information.

   The information on the additional stability Lot E0525630 is incomplete (only 9 months). It may serve as secondary stability support when the full term report for this lot is

provided and when the : ' are also reported for initial time after reconstitution. Please provide these data.

2. for lot E0515630 seems to increase with time at a different rate than the first three stability lots. Please explain.

3. The post-approval stability commitment is not adequate. It is not acceptable to consider validation batches as post-approval batches. The three batches manufactured at AAI could be considered the "primary" stability batches since they are the ones produced at the commercial site, with the commercial production equipment and personnel, with the final commercial container closure system, and tested with the final stability testing methods and specifications. Therefore, the post- approval stability commitment requires testing the "true" first three commercial batches (no validation or primary stability batches) of all strengths in the smallest and largest container configuration after NDA approval. After the first three batches, one annual batch for each container size configuration for 1-8 batches produced; or two batches for each configuration for every 8-15 batches produced, etc., is acceptable. Please reference the FDA stability guidelines "Guideline for Submitting Documentation for Stability of Human Drugs and Biologics".

4. The stability protocol presented in DPP-811-00 Appendix J is not consistent with stability commitment described in the post-approval commitment. Please submit an updated post-approval commitment containing a list that clearly states the testing, test methods code number and specifications to be used during post-approval stability studies. Also, include an 18-month testing time point in the final post approval scheme.

5. The protocol # DPP-811-00 is not clear since it gives different specifications for in Attachments D, E, F and H. Also, this protocol does not contain specifications set for in Attachment H. The specifications for in the powder are different from the one proposed in attachment D. Testing for is included in attachment H but not in attachment D. In addition, the Regulatory/shelf-life specifications presented in Table 35 (Section III, Drug Product, G. 1. Stability) of the NDA are different from protocol #DPP-811-00 Appendix J for tartrate. Please clarify these inconsistencies.

6. The submission lacks sufficient primary stability data to support your proposed 36-month expiration. The three lots from AAI are considered to be the primary stability batches. They represent the commercial product: packaged in the final container closure (with latest secondary cap bottle changes), tested with all final analytical methods, and manufactured at

the proposed manufacturing site for marketing. Specifically, the deficiencies in the primary stability data are:

a. There are only 3 months of stability data at and accelerated conditions for three lots.
b. Although there are two intended marketing sizes, there is only one container size tested for the AAI site.

Please provide data for at least three batches with both of the container sizes intended for marketing (20- and 50- count bottles). They need to be studied at long term (minimum 12 months) and accelerated conditions (6 months) as part of and in support of primary stability studies.

7. Also, the proposed expiration dating based on "pooled" data (lots with lots for ferric content only) is not acceptable. data may be used for support but separate analyses should be made for the AAI lots. Please provide full details on the statistical model and any assumptions made in the analysis used to determine the expiration time.

   Additionally, there is an incomplete analysis of stability parameters to justify the expiration time of 36 months. Other stability indicating tests results should also be analyzed and considered for determining the expiration dating, since these parameters must also stay within specification. Such tests as relaxivity may require 95% two-sided confidence limits. data should be primarily considered.

8. The data for the AAI stability are incomplete. Include the following tests and specifications when reporting the stability data for the AAI lots:

   - Appearance of powder/mix of
   - Appearance of for the powder FerriSeltz.
   - Appearance of for the reconstituted FerriSeltz.

   Also, the information on the analytical methods used to test stability of the AAI lots is incomplete. Describe the codes of these analytical methods as part of the stability protocol.

D. Analytical Methods Validation, DP

Four copies of the July 10, 1996, amendment containing analytical methods used by AAI are not present in the application. Please provide four copies of the set of AAI methods and transfer of methods studies, with the revisions recommended in this letter, as an amendment to the Methods Validation (MV) package.

E. Labeling, DP

The proposed labeling contains inconsistencies. The primary container label included in the July 10, 1996, amendment as part of the AAI Master batch record is different from the primary label proposed in the original NDA submission. All labels used during the manufacture and packaging of the product should be identical to those proposed in the NDA.

Please revise the primary and secondary container labels to comply with 21CFR 201.100 to include the following:

1. The cautionary statement "Caution: Federal law prohibits dispensing without prescription." should replace the currently proposed one.

2. The strength of the drug substance, i.e., Ferric ammonium citrate, brown, 600 mg.

3. The recommended designation for the dosage form is "powder" and for the route of administration the designation is "oral".

4. The name and address of the current commercial manufacturer proposed in the NDA, AAI.

5. Storage indications, should include a statement:

   "Store at Controlled Room Temperature 20-25°C (68-77°F)."

   Where space in the immediate container is limited an abbreviated labeling is acceptable provided the full labeling statement as shown before is included in the bottle, outer carton and the package insert:

   "Store between 20-25°C (68-77°F)", or
   "Store at 20-25°C (68-77°F)", or
   "Store 20-25°C (68-77°F)"

In addition to the above, it will be necessary for you to submit revised draft labeling identical in content to and revised as noted in the enclosed draft labeling dated November 15, 1996.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

The update should include tabulation and analysis of adverse events that led to discontinuation of the drug, interruption of administration and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. Also, please submit an analysis of digestive system adverse events by time after ingestion and by volume of FerriSeltz ingested. These assessments should include a gender, age and racial demographic subgroup analysis. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

Also, we request that you commit to undertake a Phase 4 trial to determine the need for and how to adjust FerriSeltz doses by body size in pediatric patients.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing,
Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Susan Cusack
Consumer Safety Officer
Telephone: (301) 443-1560

Sincerely yours,

Patricia Y. Love, M.D., M.B.A.
Director, Division of Division of Medical Imaging
and Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

FINAL PRINTED LABELING

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

MEDICAL REVIEW(S)

DIVISION DIRECTOR MEMO TO THE FILE

NDA:	20,292
DRUG:	FERRISELTZ (ferric ammonium citrate, brown) 600 mg Powder for Oral Administration
INDICATION:	Upper Gastrointestinal Enhancement during MRI
CATEGORY:	1S - Response to an Approvable Letter
SPONSOR:	Oncomembrane, Inc.
SUBMITTED:	April 14, 1997
PDUFA DATE:	October 14, 1997
COMPLETED:	October 11, 1997

RELATED REVIEWS:

Clinical - Lori Paserchia - 9/12/97
Chemistry - M. Salazar - 9/15/97
Project Manager - K. Colangelo

BACKGROUND:

FERRISELTZ (ferric ammonium citrate brown) is a aqueous solution of paramagnetic iron that is proposed for oral ingestion to delineate the gastrointestinal tract during magnetic resonance imaging. The original NDA was submitted by Oncomembrane on November 15, 1995, and an approvable letter was issued on November 15, 1996. The pending items included: a safety update that was to include data on nausea, vomiting and diarrhea; chemistry information on drug substance reference standards, drug product manufacturing process records, regulatory testing and specifications, stability, analytical methods validation; and labeling revisions. Generally all responses have been submitted and were found to be acceptable as noted in the action package reviews, and revised labeling. There are two specific changes that merit comment: 1) the expiration date, and 2) the dosage recommendations.

1. Expiration Date

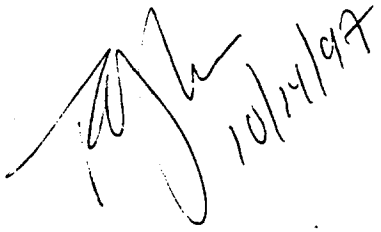
   The expiration date requested by Oncomembrane is 36 months. The submitted data support 15 months only. The latter is to be used pending the submission of data to justify a longer date.

2. Dosage

   In the approvable letter the Dosage and Administration section stated the recommended a of 6 grams, and listed 12 grams as a maximum. In the safety update, there is a statistically significant increase in adverse events in the patients who received the 12 gram dose. (See Dr. Paserchia's review for details). There is not an accompanying clinical advantage in the efficacy data of the 12 gram dose. Therefore, based upon the new safety data reasonable benefit of the 12 gram dose is no longer justified. The

labeling will be for 6 grams. The 12 gram references are deleted except to note the lack of efficacy difference and the increase in adverse events.

ACTION: APPROVAL as noted in the action package labeling and with the above phase 4 commitment



APPEARS THIS WAY
ON ORIGINAL

DEPUTY DIRECTOR'S MEMORANDUM TO FILE

NDA: 20-292; Amendment 002
DRUG: FerriSeltz™ (ferric ammonium citrate, brown)
ROUTE OF ADMINISTRATION: Oral
STRENGTH(S): 3 grams (200 mg Fe); 6 grams (400 mg Fe)
SPONSOR'S PROPOSED INDICATION: "an oral contrast agent for marking the upper gastrointestinal tract in patients undergoing T_1-weighted magnetic resonance imaging (MRI) of the upper abdomen"
TYPE OF SUBMISSION: Resubmission of a New Drug Application
PROPOSED MARKETING STATUS: Prescription Drug Product
THERAPEUTIC CLASSIFICATION: Standard
SPONSOR: Oncomembrane, Inc.
SUBMITTED: 15 November 1995
COMPLETED: 8 November 1996
REVIEWER: Victor F.C. Raczkowski, M.D., M.S.

RELATED REVIEWS:

Chemistry: Salazar-Driver 08/23/96; revised 10/18/96
Microbiology: Vincent 04/01/96
Pharmacology/Toxicology: Dundore 07/10/96
Clinical Pharmacology and Biopharmaceutics: Udo 10/25/96
Primary Medical Review: Chow 04/15/96
Secondary Medical Review: Raczkowski 11/06/96
Statistics: Davi 10/03/96

BACKGROUND:

FerriSeltz™ is a formulation of a parmamagnetic iron salt (ferric ammonium citrate, brown) that the sponsor, Oncomembrane, Inc., proposes to market as an oral contrast agent for marking the upper gastrointestinal tract in patients undergoing T_1-weighted magnetic resonance imaging (MRI) of the upper abdomen. The sponsor maintains that when given orally, ferric ammonium citrate mixes with the bowel contents and lowers T_1 relaxation times, thereby increasing intraluminal signal intensity on T_1-weighted magnetic resonance images.

Oncomembrane, Inc., first submitted a New Drug Application (NDA) for FerriSeltz on 12 November 1992. The Division determined that the original application was not acceptable for filing because of several deficiencies and sent the sponsor a "refusal-to-file" letter on 8 January 1993. Deficiencies cited in the letter included the following: a) lack of comprehensive and complete indices, b) lack of an adequate summary, c) absence of a complete environmental assessment, and d) numerous omissions in the Chemistry, Manufacturing and Controls Section. The letter also stated that a bioavailability study, measuring the absorption levels of iron, would be a required for final approval. The NDA was resubmitted on 15 November 1995. FerriSeltz has been marketed in Japan since September 1993.

Chemistry

FerriSeltz™ is formulated as a powder that dissolves in water to create a grape-flavored effervescent drink. Each 3-gram packet of FerriSeltz™ contains 600 mg of ferric ammonium citrate, brown, USP (105 mg of elemental iron); 1250 mg sodium bicarbonate, USP; 1100 mg tartaric acid, NF; 47 mg aspartame, NF; and 3 mg flavoring (grape micron ZD-3870).

Ferric ammonium citrate (FAC) has an average stoichiometric formula of $FeCit_{1.1}(NH^{+}_{4})_{1.6}(OX)_2$ and an elemental formula of $C_{6.6}H_{12.8}FeN_{1.6}O_{9.7}$. It exists as a large, polymeric coordination complex of undetermined structure and undetermined molecular weight. Its iron content ranges from (17.2% theoretical).

Microbiology

FerriSeltz is supplied as a non-sterile oral dosage formulation. In response to a request by the FDA, the sponsor provided information for microbial limits on five lots of ferric ammonium citrate, brown used in manufacturing the FerriSeltz drug product. The microbiology reviewer recommended **approval** on the basis of microbiological quality.

Pharmacology/Toxicology

Ferric ammonium citrate (FAC) has Generally Recognized as Safe (GRAS) status as a nutritional supplement, with no limitations other than good manufacuting practice (53 FR 16862). Two over-the-counter (OTC) drugs that contain ferric ammonium citrate are Geritol Liquid/oral and Geriplex-FS Liquid/oral. The proposed human dose of FerriSeltz is t
This dose of FerriSeltz also represents Arguing that for a 50 kg adult this represents a 25-fold safety factor, the sponsor states (and cites references) that the average human lethal dose for iron has been estimated to be However, the sponsor also notes that deaths have occurred in children after ingestion of doses as low as 40 mg/kg body weight.[1]

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[1] NDA Volume 1, page 010095

The maximum doses used in animal toxicity studies represented approximately 5-8 times the maximum human dose on a mg/kg basis. Preclinical toxicology studies performed by the sponsor included the following:

a) **acute oral toxicity** studies of FerriSeltz in Sprague-Dawley rats (up to 2000 mg/kg in 10 ml water), and in beagles (up to 2000 mg/kg in 10 ml water);
b) **14-day subacute oral toxicity** studies of FerriSeltz in Sprague Dawley rats (up to 1200 mg/kg in 10 ml water), New Zealand white rabbits (up to 2000 mg/kg in 10 ml water), and beagles (up to 1200 mg/kg in 10 ml water);
c) **developmental toxicity** studies of FerriSeltz in pregnant Sprague-Dawley rats (up to 1200 mg/kg in 10 ml water for ten doses on Days 6-15 of gestation), and in pregnant New Zealand white rabbits (up to 2000 mg/kg for ten doses on Days 6-18 of gestation). FerriSeltz did not produce any obvious signs of maternal toxicity, embryo-fetal toxicity, or teratogenic potential.
d) an **acute intraperitoneal toxicity** study of Ferriseltz in Sprague-Dawley rats (up to 120 mg/kg in 10 ml water). No obious toxic effects were noted.

The acute and subacute toxicity studies indicated that the gastrointestinal system is the most likely target for adverse events. For example, adverse events noted in some of the animals in these studies included diarrhea, fecal staining, soft stools, watery stools, and emesis.

No preclinical **pharmacokinetic studies** were submitted in the application. **Genetic toxicity studies** were not requested from the sponsor during the development of FerriSeltz and were not included in the application. However, the lack of genetic toxicity studies is unlikely to pose a significant safety concern given the intended use of FerriSeltz (i.e., single-dose, oral administration, and as a diagnostic agent) and the GRAS status of ferric ammonium citrate.

Toxicity after intratracheal administration was also not evaluated in preclinical animal studies. However, in the event that during clinical use FerriSeltz accidentally leaks into the peritoneum or is aspirated, the lack of obvious toxicity after intraperitoneal administration in rats is somewhat reassuring. (Note: the sponsor's proposed package insert states that FerriSeltz is contraindicated in patients with known or suspected complete bowel obstruction or perforation of the bowel).

The pharmacology/toxicology reviewer recommended **approval** of FerriSeltz.

Clinical Pharmacology and Biopharmaceutics

As noted above, the "refusal-to-file" letter of 8 January 1993 stated that a bioavailability study, measuring the absorption levels of iron, would be a required for final approval. However, in the resubmitted NDA the sponsor provided data from Phase 2/3 studies (that used doses of 200 mg and 400 mg ferric ammonium citrate) in which only two timepoints were evaluated: baseline (pre-dose) and 24 ± 4 (±SE) hours. Parameters that were evaluated included serum iron, total iron binding capacity, ferritin, and percentage saturation of transferrin. At 24 ± 4 hours, none of these parameters were significantly elevated from baseline.

Sampling at only these two times is inadequate to assess the absorption of iron, which for other oral formulations of irons usually has a time of maximal absorption (t_{max}) of 2-4 hours. Rather, a more frequent and intensive sampling scheme would allow for a more accurate assessment of potential absorption, distribution, metabolism, and elimination of iron, and hence would allow for a better estimation of systemic exposure. Nonetheless, given that the usual therapeutic dose of iron is about 200 mg per day (2 to 3 mg/kg), that FerriSeltz is to be administered as a single dose, and that the serum iron parameters in the studies cited above were not significantly increased from baseline at 24 ± 4 hours, a more intensive study, though desirable, does not appear to be necessary.

The Biopharmaceutics reviewer considered the application **approvable** from a clinical pharmacology and pharmacokinetic perspective.

Medical/Statistics

As principal support for the safety and efficacy of FerriSeltz, the sponsor submitted study reports for the following studies:

a) two dose-finding studies (#901-01 in the USA, and a study from Japan);
b) two phase 3 studies conducted under identical protocols in the USA (#901-03A ["Study A"] and #901-03B ["Study B"]);
c) a retrospective "Diagnostic Review" of the images from the two phase 3 studies from the USA;
d) one efficacy study from Japan

PHASE 1 DOSE-FINDING STUDIES:

- *Phase 1 Safety and Dose Ranging Study of OMR in Normal, Healthy Volunteers (#901-01)*
- Yoshikawa et al. *Phase II Dose-Finding Study of an Oral Abdominal Contrast Agent Containing Ferric Ammonium Citrate for Magnetic Resonance Imaging (OMR-12200).* Diagnosis and Treatment 1991; Volume 79(8), pages 1913-1922.

The following conclusions were drawn from these studies:

Dose-tolerance:

- Doses as high as 400 mg Fe/1200 ml (12 g FerriSeltz) were tolerated; the only "drug-related" adverse events observed were digestive system effects.
- Observed adverse clinical events appeared to be dose-related. A comparison of single and double doses of FerriSeltz (200 mg Fe/600 ml vs. 400 mg Fe/600 ml) showed a trend toward clinical adverse events that was more severe for the subjects receiving double doses (87% of subjects experienced a clinical adverse event; 92% of events were rated as drug-related and 21% as moderate or severe) compared to those receiving single doses (73% of subjects experienced a clinical adverse event; 91% of events were rated as drug-related; none were rated moderate or severe).

Dose-response:

- Adequate bowel distention was not achieved with a 300 ml volume, but was achieved with a 600 ml volume.
- Oral administration of FerriSeltz at doses of at least 200 mg Fe/600 ml consistently increased intraluminal signal intensity of the upper-to-middle gastrointestinal tract on both T_1- and T_2-weighted images of the abdomen and pelvis. However, no increase in signal intensity was seen in the transverse colon, descending colon, or rectum on T_1-weighted coronal images acquired an average of 45 minutes after ingestion of FerriSeltz. These observations were consistent with phantom imaging studies which showed that within the dose range given, signal intensity on T_1-weighted scans is an increasing function of FerriSeltz concentration due to the paramagnetic effects of iron, and signal intensity on T_2-weighted scans is a function of fluid load. Dilution of the contrast agent in the more distal portions of the gastrointestinal tract would be expected to decrease the degree of bowel opacifications at these sites.
- Oral administration of FerriSeltz at doses of at least 200 mg Fe/600 ml increased opacification of the small bowel in T_1-weighted upper- and middle-abdominal scans and T_2-weighted abdominopelvic scans.

- Despite the use of respiratory compensation and multiple signal averages, increased signal intensity of the bowel after FerriSeltz ingestion contributed to substantial image degradation by artifacts on long TR/TE sequences; movement of opacified bowel loops caused blurring of bowel margins and limited delineation of adjacent organs. Although artifacts were present in the images from nearly 90% of subjects, such artifacts were minimal on short TR/TE sequences (which require less time for acquisition) and generally did not impair the diagnostic quality of those images. However, artifacts were severe on T_2-weighted images (which require longer time for acquisition), leading to degradation of image quality in many instances.

PHASE 3 EFFICACY STUDIES AND THE "DIAGNOSTIC REVIEW"

- *"Study A:" An Evaluation of OMR [FerriSeltz] in Patients Undergoing MRI of the Upper Abdomen (Protocol #901-03A).*
- *"Study B:" An Evaluation of OMR [FerriSeltz]* in Patients Undergoing MRI of the Upper Abdomen (Protocol #901-03B).
- *"Diagnostic Review:" A Protocol for the supplementary analysis of MRI films from OMR [FerriSeltz]* Studies 901-03A and 901-03B.

Two phase 3 studies were conducted under identical protocols in the USA (Protocols #901-03A and #901-03B). These are commonly referred to as "Study A" and "Study B." In addition, the sponsor performed a retrospective "Diagnostic Review" of the images from these two studies in an attempt to demonstrate the clinical utility of FerriSeltz.

In brief, these studies demonstrated that FerriSeltz increases the severity of **artifacts**, even on T_1-weighted image acquisition. FerriSeltz may also adversely affect the **quality of images** for radiologic interpretation.

In these studies, most of the evaluated **"contrast efficacy"** parameters (e.g., "bowel marking," organ delineation) were increased, both in number and in extent, after administration of either dose of FerriSeltz. Although numerically the increases were sometimes greater in the 400-mg dose group, statistically the increases were generally similar for both dose groups, both in number and in extent. For both studies, the increases (both in number and in extent) were generally greater for the proximal gastrointestinal tract than for the distal gastrointestinal tract. Specifically, increases in signal intensity, opacification, signal homogeneity, distention tended to be greatest in the following sequence: stomach>duodenum>jejunum. Gastrointestinal delineation also followed this sequence for Study A, but not for Study B.

Finally, retrospective **"diagnostic assessments"** were made for the stomach, duodenum, and pancreas. These "standard-of-truth" data were of limited quality, and abnormalities were relatively scarce, further limiting any conclusions that might be drawn. Specifically, a full 73% of the "standard-of-truth" diagnoses were based on something less than the conventional standards of truth (surgery or biopsy). In addition, inclusion of the pre-FerriSeltz image as part of the definition of the "standard-of-truth" may also have caused the diagnoses obtained from the pre-FerriSeltz images to agree with the "standard-of-truth" diagnoses more than they otherwise would. Although the sponsor maintains that FerriSeltz may have clinical utility in identifying normal tissue (i.e., improves specificity), any conclusions about the effects of FerriSeltz on sensitivity, specificity, or accuracy must remain tentative because of the limited quality of the data on which such conclusions are based.

Study A and Study B: The primary objective of Phase-3 Studies A and B was to demonstrate the effectiveness of FerriSeltz, at two dose levels, as a contrast agent to visualize the gastrointestinal tract in magnetic resonance imaging (MRI) of the upper abdomen. These were open-label, multicenter studies of a parallel design in which patients undergoing MRI of the upper abdomen were randomized to receive a single oral dose of FerriSeltz (either 200 or 400 mg Fe) dissolved in 600 cc water. Each patient was to

undergo an MRI before the dose of FerriSeltz (within 2 hours) and after the dose of FerriSeltz (within 5-20 minutes). The primary effectiveness parameter was the unblinded "investigator's determination of the value of FerriSeltz compared to pre-contrast in the delineation of the gastrointestinal tract." MRI images were also to be evaluated in a blinded review by independent off-site radiologists not involved in conducting the trial. To evaluate "contrast enhancement" the unblinded investigator and the blinded reader gave scores for signal enhancement, signal homogeneity, organ opacification, distention improvment, and organ delineation improvement. For example, the blinded reader graded the parameters on absolute, non-comparative scales for both the pre-contrast image and the post-contrast image:

- signal enhancement (0=dark/air, 1=soft tissue, 2=intermediate, 3=body fat, 4=bright)
- signal homogeneity (0=not applicable, low intensity signal, 1=patchy/compromises interpretation, 2=slightly patchy/acceptable, 3=uniform in regions of high intensity)
- organ opacification (0=unmarked, 1=faintly marked, 2=moderately marked, 3=clearly marked)
- distention improvement (1=collapsed, 2=partially filled, 3=distended)
- organ delineation improvement (0=indistinct, 1=minimal, 2=moderate, 3=clear distinction)

Analyses of these parameters were performed using the pre-contrast and post-contrast image assessments from three different data sets: a) the unblinded, T_1-weighted image assessments by the investigators; b) the T_1-weighted image assessments by the blinded reviewer, and; c) a quasi, intent-to-treat analysis in which missing data from the T_1-weighted image assessments by the blinded reviewer were assigned a "worst case" value. This summary will emphasize the results of the quasi, intent-to-treat analyses. The tables are taken from the secondary medical review (Raczkowski 11/06/96).

In Study A, six investigators enrolled 160 patients. Of these, 115 patients (72%) had efficacy assessments performed by a blinded reader, and 153 patients (96%) had efficacy assessments performed by the unblinded investigator. Thirty-eight (38) patients who did not have assessments performed by the blinded reader were assigned a worst-case value for the quasi, intent-to-treat analysis.

In Study B, six investigators enrolled 115 patients. Of these, 103 patients (90%) had efficacy assessments performed by a blinded reader, and 114 patients (99%) had efficacy assessments performed by the unblinded investigator. Eleven (11) patients who did not have assessments performed by the blinded reader were assigned a worst-case value for the quasi, intent-to-treat analysis.

Artifacts in Studies A and B: In both Study A and Study B, the severity of the artifacts increased significantly in the post-FerriSeltz images compared to the pre-FerriSeltz images in both dose groups. The severity of the artifacts after FerriSeltz administration were similar for the two doses of FerriSeltz. See Tables 1 and 2.

Image Quality in Studies A and B: In Study A, image quality was not clearly adversely affected by the administration of FerriSeltz (see Table 1). However, in Study B, image quality did appear to be adversely affected by the administration of FerriSeltz (see Table 2).

Table 1: Study A
Blinded-Reviewer Comparative T_1-Weighted Image Assessment
Effect on Artifacts
Quasi "Intent-to-Treat Analysis" [2]

	200 mg Fe (6 g FerriSeltz)		400 mg Fe (12 g FerriSeltz)		Between-Group p value*
	Pre	Post	Pre	Post	
Number of Patients with Assessment	75		75		
Presence of Artifacts on Images					0.599
None	38	24	41	28	
Minimal	13	20	10	20	
Moderate	6	9	5	9	
Severe	18	21	21	21	
Not Rated	0	1	1	0	
Within group p value**	0.001		0.021		
Quality of Images for Radiologic Interpretation					0.616
Excellent	30	26	31	26	
Good	21	24	23	27	
Poor	6	7	4	5	
Inadequate	0	0	0	0	
Within group p value**	0.329		0.208		

* Between group comparison of changes from pre- to post-FerriSeltz evaluated using Wilcoxon rank-sum test, blocked by study site

** Changes from pre- to post-FerriSeltz evaluated using Wilcoxon signed-rank test

APPEARS THIS WAY
ON ORIGINAL

[2] Adapted from Table 17; Volume 29; page 290041.

Table 2: Study B
Blinded-Reviewer Comparative T_1-Weighted Image Assessment
Effect on Artifacts
Quasi "Intent-to-Treat Analysis" [3]

	200 mg Fe (6 g FerriSeltz)		400 mg Fe (12 g FerriSeltz)		Between-Group p value*
	Pre	Post	Pre	Post	
Number of Patients with Assessment	60		54		
Presence of Artifacts on Images					0.285
None	12	11	15	7	
Minimal	27	19	28	26	
Moderate	10	12	6	14	
Severe	10	15	3	7	
Not Rated	1	3	2	0	
Within group p value**	0.029		<0.001		
					0.285
Quality of Images for Radiologic Interpretation					
Excellent	12	8	17	6	
Good	28	24	24	35	
Poor	19	26	11	12	
Inadequate	1	2	1	0	
Not rated	0	0	1	1	
Within group p value**	0.022		0.066		

* Between group comparison of changes from pre- to post-FerriSeltz evaluated using Wilcoxon rank-sum test, blocked by study site

** Changes from pre- to post-FerriSeltz evaluated using Wilcoxon signed-rank test

Contrast Assessments ("Bowel Marking" and "Organ Delineation") for Studies A and B: For Study A, as shown in the tables 3 and 4 below, all of the evaluated "contrast efficacy" parameters were increased, both in number and in extent, after administration of either dose of FerriSeltz. The increases were similar for both dose groups, both in number and in extent, with the exception of duodenal opacification. For duodenal opacification, the 400-mg dose had significantly greater increases than the 200-mg dose.

For Study B, as shown in the tables 5 and 6 below, most of the evaluated "contrast efficacy" parameters were increased, both in number and in extent, after administration of either dose of FerriSeltz. The

[3] Adapted from Table 17; Volume 33; page 330041.

increases generally were numerically larger in the 400-mg dose group than in the 200-mg dose group, both in number and in extent. With the exception of the increase in the signal homogeneity for the stomach, however, the assessments were not significantly different. For stomach signal homogeneity, the 400 mg dose had significantly greater increases than the 200 mg dose.

For both Study A and Study B, the increases (both in number and in extent) were generally greater for the proximal gastrointestinal tract than for the distal gastrointestinal tract. Specifically, increases in signal intensity, opacification, signal homogeneity, distention tended to be greatest in the following sequence: stomach>duodenum>jejunum. Gastrointestinal delineation also followed this sequence for Study A, but not for Study B.

SAFETY

ACTION: Approvable

NEEDED ITEMS:

1. List Chemistry Issues Here

3. Provide labeling comments to Susan

Table 3: Study A Contrast Assessments
Comparative T_1-Weighted Image Assessment by Blinded Reviewer:
Mean Change in Scores and Percent Images Showing Increase in Scores***
Bowel Marking with FerriSeltz: Quasi "Intent-to-Treat" Analysis[4]

		200 mg Fe (6 g FerriSeltz)	400 mg Fe (12 g FerriSeltz)	Between-group p value*
Number of Patients Assessed		75	78	
Signal Intensity				
Stomach	% increased	71%	73%	0.409
	mean ± S.E.	2.0±0.2	2.2±0.2	
	p-value**	<0.001	<0.001	
Duodenum	% increased	67%	72%	0.083
	mean ± S.E.	1.5±0.1	1.8±0.1	
	p-value**	<0.001	<0.001	
Jejunum	% increased	51%	56%	0.296
	mean ± S.E.	1.0±0.1	1.1±0.1	
	p-value**	<0.001	<0.001	
Opacification				
Stomach	% increased	69%	73%	0.405
	mean ± S.E.	2.0±0.2	2.2±0.2	
	p-value**	<0.001	<0.001	
Duodenum	% increased	65%	73%	0.008
	mean ± S.E.	1.3±0.1	1.8±0.1	
	p-value**	<0.001	<0.001	
Jejunum	% increased	53%	56%	0.506
	mean ± S.E.	0.9±0.1	1.0±0.1	
	p-value**	<0.001	<0.001	
Signal Homogeneity				
Stomach	% increased	69%	73%	0.438
	mean ± S.E.	1.9±0.2	2.1±0.2	
	p-value**	<0.001	<0.001	
Duodenum	% increased	65%	73%	0.046
	mean ± S.E.	1.2±0.1	1.5±0.1	
	p-value**	<0.001	<0.001	
Jejunum	% increased	52%	58%	0.356
	mean ± S.E.	0.6±0.1	0.7±0.1	
	p-value**	<0.001	<0.001	
Distention				
Stomach	% increased	71%	73%	0.833
	mean ± S.E.	1.2±0.1	1.2±0.1	
	p-value**	<0.001	<0.001	
Duodenum	% increased	52%	60%	0.220
	mean ± S.E.	0.6±0.1	0.8±0.1	
	p-value**	<0.001	<0.001	
Jejunum	% increased	27%	35%	0.313
	mean ± S.E.	0.3±0.1	0.4±0.1	
	p-value**	<0.001	<0.001	

* Evaluated using Wilcoxon rank-sum test, blocked by study site
** Evaluated using Wilcoxon signed-rank test
*** Percent increased indicates at least a one-unit positive increase in scores

[4] Adapted from Table 18; Volume 29, page 290043.

Table 4: Study A Contrast Assessments
Comparative T_1-Weighted Image Assessment by Blinded Reviewer:
Mean Change in Scores and Percent Images Showing Increase in Score* in**
Organ Delineation with FerriSeltz: Quasi "Intent-to-Treat" Analysis[5]

		200 mg Fe (6 g FerriSeltz)	400 mg Fe (12 g FerriSeltz)	Between-group p value*
Number of Patients Assessed		75	78	
Delineation (GI tract)				
Stomach	% increased	65%	73%	0.228
	mean ± S.E.	1.5±0.2	1.7±0.1	
	p-value**	<0.001	<0.001	
Stomach wall	% increased	64%	68%	0.689
	mean ± S.E.	1.5±0.2	1.5±0.1	
	p-value**	<0.001	<0.001	
Duodenum	% increased	56%	60%	0.144
	mean ± S.E.	0.9±0.1	1.2±0.1	
	p-value**	<0.001	<0.001	
Jejunum	% increased	32%	38%	0.434
	mean ± S.E.	0.4±0.1	0.5±0.1	
	p-value**	<0.001	<0.001	
Bowel Wall	% increased	11%	14%	0.657
	mean ± S.E.	0.2±0.1	0.2±0.1	
	p-value**	0.008	0.001	
Delineation (pancreatic margins)				
Head	% increased	43%	45%	0.169
	mean ± S.E.	0.6±0.1	0.8±0.1	
	p-value**	<0.001	<0.001	
Body	% increased	43%	33%	0.294
	mean ± S.E.	0.7±0.1	0.5±0.2	
	p-value**	<0.001	<0.001	
Tail	% increased	37%	32%	0.753
	mean ± S.E.	0.4±0.1	0.4±0.1	
	p-value**	<0.001	<0.001	

* Evaluated using Wilcoxon rank-sum test, blocked by study site
** Evaluated using Wilcoxon signed-rank test
*** Percent increased indicates at least a one-unit positive increase in scores

APPEARS THIS WAY
ON ORIGINAL

[5] Adapted from Table 19; Volume 29, page 290044.

Table 5: Study B Contrast Assessments
Comparative T_1-Weighted Image Assessment by Blinded Reviewer:
Mean Change in Scores and Percent Images Showing Increase in Scores***
Bowel Marking with FerriSeltz: Quasi "Intent-to-Treat" Analysis[6]

		200 mg Fe (6 g FerriSeltz)	400 mg Fe (12 g FerriSeltz)	Between-group p value*
Number of Patients Assessed		60	54	
Signal Intensity				
Stomach	% increased	91%	92%	0.546
	mean ± S.E.	2.9 ± 0.2	3.3 ± 0.2	
	p-value**	<0.001	<0.001	
Duodenum	% increased	79%	85%	0.682
	mean ± S.E.	1.7 ± 0.2	2.1 ± 0.2	
	p-value**	<0.001	<0.001	
Jejunum	% increased	69%	75%	0.466
	mean ± S.E.	0.9 ± 0.1	1.0 ± 0.1	
	p-value**	<0.001	<0.001	
Opacification				
Stomach	% increased	91%	92%	0.897
	mean ± S.E.	2.5 ± 0.1	2.5 ± 0.1	
	p-value**	<0.001	<0.001	
Duodenum	% increased	72%	73%	0.431
	mean ± S.E.	1.1 ± 0.1	1.4 ± 0.2	
	p-value**	<0.001	<0.001	
Jejunum	% increased	74%	77%	0.832
	mean ± S.E.	1.0 ± 0.1	1.1 ± 0.1	
	p-value**	<0.001	<0.001	
Signal Homogeneity				
Stomach	% increased	91%	92%	0.047
	mean ± S.E.	2.0 ± 0.1	2.5 ± 0.1	
	p-value**	<0.001	<.001	
Duodenum	% increased	72%	75%	0.176
	mean ± S.E.	0.9 ± 0.1	1.2 ± 0.1	
	p-value**	<0.001	<0.001	
Jejunum	% increased	77%	75%	0.730
	mean ± S.E.	0.8 ± 0.1	0.8 ± 0.1	
	p-value**	<0.001	<0.001	
Distention				
Stomach	% increased	72%	81%	0.259
	mean ± S.E.	1.0 ± 0.1	1.2 ± 0.1	
	p-value**	<0.001	<0.001	
Duodenum	% increased	43%	44%	0.552
	mean ± S.E.	0.4 ± 0.1	0.4 ± 0.1	
	p-value**	<0.001	<0.001	
Jejunum	% increased	40%	42%	0.588
	mean ± S.E.	0.4 ± 0.1	0.5 ± 0.1	
	p-value**	<0.001	<0.001	

* Evaluated using Wilcoxon rank-sum test, blocked by study site
** Evaluated using Wilcoxon signed-rank test
*** Percent increased indicates at least a one-unit positive increase in scores

[6] Adapted from Table 18; Volume 33, page 330042.

Table 6: Study B Contrast Assessments
Comparative T_1-Weighted Image Assessment by Blinded Reviewer:
Mean Change in Scores and Percent Images Showing Increase in Score* in**
Organ Delineation with FerriSeltz: Quasi "Intent-to-Treat" Analysis[7]

		200 mg Fe (6 g FerriSeltz)	400 mg Fe (12 g FerriSeltz)	Between-group p value*
Number of Patients Assessed		60	54	
Delineation (GI tract)				
Stomach	% increased	28%	39%	0.108
	mean ± S.E.	0.09±0.11	0.30±0.11	
	p-value**	0.420	0.005	
Stomach wall	% increased	41%	55%	0 .167
	mean ± S.E.	0.30±0.14	0.60±0.15	
	p-value**	0.056	<0.001	
Duodenum	% increased	14%	29%	0.104
	mean ± S.E.	-0.50±0.13	-0.04±0.16	
	p-value**	<0.001	0.686	
Jejunum	% increased	41%	53%	0.282
	mean ± S.E.	0.40±0.14	0.60±0.13	
	p-value**	0.005	<0.001	
Bowel Wall	% increased	26%	29%	0.662
	mean ± S.E.	0.30±0.11	0.40±0.11	
	p-value**	0.004	<0.001	
Delineation (pancreatic margins)				
Head	% increased	18%	15%	0.697
	mean ± S.E.	-0.30±0.11	-0.30±0.14	
	p-value**	0.018	0.091	
Body	% increased	14%	18%	0.734
	mean ± S.E.	-0.20±0.12	-0.20±0.13	
	p-value**	0.220	0.166	
Tail	% increased	16%	18%	0.209
	mean ± S.E.	-0.30 ± 0.13	-0.10 ± 0.13	
	p-value**	0.012	0.439	

* Evaluated using Wilcoxon rank-sum test, blocked by study site
** Evaluated using Wilcoxon signed-rank test
*** Percent increased indicates at least a one-unit positive increase in scores

APPEARS THIS WAY
ON ORIGINAL

[7] Adapted from Table 19; Volume 33, page 330044.

"Diagnostic Assessments" for Studies A and B: Retrospective diagnostic assessments were made for the stomach, duodenum, and pancreas. A quasi, "standard-of-truth" diagnosis was established for 264 patients (151 of the 160 patients in Study A and 113 of the 115 patients in Study B).[8] The "standard-of-truth" diagnosis had three levels of certainty, depending on whether they were (a) proven by surgery or biopsy, (b) based on other non-invasive diagnostic procedures other than the study MRI; or (c) based on available clinical findings and the pre-FerriSeltz image. The "standard--of-truth" diagnoses were proven by surgery or biopsy in only 27% (70/264) of the patients. The diagnoses in 50% (133/264) of the patients were based on other non-invasive procedures other than the study MRI. The diagnoses in 23% (61/264) of the patients were based on available clinical findings and the pre-FerriSeltz image.[9] Hence, a full 73% of the "standard-of-truth" diagnoses were based on something less than the conventional standards of truth (surgery or biopsy). In addition, inclusion of the pre-FerriSeltz image as part of the definition of the "standard-of-truth" may also have caused the diagnoses obtained from the pre-FerriSeltz images to agree with the "standard-of-truth" diagnoses more than they otherwise would. Thus, given the significant limitations of these "standard-of-truth" data, any conclusions about the effects of FerriSeltz on sensitivity, specificity, or accuracy must remain tentative. Tables showing the data on the performance characteristics (e.g., sensitivity, specificity, accuracy) of FerriSeltz may be found in the secondary medical review (Raczkowski, 11/06/96). These data are only summarized in the following paragraphs.

In general, the ability of FerriSeltz to increase the sensitivity of MRI scans in detecting mass lesions or wall thickness abnormalities was limited in this study by the small numbers of such abnormalities. Given this limitation, FerriSeltz administration did not increase the sensitivity of MRI scans in detecting abnormalities of the duodenum or pancreas. Sensitivity assessments for the stomach were significantly increased for one blinded reviewer but not the other.

FerriSeltz administration appeared to increase the specificity of MRI scans for the stomach and duodenum. Assessments of specificity for the pancreas were significantly increased for one blinded reviewer but not the other. However, given the limited number of abnormalities, the assessments of specificity remain unvalidated for all three organs.

In this study, the effects of FerriSeltz administration on the accuracy of MRI scans were similar to those of FerriSeltz administration on specificity, and were influenced primarily by the large number of "normal" results and were limited by the small number of abnormalities.

SAFETY:

ACTION: Approvable

NEEDED ITEMS:

1. List Chemistry items here

- the lack of a reference standard for the drug substance, ferric ammonium citrate, brown;
- inadequate production data;

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[8] The stomach, duodenum, and pancreas were considered abnormal only if data confirmed the presence of mass leasions or abnormalities of wall thickness.

[9] In this review these diagnoses are termed *"quasi*, standard-of-truth" diagnoses [italics for emphasis], because the diagnoses in about three-fourths of the patients were based on results from modalities other than biopsy or surgery.

- the applicant's withdrawal of readiness for inspection after the 45-day filing commitments;
- inadequate explanation and data to justify some of the proposed specifications;
- inadequate stability studies in support of the expiration dating for FerriSeltz intended for marketing;
- an inadequate environmental assessment report, and;
- inadequate post-approval commitments to monitor the stability of FerriSeltz.

3. Give Susan Cusack Labeling Mark-up
   a. Patients with iron overload
   b. Better for proximal GI tract
   c. Restrict Indication to adults

APPEARS THIS WAY
ON ORIGINAL

MEDICAL REVIEW

NDA:	20292
CATEGORY:	Amendment
DRUG:	FerriSeltz (ferric ammonium citrate, brown)
SPONSOR:	Oncomembrane, Inc.
REVIEWER:	Lori A. Paserchia, MD
DOC. DATE:	2-20-97
PDUFA DATE:	10-14-97
REVIEWER REC'VED:	8-5-97
REVIEWED:	8-15-97
REVISIONS: (final)	9-12-97

REVIEW TEAM
D Udo, Biopharm
M Salazar, CMC
K Colangelo, CSO
N Sadrieh, Pharm/Tox
R Davi, Stats

INDICATION: In adult patients for use with T1-weighted MRI to enhance the delineation of the bowel to distinguish it from organs and tissues that are adjacent to the upper regions of the GI tract.

ABSTRACT

This safety update almost doubled the size of the safety database and did not introduce any obviously new or overwhelmingly significant safety concerns. As noted in the medical officer review of the original NDA, digestive system-related AE's are the most predominant.

The sponsor has stated their intention to conduct a to date, a protocol has yet to be received by the Division.

The labeling has been revised accordingly.

BACKGROUND

FerriSeltz (ferric ammonium citrate, brown) 600 mg is an aqueous solution of paramagnetic iron intended for oral administration as an MRI contrast agent. The NDA was submitted in November, 1995 and was deemed **approvable** (pending some CMC modifications including labeling revisions, a clinical safety update,

The present NDA amendment contains the safety update.

INTRODUCTION TO THE REVIEW

This review will focus solely on the <u>additional</u> safety information submitted in this amendment unless noted otherwise. The reader is referred to the medical officer review by Dr. Chow, dated 4-15-96, for comments regarding the information submitted in the original NDA.

The format for the remainder of this MOR will parallel the format used in the sponsor's response letter. In each section I briefly note the pertinent information, my comments, and a reference to an appendix that contains more detailed information if required by the reader. The following index is provided for the reader's convenience:

INDEX

SAFETY UPDATE

1. **Retabulate all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted v. now will certainly facilitate review. The update should include tabulation and analysis of adverse event that led to discontinuation of the drug, interruption of administration, and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. Also, please submit an analysis of digestive system adverse events by time after ingestion and by volume of FerriSeltz ingested. These assessments should include a gender, age and racial demographic subgroup analysis The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.**

Additional Studies and Total Sample Size

The safety database was updated by the inclusion of data from 2 multicenter, randomized, double-blind, parallel group (i.e., "pivotal" according to the sponsor) studies that were ongoing at the time of the original NDA submission: 1 study was conducted in the United Kingdom (UK) and the other in Belgium (from this point, I will refer to these countries as "European"). The same 2 dosages (6 gm and 12 gm) were investigated in each study and these dosages are identical to those studied in the US. This NDA amendment contains the protocol and study report for each non US-based study but not the CRF's or subject data listings. The sponsor considers these 2 European studies to be "pivotal" in nature and therefore, in the safety update, compared these data to the data from the 2 US-based Phase 2/3 pivotal studies originally submitted in the NDA. In other words, the data from the 1 US-based Phase 1 study in healthy subjects (n= 64) that were submitted in the original NDA were not used as a comparator in the discussion. From this point forward, this MOR will concern only the safety issues for the patient population investigated.

This safety update significantly expanded the size of the database (from 269 to 476 subjects for a 77% increase). Appendix 2 contains a table from the amendment that demonstrates the number enrolled, exposed to drug, and evaluable for safety. Based on the similar socioeconomic status of the UK, Belgium and US, the additional subjects are comparable to the US population and I believe it is reasonable to include these data. For a safety database, however, this sample size is barely acceptable.

Demographics

The demographic profile of these additional subjects is also comparable to the US-based subject population except for gender and race: the European data increased the number and proportion of women studied and hence the amount of safety information available; all of the European subjects were white except for 1 Asian subject in the UK. The medical histories of the European subjects were also comparable. In Appendix 3 the first table presents the demographic information and the second table presents the medical history information.

Adverse Experiences in Clinical Trials

The table in Appendix 4 demonstrates the non-laboratory-associated adverse events (AE's) overall and by body system.

Overall, the US data showed that 25% and 36% of subjects experienced an AE in the 6 gm and 12 gm dose groups, respectively. This suggested a trend in dose-dependence although the difference failed to achieve statistical significance (p= 0.063). With the addition of the European data (i.e., enhanced database), the larger sample size produced only a small reduction in the percentage of subjects with AE per dose (21% and 31% for the 6 gm and 12 gm dose groups, respectively). More importantly, however, is the statistically significant difference now achieved between the dose groups (p= 0.016), representing a dose dependence. This difference is noted in the labeling and is clinically significant as well: the efficacy database noted that the change in enhancement was similar for both the 6 and 12 gm doses, hence the benefit/risk ratio is higher for

the 6 gm dose than for the 12 gm dose. This latter point is also, peripherally, noted in the Clinical Trials section of the labeling.

When examined by body system, the digestive system was the source of the highest frequency of AE's, regardless of dose, in both the US-only and enhanced databases. In fact, these frequencies far exceeded those seen in all of the remaining body systems combined. The details regarding the specific digestive system AE's are discussed below in the section entitled Digestive System Events.

In general, the AE frequencies per body system, regardless of dose, did not differ significantly between the US-based and enhanced databases. Dose dependence by body system was not seen except for the digestive system. The hint of dose dependence noted for the nervous system in the enhanced database is of little significance given the very small number of AE's.

In conclusion, the digestive system-related AE's clearly are the overwhelming safety concern with FerriSeltz based on these databases. These particular AE's demonstrate dose dependence. The clinical significance is noted in the labeling.

Relationship of Adverse Events to Study Drug

The sponsor reported that, based on the investigator's rating of relationship of AE to FerriSeltz, "33% (61/185: 35 in US, 9 in UK, 17 in Belgium) were judged as definitely or probably related to drug ingestion, and 22% (41/185: 33 in US, 2 in UK, 6 in Belgium) were judged as possibly related to drug ingestion." All of these AE's were digestive system-related except for 1 headache in a US subject and 1 fever in a UK subject. The sponsor did not submit listings or data tables to support these statements. In general, I agree with the sponsor's assessment and have nothing to add. The digestive system-related AE's were briefly addressed above and will be discussed in detail below.

Digestive System Events

In the enhanced database, 105 subjects of the 124 total number of subjects who reported an AE (85%) had at least 1 digestive system-related AE. This percentage is reduced from the 89% (73/82) reported from the US-only database. The frequencies for each dose group are also lower in the enhanced database compared to the US-only database. Given the larger sample size of the enhanced database, and the lack of any obvious clinically significant difference in AE reporting methodology between the US and European studies, I have more confidence in the frequencies from the enhanced database. The larger database also strengthens the statistically significant dose dependence difference between the 2 dose groups.

The table in Appendix 4 shows the frequencies of the specific digestive system-related AE's. In the enhanced database, the frequencies per dose group for each AE are small with some notable exceptions: diarrhea, abdominal pain, vomiting, and nausea (in descending order of frequency). The frequencies per dose group tend to be similar except for diarrhea and abdominal pain where subjects in the higher dose group experienced a 3-fold increase in AE frequency. The reports of diarrhea and abdominal pain were clearly the driving force for the dose dependence. The above noted frequency relationships are comparable to the frequency relationships seen in the US-only database albeit the absolute frequencies are slightly smaller due to the larger sample size.

The dose dependence and the higher frequency of diarrhea noted with the 12 gm dose (21% of subjects) is a clinically significant AE that is definitely or probably related to FerriSeltz (as noted above in the section entitled Relationship of Adverse Events to Study Drug) although usually mild in severity and self-limited. The risk of this AE should be balanced by the possibility of significantly enhanced efficacy to justify using the higher dose; this point is noted in the labeling.

The sponsor was asked to analyze the specific digestive system AE's by time after ingestion and volume ingested. The reader should be aware that the sponsor was able to submit AE frequencies (as seen in Appendix 4) based on the combination of US and European data but subject-specific data are available only for the US subjects. Hence, the time and volume analyses were performed for only the US-based database:

AE's by Time after Ingestion

The proposed labeling calls for the administration of 600-900 ml of FerriSeltz over 15-30 minutes. MR scanning should then be initiated within 5-20 minutes of complete administration. The first table in Appendix 5 contains the subject listings of AE's by time and volume; for the reader's convenience, below, I have summarized the findings by time after complete ingestion and predominant type of AE:

Number of Subjects with, and Predominant Type of, Adverse Events Per Dose Group: by Time after Complete Ingestion

	6 gm dose	Predominant AE	12 gm dose	Predominant AE
AE onset:				
pre-administration	2	nausea/vomiting	2	none
≤30 minutes after complete ingestion	5	nausea/vomiting	4	abdominal pain
31 min to 2 hr after complete ingestion	3	diarrhea	8	diarrhea
>2 hr after complete ingestion	10	diarrhea	28	diarrhea
timing not available	7	—	7	—
TOTAL NUMBER OF SUBJECTS	27		49*	

* 2 subjects reported more than 1 AE- each AE at different timepoints (true n= 46).

Nausea and vomiting were more prevalent immediately after complete ingestion while diarrhea was more prevalent during MR scanning or post-study. The timing of each type of AE is emphasized because of the possible impact on the efficacy of FerriSeltz, either due to inadequate contrast during imaging due to vomiting, or inadequate time for MR acquisition due to the diarrhea. This is despite the sponsor's statement that no subject experienced vomiting or diarrhea during MR imaging in these studies. The potential for the onset of diarrhea to interfere with MR scanning is greater for the 12 gm dose. Since the volume used to deliver the 6 gm and the 12 gm doses is identical, an intrinsic effect of the drug is the most likely reason for the diarrhea.

To be complete, the following information is taken verbatim from the sponsor's response: the median (range) time of onset was: 1.75 hr (7 min to 30.5 hr) for abdominal pain;
3 hr (5 min to 9.5 hr) for nausea;
3 hr (15 min to 19 hr) for diarrhea; and
7 hr (5 min to 30.5 hr) for vomiting

AE's by Volume Ingested

Once again, the first table in Appendix 5 contains the subject listings of AE's by time and volume; for the reader's convenience, below, I have summarized the findings by total volume ingested:

Number of Subjects with Adverse Events Per Dose Group: by Total Volume Ingested

	6 gm dose	12 gm dose
600 ml (full dose)	23	41
500-599 ml	2	1
400-499 ml	1	2
300-399 ml	0	1
200-299 ml	0	1
100-199 ml	1	0
<100 ml	0	0
TOTAL NUMBER OF SUBJECTS	27	46

In these studies most subjects were able to consume the full dose. The type of AE's seen after the ingestion of 600 ml spans the spectrum of all reported AE's for both dose groups, i.e., 1 specific AE was not predominant. This is also true for the remaining volume categories. To be complete, the second table in Appendix 5 contains the listing of subjects who ingested <600 ml of FerriSeltz and had an AE. The sponsor did not provide the reasons for the incomplete ingestion for the remaining 18 subjects in this table and the first MOR did not address the issue therefore the sponsor will be asked to provide this information.

Serious Adverse Events

The sponsor labeled an AE as serious if it was rated a grade of 2 or more on a toxicity scale of 0 to 4. Appendix 6 contains the relevant table of information from the NDA amendment.

The total frequency of serious AE's was 10% and 7% in the US-based and enhanced databases, respectively. There was no indication of dose dependence.

For each body system, the total frequency of serious AE's is small (≤2% in either the US-based or enhanced database) except for the digestive system (8% and 5% in the US-based and enhanced databases, respectively). Again, there was no indication of dose dependence.

The very small number of reports for any specific AE, despite the relatively small size of the safety database, leads to a very small AE frequency and precludes a reasonable assessment of clinical significance. The 1 exception to this statement is diarrhea, which is not surprising.

Withdrawals Due to Adverse Events

As shown in the table in Appendix 2, 5/476= 1% subjects withdrew from the study due to an AE (and all of these AE's were digestive system-related). Two of these subjects were in the US-based studies therefore a CRF was submitted for each. CRF's for the 3 European subjects were not available for review. Regardless, the sponsor submitted a brief synopsis for each subject; these synopses can be found in Appendix 7. In general, I believe that the ADO was either possibly related/enhanced, or probably-related to the ingestion of FerriSeltz for each of the 5 subjects. The self-limited nature of the AE and the small percentage of ADO's is reassuring.

Patient Deaths

There were no subject deaths during the study period. The sponsor did not submit CRF's but did submit a synopsis for each of 8 US subjects and 3 European subjects who died within 2 months of ingesting FerriSeltz. This represents a death frequency of 11/476= 2.3%. These synopses are located in Appendix 8.

After a quick look at these synopses, I believe 8 of the deaths were unrelated, and the remaining 4 deaths were most probably unrelated to the administration of FerriSeltz. Two of the latter 4 deaths involved a disturbance in the coagulation system: 1 subject had intra-operative bleeding during hepatectomy 1 day after FerriSeltz ingestion, and 1 subject with hepatocellular carcinoma had hepatic vein thrombosis 9 days after ingestion. Based on the AE list and the laboratory results submitted in this amendment, there is no obvious affect of FerriSeltz on platelet count (?function) or other obvious bleeding tendency noted. Certainly, there is not enough evidence to suggest a safety issue, and the underlying disease/health status of these subjects confounds the picture. The other 2 deaths to note were in subjects who had developed pneumonia. The timing of the symptoms and signs suggests that FerriSeltz was not the cause but aspiration-induced pneumonia should always be kept in mind.

In summary, there is no overwhelming safety issue indicated by these data/ nothing new added by the additional safety data.

Clinical Laboratory Evaluations

The safety update increases the size of the laboratory-associated database by 150 subjects (101 from UK and 49 from Belgium). Therefore a total of 414 subjects had clinical chemistry and hematology assessments performed at baseline and 24 hrs postdose. In addition, 313 subjects (from the US and Belgium) also had iron metabolism labs checked at baseline and 24 hr postdose.

The addition of the Belgium subject data does not suggest a safety issue and does not significantly alter the conclusions regarding the iron metabolism parameters based on just the US-based data for either dose level. The first page of Appendix 9 contains the pertinent tables.

The addition of the European subject data does not suggest a safety issue and does not significantly alter the conclusions regarding the liver function, renal function, or hematology parameters based on just the US-based data for either dose level. The pertinent tables for each set of laboratory parameters can be found on pages 2, 3 and 4 (respectively) in Appendix 9.

Adverse Events, Including Laboratory Abnormalities, from Sources Other Than Clinical Trials

This safety update added 5 distinct AE reports that occurred in patients in Japan. The table in Appendix 10 shows these reports in addition to those that were included and reviewed in the original NDA. An obvious safety concern is not raised by these additional reports.

Analysis of Dose-Response Information

This information was submitted in the original NDA and reviewed by the medical officer (see pp. 7-9 of MOR dated 4-15-96).

Drug-Demographic Information

This information was submitted in the original NDA and reviewed by the medical officer (see the Integrated Summary of Safety in the MOR starting on page 51)

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

The UK and Belgium studies added 3 drop-out outs to the database (2 from Belgium and 1 from the UK). These drop-out were noted in the above section entitled Withdrawals Due to Adverse Events and will not be discussed further here.

3. Provide details of any significant changes or findings, if any.

The sponsor noted that the European data doubled the size of the safety database but did not change any conclusions.

4. Summarize worldwide experience on the safety of the drug.

No new information was addressed in this section of the sponsor's response (beyond what has already been commented upon by me in this review).

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

The sponsor did not introduce new information in this response. Please see the above sections of this review entitled Withdrawals Due to Adverse Events, and Patient Deaths for my comments.

PHASE 4 COMMITMENT

REVISED PROPOSED LABELING

I made handwritten comments directly on the revised draft labeling submitted by the sponsor in this amendment; please see Appendix 11. An electronic version of these revisions has been requested of the sponsor and is pending. I will make my final comments to the electronic version. In general, the sponsor adequately complied with the Division's requests and/or recommendations.

ACTION

APPROVED.

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Lori A. Paserchia, MD
Medical Reviewer

9-12-97

APPEARS THIS WAY
ON ORIGINAL

10/01/97

Patricia Y. Love, MD, MBA
Medical Imaging Division Director

APPEARS THIS WAY
ON ORIGINAL

cc: NDA ARCH
HFD-160/DIV FILES
HFD-160/Love/Raczkowski/Jones, AE/Salazar/Sadrieh/Paserchia
HFD-720/Davi
HFD-870/Udo

Table 1. **Patient Demographics**

	6 g FerriSeltz			12 g FerriSeltz		
	U.S.	U.K.	Belgium	U.S.	U.K.	Belgium
# patients enrolled	138	52	50	137	56	49
Age (years)						
mean ± SD	60.0 ± 1.4	56.1 ± 15.3	56.3 ± 15.8	57.5 ± 1.2	53.3 ± 14.0	54.2 ± 15.1
range						
Sex						
male	84	26	26	83	34	29
female	54	26	24	54	22	20
Race						
Caucasian	117	52	50	100	55	49
Black	10	0	0	15	0	0
Hispanic	8	0	0	7	0	0
Asian	3	0	0	9	1	0
other	0	0	0	6	0	0
Height (inches)						
mean ± SD	67.0 ± 0.32	66.2 ± 3.81	66.3 ± 2.88	67.3 ± 0.34	66.9 ± 2.95	67.3 ± 3.83
range						
Weight (pounds)						
mean ± SD	157 ± 2.8	155 ± 29.9	147 ± 27.4	158 ± 2.9	154 ± 24.5	153 ± 30.2
range						

Table 2. **Abnormalities Identified from Medical Histories at Study Entry**

	U.S. Studies Only			US, UK & Belgium Studies		
	6 g FerriSeltz	12 g FerriSeltz	Total	6 g FerriSeltz	12 g FerriSeltz	Total
# patients enrolled	138	137	275	240	242	482
Gastrointestinal	109 (79%)	119 (87%)	228 (83%)	187 (78%)	207 (86%)	394 (82%)
Hepatic*	---	---	---	38 (37%)	50 (48%)	88 (43%)
Genitourinary	52 (38%)	68 (50%)	120 (44%)	70 (29%)	88 (36%)	158 (33%)
Renal*	---	---	---	18 (18%)	13 (12%)	31 (15%)
Head/Neck/EENT	56 (41%)	56 (41%)	112 (41%)	68 (28%)	75 (31%)	143 (30%)
Musculoskeletal	46 (33%)	45 (33%)	91 (33%)	66 (28%)	65 (27%)	131 (27%)
Cardiovascular	42 (30%)	43 (31%)	85 (31%)	72 (30%)	74 (31%)	146 (30%)
Dermatological	34 (25%)	33 (24%)	67 (24%)	45 (19%)	47 (19%)	92 (19%)
Metabolic/Endocrine	37 (27%)	31 (23%)	68 (25%)	50 (21%)	61 (25%)	111 (23%)
Respiratory	29 (21%)	23 (17%)	52 (19%)	50 (21%)	41 (17%)	91 (19%)
Hematologic/Lymphatic	25 (18%)	25 (18%)	50 (18%)	38 (16%)	39 (16%)	77 (16%)
Neurologic	28 (20%)	22 (16%)	50 (18%)	33 (14%)	30 (12%)	63 (13%)
Other	50 (36%)	43 (31%)	93 (34%)	63 (26%)	59 (24%)	122 (25%)

* Hepatic and renal were reported only for the UK and Belgium studies

Table 3. **Patients Enrolled and Evaluable for Safety**

Number of patients	6 g FerriSeltz			12 g FerriSeltz		
	U.S.	U.K.	Belgium	U.S.	U.K.	Belgium
Enrolled	138	52	50	137	56	49
Withdrawn before receiving drug	2	0	0	4	0	0
Evaluable for safety	136	52	50	133	56	49
Incomplete drug administration*	13	9	1	14	6	4
Withdrawn for AE**	1	0	1	1	1	1
• vomiting	1	0	0	1	1	0
• nausea	0	0	0	0	0	1
• unspecified pain	0	0	1	0	0	1

* Patients ingesting less than 600 mL FerriSeltz

** Withdrawals due to adverse reactions included patients 112A (6 g) and 606A (12 g) in the U.S. studies; patients 206A (6 g) and 215B (12 g) in the Belgium study; and patient 3/12 (12 g) in the U.K. study.

Table 4. **Incidence of Adverse Events by Body System: Pooled Phase II/III Studies**
(number of patients with event,** excluding laboratory parameters)

	US studies only			US, UK, & Belgium studies		
	6 g FerriSeltz	12 g FerriSeltz	Between Group p-value*	6 g FerriSeltz	12 g FerriSeltz	Between Group p-value*
# patients assessed	136	133		238	238	
# (%) patients with AE	34 (25%)	48 (36%)	0.063	50 (21%)	74 (31%)	0.0
Body as Whole:	8 (6%)	6 (5%)	0.785	11 (5%)	10 (4%)	1.0
fever	0	1 (1%)		2 (1%)	2 (1%)	
headache	5 (4%)	5 (4%)		5 (2%)	5 (2%)	
pain	3 (2%)	0		4 (2%)	3 (1%)	
Cardiovascular:	2 (1%)	2 (2%)	1.000	3 (1%)	5 (2%)	0.7
arrhythmia	0	0		0	2 (1%)	
hypotension	1 (1%)	0		2 (1%)	0	
sickle crisis	0	1 (1%)		0	1 (0.4%)	
tachycardia	2 (1%)	1 (1%)		2 (1%)	1 (0.4%)	
thrombophlebitis	0	0		0	1 (0.4%)	
Digestive:	27 (20%)	46 (35%)	0.008	38 (16%)	67 (28%)	0.002
constipation	3 (2%)	0		3 (1%)	0	
diarrhea	14 (10%)	36 (27%)		19 (8%)	50 (21%)	
dyspepsia	1 (1%)	0		1 (0.4%)	0	
flatulence	1 (1%)	1 (1%)		1 (0.4%)	1 (0.4%)	
nausea	6 (4%)	8 (6%)		6 (2%)	8 (3%)	
pain, abdominal	4 (3%)	12 (9%)		6 (2%)	13 (6%)	
pain, rectal	0	1 (1%)		0	1 (0.4%)	
vomiting	4 (3%)	3 (2%)		8 (3%)	9 (4%)	
Nervous system:	3 (2%)	0	0.247	5 (2%)	0	0.061
anxiety	1 (1%)	0		1 (0.4%)	0	
cerebrovasc accident	0	0		1 (0.4%)	0	
confusion	0	0		1 (0.4%)	0	
convulsions	1 (1%)	0		1 (0.4%)	0	
insomnia	2 (1%)	0		2 (1%)	0	
Respiratory system:	1 (1%)	2 (2%)	0.619	2 (1%)	4 (2%)	0.686
coughing	0	1 (1%)		0	1 (0.4%)	
dyspnea	0	0		1 (0.4%)	0	
epistaxis	1 (1%)	0		1 (0.4%)	0	
lung edema	0	0		1 (0.4%)	0	
pneumonia	0	0		0	1 (0.4%)	
rhinitis	0	1 (1%)		0	1 (0.4%)	
sinusitis	0	0		0	1 (0.4%)	
Skin:	0	1 (1%)	0.494	0	1 (0.4%)	1.000
pruritis	0	1 (1%)		0	1 (0.4%)	
Urogenital system:	1 (1%)	1 (1%)	1.000	1 (0.4%)	1 (0.4%)	1.000
dysmenorrhea	1 (1%)	0		1 (0.4%)	0	
urinary tract infection	0	1 (1%)		0	1 (0.4%)	

Table 5. **Listing of Digestive System Events by Time After Ingestion and Volume Ingested**

Patient #	Volume	AE Onset	AE Description
		6 g FerriSeltz	
102A	600 mL	15 min	abdominal pain
104A	600 mL	5 min	nausea
112A	100 mL	pre-admin	nausea, vomiting
121A	600 mL	13 min	abdominal pain
201A	600 mL	10 hr	diarrhea
202A	600 mL	N/A	diarrhea
254A	600 mL	2 hr	diarrhea, nausea
309A	600 mL	8.5 hr	diarrhea
310A	600 mL	N/A	diarrhea
405A	475 mL	2 hr	diarrhea
427A	600 mL	N/A	constipation
429A	600 mL	8 hr	dyspepsia
435A	600 mL	21 hr	diarrhea
512A	600 mL	10 min	nausea, vomiting
602A	600 mL	5 hr	diarrhea
607A	600 mL	N/A	abdominal pain
628A	500 mL	3 hr	diarrhea
118B	600 mL	N/A	constipation
401B	550 mL	pre-admin	nausea, vomiting
407B	600 mL	11 hr	abdominal pain
508B	600 mL	2 hr	diarrhea
510B	600 mL	N/A	diarrhea
516B	600 mL	3 hr	diarrhea
517B	600 mL	24 hr	constipation
518B	600 mL	7 hr	vomiting
606B	600 mL	N/A	diarrhea
613B	600 mL	30 min	diarrhea
		12 g FerriSeltz	
101A	600 mL	15 min	diarrhea, abd pain
103A	600 mL	2.5 hr	diarrhea
107A	600 mL	1.5 hr	diarrhea, abd pain
110A	600 mL	2 hr	diarrhea
117A	600 mL	19 hr	diarrhea
119A	600 mL	8.5 hr	nausea
122A	600 mL	55 min	diarrhea
207A	600 mL	N/A	diarrhea, nausea
210A	600 mL	N/A	diarrhea
215A	600 mL	N/A	diarrhea, abd pain
219A	600 mL	N/A	diarrhea
253A	600 mL	1 hr	diarrhea
255A	600 mL	2 hr	diarrhea, abd pain
260A	600 mL	1.25 hr	diarrhea
304A	400 mL	20 min	abdc[illegible]
		1.5 hr	diarr
		25.5 hr	vom
308A	200 mL	pre-admin	naus
312A	600 mL	N/A	diarr
407A	600 mL	2.5 hr	diarr
412A	600 mL	9.5 hr	naus
		30.5 hr	vomi
426A	600 mL	7 hr	abdo
436A	600 mL	11 hr	abdo[illegible] pain
503A	600 mL	7.5 hr	diarrhea
516A	600 mL	N/A	diarrhea
518A	600 mL	2.5 hr	diarrhea
601A	600 mL	10.5 hr	diarrhea
604A	600 mL	8.5 hr	abdominal pain
606A	600 mL	5 min	vomiting
611A	600 mL	7 min	abdominal pain
617A	600 mL	22 hr	diarrhea
620A	600 mL	10.5 hr	diarrhea
621A	600 mL	4 hr	diarrhea
626A	475 mL	2 hr	flatulence
103B	600 mL	N/A	nausea, abd pain
104B	600 mL	pre-admin	diarrhea
112B	600 mL	3 hr	diarrhea, nausea
115B	600 mL	4.5 hr	diarrhea
116B	600 mL	1.5 hr	diarrhea
201B	600 mL	3.5 hr	diarrhea, abd pain
202B	600 mL	6 hr	diarrhea, rectal pain
403B	300 mL	6 hr	diarrhea, nausea
406B	600 mL	8.5 hr	diarrhea
511B	600 mL	2.5 hr	diarrhea
514B	600 mL	6.5 hr	diarrhea
515B	515 mL	2 hr	diarrhea
519B	600 mL	5 hr	diarrhea
702B	600 mL	10 hr	diarrhea

Table 6. **Listing of AEs for Subjects Who Ingested Less than 600 mL FerriSeltz**

Patient #	Dose	Volume	AE Onset	AE Description
112A	6 g	100 mL	5 min	emesis
205A	6 g	520 mL		
303A	6 g	400 mL		
405A	6 g	475 mL	2 hr	diarrhea
410A	6 g	400 mL		
423A	6 g	350 mL		
603A	6 g	325 mL		
608A	6 g	500 mL		
610A	6 g	500 mL		
627A	6 g	525 mL		
628A	6 g	500 mL	3 hr	diarrhea
401B	6 g	550 mL	pre-admin	nausea, vomiting
701B	6 g	550 mL		
216A	12 g	300 mL		
258A	12 g	550 mL		
304A	12 g	400 mL	20 min	abdominal pain
			1.5 hr	diarrhea
			25.5 hr	vomiting
308A	12 g	200 mL	pre-admin	nausea
311A	12 g	550 mL		
418A	12 g	400 mL		
419A	12 g	350 mL		
424A	12 g	425 mL		
612A	12 g	520 mL		
613A	12 g	450 mL		
626A	12 g	475 mL	2 hr	flatulence
629A	12 g	350 mL		
403B	12 g	300 mL	6 hr	diarrhea, nausea
515B	12 g	515 mL	2 hr	diarrhea

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Table 7. **Incidence of Moderate or Severe Adverse Events by Body System: Pooled Phase II/III Studies**
(number of patients with event,** excluding laboratory parameters)

	US studies only			US, UK, & Belgium studies		
	6 g FerriSeltz	12 g FerriSeltz	Between Group p-value*	6 g FerriSeltz	12 g FerriSeltz	Between Group p-value*
# patients assessed	136	133		238	238	
# (%) pts with AE	13 (10%)	15 (11%)	0.693	16 (7%)	19 (8%)	0.726
Body as Whole:	3 (2%)	2 (2%)	1.000	4 (2%)	3 (1%)	1.000
fever	0	1 (1%)		0	2 (1%)	
headache	1 (1%)	1 (1%)		1 (0.4%)	1 (0.4%)	
pain	2 (1%)	0		3 (1%)	0	
Cardiovascular:	0	1 (1%)	0.494	0	3 (1%)	0.
arrthymia	0	0		0	1 (0.4%)	
sickle crisis	0	1 (1%)		0	1 (0.4%)	
thrombophlebitis	0	0		0	1 (0.4%)	
Digestive:	9 (7%)	11 (8%)	0.648	9 (4%)	13 (5%)	0.
constipation	1 (1%)	0		1 (0.4%)	0	
diarrhea	4 (3%)	7 (5%)		4 (2%)	9 (4%)	
nausea	2 (1%)	3 (2%)		2 (1%)	3 (1%)	
pain, abdominal	2 (1%)	3 (2%)		2 (1%)	3 (1%)	
pain, rectal	0	1 (1%)		0	1 (0.4%)	
vomiting	1 (1%)	2 (2%)		1 (0.4%)	2 (1%)	
Nervous system:	3 (2%)	0	0.247	5 (2%)	0	0.061
anxiety	1 (1%)	0		1 (0.4%)	0	
cerebrovasc. accident	0	0		1 (0.4%)	0	
confusion	0	0		1 (0.4%)	0	
convulsions	1 (1%)	0		1 (0.4%)	0	
insomnia	2 (1%)	0		2 (1%)	0	
Respiratory system:	0	1 (1%)	0.494	1 (0.4%)	2 (1%)	1.000
coughing	0	1 (1%)		0	1 (0.4%)	
dyspnea	0	0		1 (0.4%)	0	
lung edema	0	0		1 (0.4%)	0	
pneumonia	0	0		0	1 (0.4%)	

* Based on Fishers Exact test (two-tailed)

** A patient may appear more than once within a body system

Withdrawals Due to Adverse Events: Five patients (two in the U.S. studies, one in the U.K. study, and two in the Belgium study) withdrew from study due to digestive system events. These are summarized below:

- In the U.S. study, patient 112A was nauseated prior to receiving FerriSeltz and was unable to ingest more than 100 mL of FerriSeltz (6 g/600 mL) without vomiting; since the patient was nauseated prior to ingestion of FerriSeltz, the adverse events were considered to be unrelated to drug treatment.
- In the U.S. study, patient 606A ingested the full dose of FerriSeltz (12 g/600 mL), but experienced 325 mL emesis 5 minutes after ingestion; the emesis was considered to be possibly related to drug treatment.
- In the U.K. study, patient 3/12 ingested the full dose of FerriSeltz (12 g/600 mL), but experienced nausea and vomiting of moderate intensity starting 14 minutes after ingestion and lasting for 2 hours and 50 minutes; these events were attributed to chemotherapy treatment and considered to be unrelated to the study drug.
- In the Belgium study, patient 206 ingested the full dose of FerriSeltz (6 g/600 mL), but withdrew prior to post-contrast MRI imaging due to abdominal pain.
- In the Belgium study, patient 215 stopped drinking FerriSeltz after the first sip due to revulsion against the taste.

Patient Deaths: No subjects died during their participation in the clinical studies. However, 8 patients in the U.S. studies and 3 patients in the U.K. study died within two months after ingesting FerriSeltz. These cases are summarized below:

#129A: Patient #129A was a 66 year old white male with a history of vocal cord cancer (surgical resection and irradiation therapy in 1980) and gall bladder cancer (found incidentally at cholecystectomy in July 1991 and followed by approximately one year of adjuvant chemotherapy). MR imaging with FerriSeltz™ was performed on 3/24/92 to confirm the presence of liver metastases. On 3/25/92 the patient underwent exploratory laparotomy with periportal lymph node dissection and a right hepatectomy. Intraoperatively the patient experienced two hypotensive episodes and had a blood loss. Postoperatively he became hypoxic and progressed to ARDS. From that point, the patient continued to slowly decline over the next month, developing progressive hepatic insufficiency as well as other symptoms of multisystem organ failure, including acute renal failure as well as cardiac arrhythmias. On 4/27/92, the patient became hypotensive, progressed to asystole, and died. The family denied autopsy; death was judged to be unrelated to ingestion of FerriSeltz™.

#255A: Patient #255A was a 68 year old white male with advanced adenocarcinoma of the pancreatic tail. Evaluations showed multiple hepatic metastas partial thrombosis of the splenic vein, an enlarged spleen, and a mod

large amount of ascites. His disease was inoperable. MR imaging with FerriSeltz™ was performed on 2/27/92 and the patient died of his disease on 4/28/92. The investigator judged that death was unrelaed to FerriSeltz™ ingestion.

On admission to the study and during follow-up, this patient was anemic and had abnormal LFTs. Following FerriSeltz™ ingestion, the patient experienced abdominal cramping and intermittent grade 3 diarrhea which lasted about 5 hours and resolved spontaneously. The investigator judged that the diarrhea was drug-related, and perhaps aggravated by the patient's underlying clinical condition.

#419A: Patient #419A was a 53 year old Asian female with a history of omental cholangitis and hypertension. She was admitted to the hospital on 12/13/91 for work-up of shortness of breath. Pulmonary function tests showed restrictive lung disease; pulmonary biopsy specimens were without alveoli, so were unable to assess the possibility of malignant lesions. MRI with FerriSeltz™ was performed on 12/22/91 to evaluate the possibility of tumor involving the bile ducts; findings were remarkable for the presence of ascites in the RUQ lateral to the upper outer surface of the liver and dilatation of the intrahepatic bile ducts. On 12/31/91, the patient underwent exploratory laparotomy with an omental biopsy; the biopsy later proved to be cholangio-carcinoma and malignant adenocarcinoma, but was diffusely found throughout the abdomen. On the third postoperative day (1/3/92), the patient had an episode of respiratory distress which required intubation. From this point, the patient continued to decline, despite aggressive pulmonary treatment. An echocardiogram showed massive right ventricular failure and pulmonary hypertension. The patient died of respiratory failure on 1/8/92. Death was judged to be unrelated to FerriSeltz™ ingestion.

#425A: Patient #425A was a 63 year old Hispanic male with a suspected gastric mass and hepatomegaly. Esophagogastrodudenoscopy performed on 12/30/91 showed a mass in the cardia of the stomach approximating the gastroesophageal junction and a biopsy proved adenocarcinoma. MRI with FerriSeltz™ was performed on 1/4/92 to confirm the suspected gastric mass and hepatomegaly; findings confirmed an extensive mass along the medial wall of the stomach extending inferiorly from the region of the gastro-esophageal junction and an enlarged liver with evidence for extensive hepatic metastases. Following evaluation, the patient returned to El Salvador and died in 2/4/92. Death was judged to be unrelated to FerriSeltz™ ingestion.

#201B: Patient #201B was a 63 year old black female with end-stage renal disease (pre-FerriSeltz™ evaluations showed and creatinine and a history of hypertension and insulin-dependent diabetes mellitus. She was receiving peritoneal dialysis for her kidney disease. At study enrollment she presented with tachycardia and arrhythmia and reported

fever, chills, anorexia, and malaise of one week duration. The patient underwent MRI with FerriSeltz™ on 12/12/91. Eight days later (12/20/91), the patient suffered from cardiopulmonary arrest associated with shock, hypoxia, pneumonitis, sepsis, and end-stage renal disease. The patient died ten days later (12/30/91). The investigator judged the death to be unrelated to FerriSeltz™ ingestion.

#203B: Patient #203B was a 68 year old Hispanic female who presented with anorexia, weight loss, and intolerance to oral feeding. Examinations on 1/23/92, including MRI with FerriSeltz™, led to a diagnosis of pulmonary edema, pneumonia, and ARDS. The patient was admitted to the hospital on 1/24/92. She died on 1/28/92 due to ARDS resulting from broncopneumonia (right lower lobe). Autopsy results confirmed bilateral, extensive, acute bronchopneumonia; acute and chronic focal endocarditis; and micronodular cirrhosis. The investigator judged death to be unrelated to FerriSeltz™ ingestion.

#511B: Patient #511B was an 84 year old white male with a history of metastatic prostate cancer; peripheral vascular disease and coronary artery disease; and chronic dizziness. Examinations performed on 2/19/92, including MRI with FerriSeltz™, confirmed the presence of abdominal/iliac aneurysm and hypotension. On 4/2/92, the patient presented to the emergency room with hypotension and tenesmus; he underwent emergency surgery for resection of his abdominal aortic aneurysm, isolation of his iliac aneurysms and aortofemoral reconstruction. At the time of closure of the abdomen, the patient developed an acute DIC, concomitant with infusion of his shed blood as well as platelets and fresh frozen plasma. Although the DIC was treated aggressively, the patient sustained prolonged hypotension complicated by ventricular tachycardia/ fibrillation requiring aggressive cardiopulmonary resuscitation and defibrillation. The patient died of cardiogenic shock about 90 minutes after surgery. Death was judged to be unrelated to ingestion of FerriSeltz™.

#707B: Patient #707B was a 45 year old black male with a 30 to 40 year history of sickle cell anemia with disease-related complications including thrombotic vascular crisis (1988), pneumonia (1989), and cholecystecomy and splenectomy (1985). At study enrollment the patient presented with abdominal pain of unknown origin (possible sickle cell crisis) and swollen elbows and knees. MRI with FerriSeltz™ was performed on 11/18/91. Five days later (11/23/91), the patient was hospitalized with sickle cell crisis. He recovered after two days and was discharged from the hospital. Forty-two days later (1/6/92), the patient was again hospitalized for sickle cell crisis. On the day of admission, he suffered a grand mal seizure and cardiac arrest, and he died. The investigator considered the remote sickle cell crisis to be

unrelated to FerriSeltz™ ingestion.

#6/2: Patient 6/2 suffered from progressive ovarian cancer and was undergoing MRI to rule out involvement of lymph glands. She developed motor aphasia 6 to 8 hours after ingesting FerriSeltz and experienced a cerebrovascular incident 10 hours post-contrast. The patient died two weeks later of events secondary to cerebrovascular sequelae. Death was considered to be unrelated to FerriSeltz ingestion.

#6/1: Patient 6/1 developed fever six hours after ingesting FerriSeltz, which was treated with 500 mg effervescent paracetamol. Then 23 hours post-contrast, the patient developed pneumonia, which was treated with three doses of 1.5 g cefuroxime and four doses of 400 mg co-trimoxazole. The patient died of pneumocystis carinii pneumonia on day 4 post-contrast, one hour after onset of cardiac arrhythmia. Autopsy confirmed that death was due to ongoing infection with pneumocystis carinii, exacerbated by low WBC. All these events were considered to be unrelated to FerriSeltz ingestion.

#8/7: Patient 8/7 developed hepatic coma 8 days post-contrast. One day later (9 days post-contrast), the patient experienced acute hepatic vein thrombosis and died about 11 hours later. Death was attributed to hepatocellular carcinoma, which was confirmed by biopsy, and the adverse events were considered to be unrelated to FerriSeltz ingestion.

Table 8. **Shifts in Iron Metabolism Parameters Within and Outside Normal Range from Pre- to Post-Contrast; Pooled Phase II/III Studies - 6 g FerriSeltz**

Parameter			Post-Contrast U.S. Studies Low	Normal	High	Post-Contrast U.S & Belgium Studies Low	Normal	High
Serum Iron (mcg/dL)	Pre-Contrast	Low						
		Normal		76			84	
		High						
			p-value = 0.162			p-value = 0.162		
			Low	Normal	High	Low	Normal	High
Ferritin (ng/mL)	Pre-Contrast	Low						
		Normal		93			102	
		High						
			p-value = NS*			p-value = 0.607		
			Low	Normal	High	Low	Normal	High
Transferrin (mg/dL)	Pre-Contrast	Low						
		Normal		99			106	
		High						
			p-value = 0.717			p-value = 0.932		

p-values based on Stuart-Maxwell test to evaluate shift from pre- to post-FerriSeltz;
* Undefined test (zero denominator); too few patients shifting categories

Table 9. **Shifts in Iron Metabolism Parameters Within and Outside Normal Range from Pre- to Post-Contrast: Pooled Phase II/III Studies - 12 g FerriSeltz**

Parameter			Post-Contrast U.S. Studies Low	Normal	High	Post-Contrast U.S. & Belgium Studies Low	Normal	High
Serum Iron (mcg/dL)	Pre-Contrast	Low						
		Normal		75			82	
		High						
			p-value = 0.634			p-value = 0.205		
			Low	Normal	High	Low	Normal	Hig
Ferritin (ng/mL)	Pre-Contrast	Low						
		Normal		85			95	
		High						
			p-value = NS*			p-value = NS*		
			Low	Normal	High	Low	Normal	Hig
Transferrin (mg/dL)	Pre-Contrast	Low						
		Normal		88			93	
		High						
			p-value = 0.607			p-value = 0.497		

p-values based on Stuart-Maxwell test to evaluate shift from pre- to post-FerriSeltz;
* Undefined test (zero denominator); too few patients shifting categories

Table 10. Shifts in Liver Function Parameters
Within and Outside Normal Range from Pre- to Post-Contrast:
Pooled Phase II/III Studies - 6 g FerriSeltz

Parameter			Post-Contrast U.S. Studies Low	Normal	High	Post-Contrast U.S., U.K. & Belgium Studies Low	Normal	High
AST (SGOT) (IU/L)	Pre-Contrast	Low						
		Normal		101			142	
		High						
			p-value = 0.160			p-value = 0.064		
ALT (SGPT) (IU/L)	Pre-Contrast	Low						
		Normal		102			149	
		High						
			p-value = NS*			p-value = 0.247		
GGT (IU/L)	Pre-Contrast	Low						
		Normal		78			103	
		High						
			p-value = NS*			p-value = NS*		
Alkaline Phosphatase (IU/L)	Pre-Contrast	Low						
		Normal		81			120	
		High						
			p-value = 0.513			p-value = 0.549		
Total Bilirubin (mg/dL)	Pre-OMR	Low						
		Normal		115			160	
		High						
			p-value = NS*			p-value = 0.946		

p-values based on Stuart-Maxwell test to evaluate shift from pre- to post-FerriSeltz;
* Undefined test (zero denominator); too few patients shifting categories

Table 11. Shifts in Liver Function Parameters
Within and Outside Normal Range from Pre- to Post-Contrast:
Pooled Phase II/III Studies - 12 g FerriSeltz

Parameter			Post-Contrast U.S. Studies Low	Normal	High	Post-Contrast U.S., U.K. & Belgium Studies Low	Normal	High
AST (SGOT) (IU/L)	Pre-Contrast	Low						
		Normal		99			142	
		High						
			p-value = 0.565			p-value = 0.708		
ALT (SGPT) (IU/L)	Pre-Contrast	Low						
		Normal		100			140	
		High						
			p-value = 0.607			p-value = 0.803		
GGT (IU/L)	Pre-Contrast	Low						
		Normal		81			117	
		High						
			p-value = NS*			p-value = NS*		
Alkaline Phisphatase (IU/L)	Pre-Contrast	Low						
		Normal		91			130	
		High						
			p-value = NS*			p-value = 0.514		
Total Bilirubin (mg/dL)	Pre-Contrast	Low						
		Normal		113			164	
		High						
			p-value = 0.247			p-value = 0.475		

p-values based on Stuart-Maxwell test to evaluate shift from pre- to post-FerriSeltz;
* Undefined test (zero denominator); too few patients shifting categories

Table 12. Shifts in Renal Function Parameters
Within and Outside Normal Range from Pre- to Post-Contrast:
Pooled Phase II/III Studies - 6 g FerriSeltz

Parameter			Post-Contrast: U.S. Studies			Post-Contrast: U.S., U.K. & Belgium Studies		
			Low	Normal	High	Low	Normal	High
Creatinine (mg/dL)	Pre-Contrast	Low						
		Normal		113			157	
		High						
			p-value = 0.311			p-value = 0.932		
			Low	Normal	High	Low	Normal	High
Potassium (mEq/L)	Pre-Contrast	Low						
		Normal		120			162	
		High						
			p-value = 0.648			p-value = 0.333		
			Low	Normal	High	Low	Normal	High
Sodium (mEq/L)	Pre-Contrast	Low						
		Normal		115			164	
		High						
			p-value = 0.273			p-value = 0.165		
			Low	Normal	High	Low	Normal	High
Chloride (mEq/L)	Pre-Contrast	Low						
		Normal		108			150	
		High						
			p-value = 0.232			p-value = 0.475		

p-values based on Stuart-Maxwell test to evaluate shift from pre- to post-FerriSeltz;
* Undefined test (zero denominator); too few patients shifting categories

Table 13. Shifts in Renal Function Parameters
Within and Outside Normal Range from Pre- to Post-Contrast:
Pooled Phase II/III Studies - 12 g FerriSeltz

Parameter			Post-Contrast: U.S. Studies			Post-Contrast: U.S., U.K. & Belgium Studies		
			Low	Normal	High	Low	Normal	High
Creatinine (mg/dL)	Pre-Contrast	Low						
		Normal		109			164	
		High						
			p-value = 0.368			p-value = 0.267		
			Low	Normal	High	Low	Normal	High
Potassium (mEq/L)	Pre-Contrast	Low						
		Normal		120			172	
		High						
			p-value = 0.838			p-value = 0.715		
			Low	Normal	High	Low	Normal	High
Sodium (mEq/L)	Pre-Contrast	Low						
		Normal		118			180	
		High						
			p-value = NS*			p-value = 0.525		
			Low	Normal	High	Low	Normal	High
Chloride (mEq/L)	Pre-Contrast	Low						
		Normal		108			166	
		High						
			p-value = 0.352			p-value = 0.589		

p-values based on Stuart-Maxwell test to evaluate shift from pre- to post-FerriSeltz;
* Undefined test (zero denominator); too few patients shifting categories

Table 14. Shifts in Hematology Parameters
Within and Outside Normal Range from Pre- to Post-Contrast:
Pooled Phase II/III Studies - 6 g FerriSeltz

Parameter			Post-Contrast: U.S. Studies Low	Normal	High	Post-Contrast: U.S., U.K. & Belgium Studies Low	Normal	High
Hemoglobin (g/dL)	Pre-Contrast	Low						
		Normal		86			121	
		High						
			p-value = 0.211			p-value = 0.214		
Hematocrit (%)	Pre-Contrast	Low						
		Normal		78			111	
		High						
			p-value = 0.403			p-value = 0.195		
RBC ($x10^6/mm^3$)	Pre-Contrast	Low						
		Normal		92			125	
		High						
			p-value = 0.846			p-value = 0.932		
WBC ($x10^3/mm^3$)	Pre-Contrast	Low						
		Normal		105			142	
		High						
			p-value = 0.549			p-value = 0.533		
Platelets ($x10^3/mm^3$)	Pre-OMR	Low						
		Normal		109			161	
		High						
			p-value = 0.223			p-value = 0.607		

p-values based on Stuart-Maxwell test to evaluate shift from pre- to post-FerriSeltz;
* Undefined test (zero denominator); too few patients shifting categories

Table 15. Shifts in Iron Metabolism Parameters
Within and Outside Normal Range from Pre- to Post-Contrast:
Pooled Phase II/III Studies - 12 g FerriSeltz

Parameter			Post-Contrast: U.S. Studies Low	Normal	High	Post-Contrast: U.S., U.K. & Belgium Studies Low	Normal	High
Hemoglobin (mg/dL)	Pre-Contrast	Low						
		Normal		67			98	
		High						
			p-value = 0.043			p-value = 0.202		
Hematocrit (%)	Pre-Contrast	Low						
		Normal		68			99	
		High						
			p-value = 0.011			p-value = 0.073		
RBC ($x10^6/mm^3$)	Pre-Contrast	Low						
		Normal		76			109	
		High						
			p-value = 0.082			p-value = 0.155		
WBC ($x10^3/mm^3$)	Pre-Contrast	Low						
		Normal		94			141	
		High						
			p-value = 0.430			p-value = 0.962		
Platelets ($x10^3/mm^3$)	Pre-Contrast	Low						
		Normal		94			142	
		High						
			p-value = 0.223			p-value = 0.097		

p-values based on Stuart-Maxwell test to evaluate shift from pre- to post-FerriSeltz;
* Undefined test (zero denominator); too few patients shifting categories

Table16. **Adverse Events from Japanese Marketing Experience**

Date of Event	Adverse Event	Severity	Dose	Reason for MRI	Outcome
1/21/94	nausea	mild	3 g	Suspected pancreatic tumor	Resolved spontaneously
3/1/94	diarrhea	mild	3 g	Suspected pancreatic tumor	Resolved spontaneously
4/20/94	vomiting	moderate	3 g	Assess status of retroperitoneal tumor	Resolved spontaneously
6/14/94	diarrhea	mild	6 g	Postoperative status of ovariectomy for lymphoma	Resolved spontaneously
6/27/94	flatulence, vomiting	mild	3 g	Suspected biliary tumor	Resolved spontaneously
10/5/94	recurrence of retroperitoneal hemorrhage	life-threatening	6 g	Suspected acute pancreatitis causing abdominal tumor & retroperitoneal swelling	Abdominal resection performed to aspirate hematoma & restore hemostasis
10/20/94	abdominal pain	mild	3 g	Suspected pancreatic cancer	Unknown
10/26/94	abdominal pain	mild	3 g	Suspected pancreatic cancer	Unknown
10/28/94	nausea	mild	3 g	Suspected liver mets from breast cancer	Resolved spontaneously
4/21/95	rash (attributed to concomitant megulmine gadopentetate)	mild	3 g	Evaluation of hepatoma	Resolved w/100 mg IV hydrocortisone sodium phosphate
6/17/95	nausea, vomiting	mild	3 g	Evaluation of hepatoma and hepatic cirrhosis	Resolved spontaneously
7/31/95	diarrhea	mild	3 g	Suspected duodenal ulcer	Resolved spontaneously
11/14/95	hot flushes (facial)	mild	3 g	Evaluation of gall bladder polyp and hepatic cyst	Resolved w/300 mg IV hydrocortisone sodium succinate
5/29/96	abdominal pain, increased sweating	mild	6 g	Post-operative evaluation following resection of tumor in duodenal papilla	Resolved spontaneously
9/19/96 9/21/96	anorexia diarrhea	moderate mild	6 g	Evaluation of tumor in pancreatic head	Resolved spontaneously
1/21/97	tongue discoloration	unknown	3 g	Evaluation of hepatic abscess	Not recovered

APR 15 1996

CLINICAL REVIEW

NDA 20 - 292

FerriSeltz™ (omr)

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NDA 20-292

Drug Name - Ferriseltz™ (OMR)

New Indication - Ferriseltz™ is an oral contrast agent for marking the upper gastrointestinal tract in patients undergoing T1-weighted magnetic resonance imaging of the upper abdomen.

SYNOPSIS

FerriSeltz™ (OMR) is a miscible, positive contrast, orally administered agent that has been developed by Oncomembrane, Inc, for use during Magnetic Resonance Image to visualize the gastrointestinal tract in patients undergoing MRI of the upper abdomen.

This is a second submission for FerriSultz™. It was refused to be filed on January 8,1993 simply because the application was incomplete and it did not on its face contain information required under section 505(b)(1) of the Act and 21 CFR 314.50 and 314.55.

The sponsor first submitted this IND to the Agency in January 1991. In November 1992, the sponsor submitted an NDA for(OMR).

During the meeting (between 0ncomembrane and FDA) on August 5, 1994, the Agency indicated for the first time that a placebo controlled safety trial would normally be required for the NDA, even though such a study is not a statutory requirement. After the discussion, the Agency agreed that the FerriSeltz™ NDA re-submission would be accepted for filing without a placebo controlled safety study. In addition, the Agency expressed an interest in the effects of patient demographics and magnetic field strength on the contrast effectiveness of OMR. Other Phase II/III studies were carried out by Otsuka Pharmaceutical Co. in Japan.

The Code of Federal Regulations (CRF) provides a definition of the adequate and well-controlled studies required to demonstrate the efficacy of a drug (section 314.126).

This NDA submission is more or less similar to the one that was previously submitted as NDA 20-292 with exception that the sponsor has revised analytic format and added 46 more patients into the 03A.and 03B. clinical analysis. However, this was agreed by the Agency during pre-NDA meeting.

REVIEWER'S OVERALL SUMMARY

A total of 275 patients were enrolled in the two pivotal studies (six investigators enrolled a total of 160 patients in Protocol 901-03A, and six investigators enrolled a total of 115 patients in Protocol 901-03B). The demographic profiles were predominantly Caucasian (79%: 217/275) and predominantly male patients (61%: 167/275), but included a wide range of ages. The two randomized dose groups 200mg Fe (6g OMR) and 400mg Fe (12g OMR) were comparable with respect to baseline data including age, gender, race, height, and weight.

Safety - A total of 275 patients was studied. Of the 269 patients who received the study drug and who were included in the safety analysis but 6 patients did not receive the study drug. Thirty-five (35) of 136 (26%) patients who received 200mg Fe OMR and 49 of 133 (37%) patients who received 400mg Fe OMR experienced a total of 53 and 75 adverse events, respectively. In the U.S. dose comparison studies, there was a trend toward a higher incidence of clinical adverse events in the 400mg Fe compared with the 200mg Fe OMR group; however, it did not reach statistical significance (37% versus 26%, p=0.065). The most frequently occurring adverse events were diarrhea (19% in low dose group and 27% in the high dose group), abdominal pain (3% vs 8%), and nausea (4% vs 7%), respectively. The majority of the adverse events were mild in intensity. There was no significant difference between the dose groups in the incidence of moderate or severe adverse events.

Subset Analysis of Safety (adverse events)

Age - There appeared to be higher incidence of adverse events in the <65 years of age compared with the >65 years of age (61 vs 21, respectively) for the two dose groups. There was no relationship with gender.

Body Weight /Gender - In the Women group, the incidence of adverse events appeared to be greater in the low body weight group compared with the heavy body weight group (28 vs 9, respectively). In the Men group, however, there was a trend toward heavy body weight as compared with the low body weight group (31 vs 14, respectively) for both low and high doses.

Race - There appeared to be higher incidence of adverse events in the Caucasian group compared with the non-caucasian group (65 vs 14, respectively) for the two dose groups. There was no relationship with gender.

Serious Adverse Events - Although 8 deaths have been reported in the U.S. clinical trial, the deaths are not felt to be related to OMR ingestion.

Vital Signs - No consistent or clinically significant effects on vital signs , blood chemistry or urinalysis parameters were observed; in particular, there was no evidence of iron metabolism parameters (serum iron, %saturation, TIBC, ferritin, and transferrin) to suggest systemic iron toxicity associated with ingestion of OMR.

The safety profiles of study A and B were similar.

Contrast Efficacy - Of the 275 patients enrolled in the U.S. dose comparison controlled, clinical studies, 267 received OMR and completed post-contrast imaging. Both on-site and off-site readers completed side-by-side assessment of pre-and post-contrast images for all 267 patients.

In both studies A and B, investigator ratings showed a significant dose effect in favor of the higher dose (400 mg Fe/600 mL; 12 g OMR) for delineation of the stomach wall and jejunum. Pooled data for investigator ratings, however, also suggest a trend toward increased contrast efficacy with the higher dose group. Pooled data for blinded reader ratings showed no significant dose effects for contrast efficacy parameters.

A direct comparison of the on-site and off-site readers ratings of contrast efficacy was performed using the results of an "intent-to-treat" analysis, in which worst possible ratings (i.e., no improvement in post-contrast images) were assessed for the 46 patients without blinded contrast reviews.

Image quality assessment (good and excellent) - For on-site readers were graded 94% (252/267) vs 66% (176/267) with the off-site reader assessments. Artifacts (none or minimal) were graded 70% (187/267) vs 58% (155/267), respectively.

Intent-to-treat bowel marking and organ delineation assessments - both on-site and off-site readers revealed that OMR improved signal intensity, opacification and signal homogeneity of the stomach in over 75% scores by both readers. The delineation parameters also yielded similar improvements in the organ delination (stomach, stomach wall, duodenum, jejunum, and bowel wall by both assessments). Again, the overall bowel marking, and organ delineation parameters were achieved better ratings in the high dose group (400mg Fe) compared with the low dose group (200mg Fe OMR).

Retrospective Analysis of Clinical Utility - For each anatomical location (stomach, duodenum, and pancreas) and each of the 2 blinded readers, McNemar chi-square tests were applied to each 2x2 table to evaluate the change from pre-to post-contrast OMR in diagnostic sensitivity, specificity and accuracy.

The results indicate that OMR had a statistically significant ($p<0.001$) on the diagnostic accuracy and specificity achieved by both blinded readers (data pooled).

Diagnosis of the Stomach

Accuracy - For reader #1 (34% vs 87%) & reader #2 (8% vs 75%).

Specificity - For reader #1 (34% vs 90%) & reader #2 (8% vs 77%).

Diagnosis of the Duodenum

Accuracy - For reader #1 (64% vs 86%) & reader #2 (26% vs 56%).

Specificity - For reader #1 (64% vs 87%) & reader #2 (26% vs 56%).

Diagnosis of the Pancreas

Accuracy - For reader #1 (67% vs 77%) & reader #2 (68% vs 72%).

Specificity - For reader #1 (70% vs 82%) & reader #2 (68% vs 72%).

Both blinded readers provided additional diagnostic information that was not given by all available clinical information for 44% (116/265) of the cases and change in diagnosis, and patient management in 12% (32/265) of the cases.

Subset Analysis of Contrast Efficacy

Dose-Response - There is an overall trend toward higher ratings of the contrast efficacy in the 400mg Fe/12g as compared with the 200mg Fe/6g OMR group. There were no statistically significant differences in contrast efficacy for demographic (gender, race and age) parameters between the two readers.

Demographic-Response (image quality assessment by both on-site and off-site readers) -Data indicates that image quality ratings were statistically significant in the women population, non-caucasian, and greater than 65 years of age groups as compared to the men population, caucasian, and less than 65 years of age groups by both readers. The artifacts, however, yielded similar results.

Field Strength Response- There were no significant differences between tesla (1.5) and (.35 to .5). According to on-site ratings, however, there were statistically significant ($p<0.001$) in the high field compared with the low field strength of the signal intensity, signal homogeneity, and delineation of the stomach and stomach wall. The overall image quality ratings appear to score higher in the low field strength than in the high field strength for both readers. On-site reader assessment for image quality, however, shows a statistically significant 25% (48/190) in the high field versus 12% (9/77) in the low field strength ($p<0.001$) among the excellent scores. The off-site reader assessment yields similar results (28% versus 16%).

Final comments - One major statistical problem in analysis is the difficulty in the interpretation of clinical trials; that over emphasize the significance of the test results; particularly, the abundant and selective use of significant tests in clinical trials that may greately increase false positive claims. Moreover, this particular problem includes the use of multiple endpoints, interm analyses and subgroup analyses.

Summary - The number of patients studied was relatively small, but, the results support the safety and effectiveness for this indication.

Recommendation - The Reviewer recommends that this NDA is approvable pending labeling revisions.

Subset Analysis of Adverse Events in FerriSeltz Pivotal Trials

Dose	6 g FerriSeltz															
Gender	Female								Male							
Age	<65 yrs				≥65 yrs				<65 yr				≥65 yr			
# Patients (Race: W/B/O)	34 (31W/1B/2O)				20 (17W/2B/1O)				46 (39W/3B/4O)				36 (28W/4B/4O)			
Severity	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total
# Patients w/ADR (highest grade ADR)	10	0	2	12	3	2	0	5	7	4	1	12	2	1	2	5
Digestive:																
- constipation	0	0	0	0	0	0	0	0	1	0	1	2	1	0	0	1
- diarrhea	5	0	1	6	3	0	0	3	2	2	0	4	0	1	0	1
- dyspepsia	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
- flatulence	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
- nausea	2	0	0	2	1	1	0	2	1	1	0	2	0	0	0	0
- pain, abdomen	2	0	0	2	0	0	0	0	0	1	0	1	0	0	1	1
- pain, rectal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- vomiting	0	0	0	0	0	1	0	1	3	0	0	3	0	0	0	0
Body as whole:																
- fever	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- headache	1	0	0	1	1	1	0	2	2	0	0	2	0	0	0	0
- pain	1	0	1	2	0	0	0	0	0	0	0	0	0	0	1	1
Cardiovascular:																
- hypotension	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
- sickle crisis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- tachycardia	1	0	0	1	0	0	0	0	0	0	0	0	1	0	0	1
Nervous:																
- anxiety	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
- convulsions	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
- insomnia	0	0	0	0	0	0	0	0	0	1	0	1	0	0	1	1
Respiratory:																
- coughing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- epistaxis	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
- rhinitis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Skin:																
- pruritis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Urogenital:																
- dysmenorrhea	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
- UTI infection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Subset Analysis of Adverse Events in FerriSeltz Pivotal Trials

Dose	12 g FerriSeltz															
Gender	Female								Male							
Age	<65 yrs				≥65 yrs				<65 yr				≥65 yr			
# Patients (Race: W/B/O)	35 (27W/2B/6O)				16 (14W/1B/1O)				55 (34W/9B/12O)				27 (22W/2B/3O)			
Severity	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total
# Patients w/ADR (highest grade ADR)	11	3	2	16	3	1	0	4	17	1	3	21	4	1	1	7*
Digestive:																
- constipation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- diarrhea	10	1	1	13*	2	1	0	3	11	0	2	13	4	1	1	7*
- dyspepsia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- flatulence	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
- nausea	4	0	1	5	0	0	0	0	2	1	0	3	0	0	0	0
- pain, abdomen	1	1	0	2	1	0	0	1	6	1	0	7	1	0	0	2*
- pain, rectal	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0
- vomiting	0	0	0	0	1	1	0	2	0	1	0	1	0	0	0	0
Body as whole:																
- fever	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0
- headache	1	1	0	2	1	0	0	1	2	0	0	2	0	0	0	0
- pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cardiovascular:																
- hypotension	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- sickle crisis	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0
- tachycardia	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0
Nervous:																
- anxiety	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- convulsions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- insomnia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Respiratory:																
- coughing	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0
- epistaxis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- rhinitis	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0
Skin:																
- pruritis	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Urogenital:																
- dysmenorrhea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- UTI infection	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0

* includes patient with ungraded event

Analysis of Adverse Events in FerriSeltz Pivotal Trials

Dose	6 g FerriSeltz															
Gender	Female								Male							
Bodyweight	<150 lb				≥150 lb				<150 lb				≥150 lb			
# Patients	37				17				22				60			
Severity	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total
# Patients w/ADR (highest grade ADR)	9	2	2	13	4	0	0	4	2	1	2	5	7	4	1	12
Digestive:																
- constipation	0	0	0	0	0	0	0	0	1	0	0	1	1	0	1	2
- diarrhea	6	0	1	7	2	0	0	2	0	1	0	1	2	2	0	4
- dyspepsia	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
- flatulence	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
- nausea	2	1	0	3	1	0	0	1	0	0	0	0	1	1	0	2
- pain, abdomen	2	0	0	2	0	0	0	0	0	0	1	1	0	1	0	1
- pain, rectal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- vomiting	0	1	0	1	0	0	0	0	0	0	0	0	3	0	0	3
Body as whole:																
- fever	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- headache	1	1	0	2	1	0	0	1	1	0	0	1	1	0	0	1
- pain	1	0	1	2	0	0	0	0	0	0	1	1	0	0	0	0
Cardiovascular:																
- hypotension	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
- sickle crisis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- tachycardia	1	0	0	1	0	0	0	0	0	0	0	0	1	0	0	1
Nervous:																
- anxiety	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
- convulsions	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
- insomnia	0	0	0	0	0	0	0	0	0	0	1	1	0	1	0	1
Respiratory:																
- coughing	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- epistaxis	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
- rhinitis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Skin:																
- pruritis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Urogenital:																
- dysmenorrhea	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
- UTI infection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Subset Analysis of Adverse Events in FerriSeltz Pivotal Trials

Dose	12 g FerriSeltz															
Gender	Female								Male							
Bodyweight	<150 lb				≥150 lb				<150 lb				≥150 lb			
# Patients	34				17				22				60			
Severity	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total
# Patients w/ADR (highest grade ADR)	11	3	1	15	3	1	1	5	8	1	0	9	14	1	4	19
Digestive:																
- constipation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- diarrhea	9	1	0	11*	3	1	1	5	2	0	0	3*	13	1	3	17
- dyspepsia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- flatulence	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
- nausea	2	0	1	3	2	0	0	2	2	1	0	3	0	0	0	0
- pain, abdomen	1	1	0	2	1	0	0	1	4	1	0	6*	3	0	0	3
- pain, rectal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
- vomiting	1	0	0	1	0	1	0	1	0	1	0	1	0	0	0	0
Body as whole:																
- fever	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0
- headache	2	1	0	3	0	0	0	0	2	0	0	2	0	0	0	0
- pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cardiovascular:																
- hypotension	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- sickle crisis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1
- tachycardia	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Nervous:																
- anxiety	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- convulsions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- insomnia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Respiratory:																
- coughing	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0
- epistaxis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- rhinitis	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1
Skin:																
- pruritis	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
Urogenital:																
- dysmenorrhea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- UTI infection	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0

Subset Analysis of Adverse Events in FerriSeltz Pivotal Trials

Dose	6 g												6 g											
Gender	Female												Male											
Race	White				Black				Other				White				Black				Other			
# Patients	48				3				3				67				7				8			
Severity	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total
# Patients w/ADR (highest grade ADR)	11	2	2	15	2	0	0	2	0	0	0	0	8	3	2	13	1	1	0	2	1	1	0	2
Digestive:																								
- constipation	0	0	0	0	0	0	0	0					0	0	1	1	1	0	0	1	1	0	0	1
- diarrhea	8	0	1	9	0	0	0	0					2	2	0	4	0	1	0	1	0	0	0	0
- dyspepsia	1	0	0	1	0	0	0	0					0	0	0	0	0	0	0	0	0	0	0	0
- flatulence	1	0	0	1	0	0	0	0					0	0	0	0	0	0	0	0	0	0	0	0
- nausea	3	1	0	4	0	0	0	0					1	1	0	2	0	0	0	0	0	0	0	0
- pain, abdomen	2	0	0	2	0	0	0	0					0	0	1	1	0	0	0	0	0	1	0	1
- pain, rectal	0	0	0	0	0	0	0	0					0	0	0	0	0	0	0	0	0	0	0	0
- vomiting	0	1	0	1	0	0	0	0					3	0	0	3	0	0	0	0	0	0	0	0
Body as whole:																								
- fever	0	0	0	0	0	0	0	0					0	0	0	0	0	0	0	0	0	0	0	0
- headache	1	1	0	2	1	0	0	1					2	0	0	2	0	0	0	0	0	0	0	0
- pain	1	0	1	2	0	0	0	0					0	0	1	1	0	0	0	0	0	0	0	0
Cardiovascular:																								
- hypotension	0	0	0	0	0	0	0	0					1	0	0	1	0	0	0	0	0	0	0	0
- sickle crisis	0	0	0	0	0	0	0	0					0	0	0	0	0	0	0	0	0	0	0	0
- tachycardia	1	0	0	1	0	0	0	0					1	0	0	1	0	0	0	0	0	0	0	0
Nervous:																								
- anxiety	0	0	1	1	0	0	0	0					0	0	0	0	0	0	0	0	0	0	0	0
- convulsions	0	0	1	1	0	0	0	0					0	0	0	0	0	0	0	0	0	0	0	0
- insomnia	0	0	0	0	0	0	0	0					0	0	1	1	0	0	0	0	0	1	0	1
Respiratory:																								
- coughing	0	0	0	0	0	0	0	0					0	0	0	0	0	0	0	0	0	0	0	0
- epistaxis	1	0	0	1	0	0	0	0					0	0	0	0	0	0	0	0	0	0	0	0
- rhinitis	0	0	0	0	0	0	0	0					0	0	0	0	0	0	0	0	0	0	0	0
Skin:																								
- pruritis	0	0	0	0	0	0	0	0					0	0	0	0	0	0	0	0	0	0	0	0
Urogenital:																								
- dysmenorrhea	0	0	0	0	1	0	0	1					0	0	0	0	0	0	0	0	0	0	0	0
- UTI infection	0	0	0	0	0	0	0	0					0	0	0	0	0	0	0	0	0	0	0	0

Subset Analysis of Adverse Events in FerriSeltz Pivotal Trials

Dose	12 g												12 g											
Gender	Female												Male											
Race	White				Black				Other				White				Black				Other			
# Patients	41				3				7				56				11				15			
Severity	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total	gr 1	gr 2	gr 3/4	total
# Patients w/ADR (highest grade ADR)	13	3	2	18	1	0	0	1	0	1	0	1	19	1	2	22	1	0	2	3	2	1	0	3
Digestive:																								
- constipation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- diarrhea	10	2	1	14*	1	0	0	1	1	0	0	1	12	1	2	16*	1	0	1	2	2	0	0	2
- dyspepsia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- flatulence	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- nausea	3	0	1	4	0	0	0	0	1	0	0	1	2	0	0	2	0	0	0	0	0	1	0	1
- pain, abdomen	1	1	0	2	1	0	0	1	0	0	0	0	7	0	0	8*	0	0	0	0	0	1	0	1
- pain, rectal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0
- vomiting	1	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Body as whole:																								
- fever	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
- headache	2	0	0	2	0	0	0	0	0	1	0	1	2	0	0	2	0	0	0	0	0	0	0	0
- pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cardiovascular:																								
- hypotension	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- sickle crisis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0
- tachycardia	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
Nervous:																								
- anxiety	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- convulsions	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- insomnia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Respiratory:																								
- coughing	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- epistaxis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- rhinitis	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0
Skin:																								
- pruritis	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Urogenital:																								
- dysmenorrhea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
- UTI infection	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

DIVISION OF MEDICAL IMAGING, AND RADIOPHARM DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW OF NDA 20-292

NDA;	20-292
DATE SUBMITTED;	November 15, 1995
DATE RECEIVED;	November 16, 1995
DATE ASSIGNED:	November 30, 1995
SPONSOR:	ONCOMEMBRANE, INC.
REVIEW COMPLETED:	April 15, 1996
REVIEWER:	Silas Chow, M.D.

1.0 General Information

Name of Drug

(1) Generic: Ferric Ammonium Citrate, Brown

(2) Proprietary: FerriSeltz™

(3) Other: CAS 1185-57-5

(4) Drug Characterization:

1.1 Pharmacologic Category - An oral MRI contrast agent

1.2 Proposed Indication - FerriSeltz™ is an oral contrast agent for marking the upper gastrointestinal tract in patients undergoing magnetic resonance imaging(MRI) of the upper abdomen.

1.3 Dosage Forms and Routes of Administration - Oral only

1.4 Related Drugs - Superparamagnetic Iron oxide & others

2.0 Manufacturing Controls - Refer to chemist's review

3.0 Pharmacology - Refer to pharmacologist's review

3.1 Pre-clinical Data

The acute toxicity study of FAC was conducted in rats by the oral route of administration at a dose of 2000 mg/kg body weight (Japan). The clinical results were diarrhea, perianal staining and black feces. No other remarkable findings were obtained.

3.2 U.S. Data

In the rat oral acute experiment, animals receiving 1200 and 2000 mg/kg demonstrated soft stool and fecal staining. The dogs treated orally developed watery stool at 1200 mg/kg and watery stool and vomiting at 2000 mg/kg.

In the rat subacute experiment, the rat treated with 1200 mg/kg/day showed slight and transient body weight gain and food consumption decreases, and at necropsy, fecal contents were noted to be black. The dog oral subacute experiment revealed increased incidence of watery stool in 2 of 6 animals at 360 mg/kg/day and in all animals receiving 1200 mg/kg/day during the treatment period. The intraperitoneal study was conducted in rats and no treatment related abnormalities were observed.

3.3. Acute Oral Toxicity of Active Ingredient (FAC)

The most extensive review of acute animal toxicity data on iron compounds is found in the 1973 report on (general recognized as safe) food ingredients. The summary of the data on ferric ammonium citrate is shown below:

Acute Toxicity of Iron (Fe) Compounds

Compound	Animal	Route	Dose(mg/kg)	Measurement
Iron	Mouse	i.v.	16.5	LD50
(FAC)	Mouse	oral	1000.0	LD50
	G. Pig	oral	350.0	LD50
	Rabbit	oral	560.0	LD50

It is evident from the data above that wide variations in toxicity have been reported among different animal species. Doses in the lethal range produce marked erosion and mucosal sloughing if death is delayed for 24-48 hours. According to the Handbook of Veterinary Drugs, excessive quantities of FAC administered to animals may cause diarrhea.

3.4 Acute oral toxicity for FAC in Sprague-Dawley rats

The study was designed and conducted to evaluate potential toxic effects of FAC following single oral administration. FAC was dissolved in distilled water and administered to 5 male and 5 female rats at a single oral dose of 2 g/kg (approximately 333mg Fe). A control group of 5 male and 5 female rats was treated with distilled water alone. No animals of diarrhea, perianal staining, and black feces were observed in the FAC treated group. Necropsy at 14 days post treatment did not reveal any treatment related abnormalities. These results lead to the conclusion that oral administration of FAC, up to 2 g/kg. has very low toxic potential. Note: The no-observable-effect-level for FerriSeltz™ (NOEL) for the acute oral studies were 2000 mg Fe/kg (67 mg Fe/kg = 8 times the maximum human dose) for rats and dogs.

3.5 Previous therapeutic use of high dose FAC in humans

In 1933, Heath published the results of 84 cases of hypochromic anemia patients who were hospitalized and treated with various forms & dosages of iron compounds, including oral FAC. Patients were initially given 2 g FAC (0.4 g Fe) per day with gradual increases to 6 g (1.2 g Fe) daily. Patients were successfully treated on this therapeutic regimen for many months. The therapy was well tolerated by the majority of patients with reports of occasional cramps or diarrhea which disappeared during the course of treatment.

Iron toxicity in humans including severe gastritis or gastroenteritis with abdominal pain, retching, and vomiting begins 10 to 60 minutes after the ingestion. Diarrhea is sometimes violent, feces are watery and later tarry. Shock, pallor, cyanosis and coldness may evolve. More severe symptom listed for ferrous sulfate include liver injury consisting of generaly reversible hemorrhagic necrosis with pyloric stenosis and mild hepatic cirrhosis encountered as persistent sequelae; however, recovery is usually complete.

4.0 Published Clinical Articles

Sixty-four(64) publications consists of three Volumes (Vol. 42 to 44) and from 420001 to 440390 pages were submitted to support this indication. The sponsor provided no analyses for these articles (see Table below).

	West	East(Japan)	Total
MR imaging technique study	11	9	20
Efficacy study (diagnostic)	4	0	4
Safety & efficacy (ph-2/3 Japan)	2	2	4
Scientific experi. (iron absorb).	22	9	31
Point-to-consider (FDA)	2	0	2
Non-clinical experiment	1	0	1
Laboratory Text-book	2	0	2
			64

Reviewer's Summary - Much has been published in the literature on the subject of absorption and metabolism of iron and iron-containing compounds and iron toxicity. Iron is an essential element in all biological systems and the effects of iron deficiency or overload can be catastrophic to the continued well being of any organism. Maintenance of iron homeostasis is of primary importance. FerriSeltz^{TM}(OMR) is an iron-containing substance to be given in a single oral bolus dose, acute iron toxicity and the effects of iron overload were researched in the literature.

More than 500 volunteers and/or patients have been exposed to single dose administration of FerriSeltz™ during the clinical trials (majority foreign published data). Dose ranged from 1.5 gm to 12.0 gm Fe in 300 or 600 mL of water.

Post-OMR vital signs and clinical laboratory (serum chemistry, hematology, urinalysis) values revealed no clinically significant effect on any of these parameters at any dose level. In the ph-2/3 clinical trials, the majority of abnormal serum chemistry values that concerned the iron-related parameters, especially serum iron and %saturation. Most of the changes noted in the iron-related parameters were normal values that became below-normal values post-OMR ingestion. The effect of OMR on iron parameters is unclear, and in some cases a cause-effect relationship seems unlikely.

The most commonly occurring adverse event was mild diarrhea of intermittent frequency. Overall digestive system adverse events occurred in a dose-related pattern, with the highest dose of OMR 12g having the highest incidence of adverse effects (mild nausea, vomiting, diarrhea, etc.).

It has been observed both experimentally and clinically that ferrous salts are generally more readily absorbed in man than ferric salts. The absorption of ferric iron is 3 to 7 fold less than ferrous iron, depending on the dose. The probable oral lethal dose of ferric ammonium citrate (FAC) for humans is between 0.5 g and 5.0 g/kg. Severe acute iron poisoning commonly occurs with single dose about 2-5 g; obviously then, with an anticipated maximal clinical dose of 400 mg Fe, the incidence of a severe acute iron poisoning with OMR administration is a very remote possibility. The single oral ingestion of 2-4 packets of OMR will result in a total dose of 1200 to 2400 mg (about 200-400 mg Fe or 4-8 mg/kg iron in a 50 kg subject). This single dose, which is well below the doses of FAC reported to have toxic effects.

JMRI 1992: 2. 25-34. Randall M. Patten, et,al. "OMR, a positive Bowel Contrast Agent for Abdominal and Pelvic MR Imaging".

To determine the safety and imaging characteristics of OMR (an effervescent solution of ferric ammonium citrate) - as a bowel contrast agent, MRI at 1.5 T was performed in 29 volunteers. T1 and T2-weighted images of the upper abdomen and pelvis were obtained before and after oral administration of OMR at doses of 100-400 mg of iron in 300-600 mL of water. All dose levels of OMR provided marking of the bowel by increasing intraluminal signal intensity; however, the degree and percentage of small bowel specification appeared more prominent at higher dose levels of iron. There were no clinically significant changes in hematology and serum chemical parameters. OMR improved delineation of the head of the pancreas on T1-weighted images in 72% of subjects but was less useful in defining the body and tail.

OMR is a safety & effective bowel contrast agent for MR imaging. OMR may be most useful on short TR/TE or fast imaging pulse sequences or when combined with antiperistaltic agents.

Most of the subjects who experienced dark stools for 1-3 days after ingestion of OMR, but this discoloration of the stool is an expected physiologic effect due to excretion of non-absorbed iron. One-third of the subjects also experienced semisolid or mild watery diarrhea for up to 24 hours after OMR administration. Although this was reported as an adverse effect of OMR, the severity of diarrhea was reported as mild by all subjects. Four (4) subjects reported nausea after OMR ingestion.

Reviewer's Comment

Based upon the published data, I believe that there is substantial information to support the claims of safety & effectiveness for FerriSeltz™(OMR). Though largely anecdotal case reports with subjective assessments.

4.5 Phase-1 Pharmacokinetics - Refer to Dr. Udo's review.

4.6 Post-marketing experience

Ferric Ammonium Citrate (FAC) was approved for marketing as FerriSeltz™(OMR) in Japan. OMR has not been withdrawn for any reason.

5.0 Clinical Background

FerriSeltz™(OMR) is a positive contrast agent containing ferric ammonium citrate (FAC) that has been developed as an oral contrast agent for MRI of the upper abdomen. FerriSeltz is a mixture of granular : powders containing 20% by weight ferri ammonium citrate, brown, as the active ingredient. FerriSeltz powder dissolves in water to create a grape-flavored effervescent drink. The active ingredient, FAC is currently approved for unrestricted use as a food additive and is widely used in many food products. FAC is accepted by the FDA to be a food generally recognized as safe (GRAS).

FAC is an iron salt that is susceptible to magnetization due to unpaired electrons and alters spin-lattice (T1) and spin-spin (T2) relaxation rates. FAC in aqueous solution exhibits high singal intensity on both T1 and T2-weighted sequences.

In 1983 and 1985, Wesbey et al reported positive contrast enhancement of the stomach and bowel with no side effects using FAC in the OTC product Geritol as an oral MRI contrast agent of the gastrointestianl tract in rats and human volunteers. Though the FAC in Geritol has proved useful as a high intensity intraluminal contrast agent, Geritol is not approved for this indication and contains 12% (v/v) of ethanol making it unsuitable for routine use.

The proposed clinical doses of FerriSeltz™ are equivalent to doses of 4-8 mg/kg of iron. The lethal dose of iron in humans has been estimated to be 200-250 mg/kg. Therefore there is a 25-50 fold safety factor for the proposed clinical doses of FerriSeltz™. The proposed clinical doses of FerriSeltz™ are within the therapeutic range of iron administered for iron deficiency anemina, should appreciable absorption of FerriSeltz ™ occur, it would be expected to produce physiological responses of similar type and extent to those seen following single oral and divided therapeutic doses of ferrous sulfate.

The development of OMR in Japan was initiated by Otsuka Pharmaceutical Co., parent company of Oncomembrane, Inc. in order to provide an ethanol-free, palatable, effervescent solution of FAC that is effective as a high-intensity contrast agent for marking the GIT in abdominal MRI. OMR is an oral contrast agent for MRI formulated as a granular powder that readily dissolves in water to create a grape- flavored effervescent drink.

Table of Studies

A summary of U.S. studies for Phase-1 (Protocol 301-01), and Phase-II/III (protocol 901-03A,901-03B), and for non-U.S. Phase-1 (Otsuka Pharmaceutic Company Japan), and Phase-II/III (multicenters, Japan), are presented in the following Tables:

PHARMACODYNAMIC STUDIES OF FERRISELTZ™

STUDY No. SHORT TITLE LOCATION	PRINCIPAL INVESTIGATOR STUDY SITE(S) PUBLISHED REPORTS	STUDY DESIGN	No. OF SUBJECTS AGE SEX (M/F) RACE (W/B/H/O)	DOSE (mg Fe/mL) (no. subjects) ROUTE DURATION	RESULTS AND STATISTICAL SIGNIFICANCE
901-01 Phase I Dose-Finding Study of FerriSeltz™ in Normal, Healthy Volunteers Volumes 2.27-2.28	Albert A. Moss Univ of Washington Seattle, WA JMRI 2:25-34, 1992[13]	randomized, dose-tolerance, dose-response	64 subjects (all evaluable) 92% Male (59/5) 92% White (59/0/1/4)	100 mg/300 mL (4) 100 mg/600 mL (14) 200 mg/600 mL (20) 300 mg/600 mL (4) 400 mg/600 mL (7) 400 mg/1200 mL (15) p.o. single ingestion (24h)	Digestive system events as expected for oral iron agent, with trend toward more severe events with double doses (200 mg Fe/600 mL vs 400 mg Fe/1200 mL) Adequate bowel distention with 600 mL, but not with 300 mL Increased intraluminal signal intensity with doses ≥200 mg Fe/ 600 mL
Phase I Dose-Finding Study of FerriSeltz™ in Patients with Abdominal Disease Volume 2.39 Pages 1-46	*** JAPAN (6 sites): • Fukui Medical College • Kyoto University • Kanto Rosai Hospital • Nara Prefect Med Coll • Tokyo Jikeikai Med • Tokyo University Diagnosis and Treatment 79:1913-1922, 1991[12]	multicenter, randomized, dose-tolerance, dose-response	91 subjects (all evaluable) 49% Male (45/46) 100% Oriental	50 mg/300 mL (13) 100 mg/300 mL (40) 200 mg/300 mL (38) p.o. single ingestion (24h)	No clinically significant adverse experiences Inadequate signal intensity with 50 mg Fe/300 mL dose Improved contrast intensity in >95% of cases and improved identification of lesion in >70% of cases at doses of 100-200 mg Fe/300 mL

CONTROLLED CLINICAL STUDIES OF FERRISELTZ™, continued

STUDY No. SHORT TITLE LOCATION	PRINCIPAL INVESTIGATOR STUDY SITE(S) PUBLISHED REPORTS	STUDY DESIGN	No. OF SUBJECTS AGE SEX (M/F) RACE (W/B/H/O)	DOSE (mg Fe/mL) (no. subjects) ROUTE DURATION	RESULTS AND STATISTICAL SIGNIFICANCE
Phase II/IIIA Efficacy Evaluation of FerriSeltz™ in Patients Undergoing MRI of the Upper Abdomen Volume 2.39 Pages 47-312	*** JAPAN (22 sites): • Fukui Medical College • Hokkaido Universty • Kanazawa University • Kanto Rosai Hospital • Keio University • Kobe University • Kyorin University • Kyoto University • Kyushu University • Nagoya City University • Nagoya University • Nara Prefectural Med • Nihon Medical College • Okayama University • Osaka City University • Osaka University • Saint Marie Anna Univ • Tenri Yorozusodansho Hospital • Tokushima University • Tokyo Jikeikai Med • Tokyo University • University of Tokyo Diagnosis and Treatment	multicenter, open, dose comparison concurrent control	169 enrolled 62% Male (105/64) 100% Oriental	100 mg/300mL (129) 200 mg/300 mL (40) p.o. single ingestion (24h)	>90% of post-contrast images showed increased signal intensity of stomach and duodenum >66% of post-contrast images showed improved detection of lesions

CONTROLLED CLINICAL STUDIES OF FERRISELTZ™

STUDY No. SHORT TITLE LOCATION	PRINCIPAL INVESTIGATOR STUDY SITE(S) PUBLISHED REPORTS	STUDY DESIGN	No. OF SUBJECTS AGE SEX (M/F) RACE (W/B/H/O)	DOSE (mg Fe/mL) (no. subjects) ROUTE DURATION	RESULTS AND STATISTICAL SIGNIFICANCE
901-03A Phase II/IIIA Efficacy Evaluation of FerriSeltz™ in Patients Undergoing MRI of the Upper Abdomen Volumes 2.29-2.32	*** USA (7 sites): • Stanford Univ (Stanford, CA); • Harbor-UCLA Med Ctr (Torrance, CA); • Mayo Clinic (Rochester, MN & Scottsdale, AZ); • Ohio State Med School (Columbus, OH); • Univ of Pennsylvania (Philadelphia, PA); • Univ of Washington (Seattle, WA) Radiology 189: 277-283, 1993	multicenter, randomized, dose comparison concurrent control	160 enrolled, 155 treated, 153 imaged, 151 w/labs 61% Male (89/71) 75% White (120/14/12/8)	200 mg/600mL (78) 400 mg/600 mL (82) p.o. single ingestion (24h)	>95% of post-contrast images showed significant or moderate improvement in bowel marking and delineation of upper GI tract in side-by-side assessments by investigating radiologists Assessments by a blinded reviewer showed statistically significant increases from pre- to post-contrast scores for all areas of contrast assessment and for delineation of upper GI tract Mild, self-limiting digestive system events, of type and frequency previously reported for oral iron therapy

CONTROLLED CLINICAL STUDIES OF FERRISELTZ™, continued

STUDY No. SHORT TITLE LOCATION	PRINCIPAL INVESTIGATOR STUDY SITE(S) PUBLISHED REPORTS	STUDY DESIGN	No. OF SUBJECTS AGE SEX (M/F) RACE (W/B/H/O)	DOSE (mg Fe/mL) (no. subjects) ROUTE DURATION	RESULTS AND STATISTICAL SIGNIFICANCE
901-03B Phase II/IIIA Efficacy Evaluation of FerriSeltz™ in Patients Undergoing MRI of the Upper Abdomen Volumes 2.33-2.35	*** USA (6 sites): • San Francisco Gen'l (San Francisco, CA); • VA Med Ctr (San Francisco, CA); • Sequoia Hospital (Redwood, CA); • Tampa Bay Med Res (Safety Harbor, FL); • Univ of Minnesota (Minneapolis, MN); • Dartmouth Hitchcock Med Ctr (Lebanon,NH) Radiology 189: 277-283, 1993	multicenter, randomized, dose comparison concurrent control	115 enrolled, 114 treated, 114 imaged, 113 w/labs 68% Male (78/37) 84% White (97/11/3/4)	200 mg/600mL (60) 400 mg/600 mL (55) p.o. single ingestion (24h)	>85% of post-contrast images showed significant or moderate improvement in bowel marking and delineation of upper GI tract in side-by-side assessments by investigating radiologists Assessments by a blinded reviewer showed statistically significant increases from pre- to post-contrast scores for all areas of contrast assessment and for delineation of upper GI tract Mild, self-limiting digestive system events, of type and frequency previously reported for oral iron therapy

6.0 U.S. Phase I Study

This was an open-label, non-randomized study conducted at the University of Washington in normal, healthy volunteers to demonstrate the safety and efficacy of FerriSeltz. The study was conducted in two parts: (Each subject fasted for at least 6 hours prior to ingestion of OMR. Subjects were given either a single dose-part A, or a double dose-part B) of OMR.

Part A evaluated 5 dose levels of FerriSeltz for safety and effectiveness on MR imaging. Part B evaluated only safety parameters in additional subjects at the dose level identified as optimally safe and effective in Part A, using two administration protocols, single and double dosing.

Demographics - A total of 64 subjects were enrolled. All 64 subjects were evaluated for safety; (26 of the 64 subjects were evaluated for efficacy and 59 of the subjects were male; 5 subjects were female). Subject ages ranged from years with 57 of the 64 subjects in the year-old age group. The majority of the subjects were Caucasian, 4 Asian and 1 Hispanic.

Protocol Variators - Three of the subjects (#01-A27, A28, A29) at dose level of 3x1 (200mg Fe) were excluded from the efficacy analyses because MRI scanning technique was used during their MRI series (T1-weighted only).

Concomitant Medications - Except for a few subjects had taken multivitamin nutritional supplements within the 24 hours prior to OMR ingestion.

Efficacy Results

Dose level 1x1 (100 mg Fe) and 2x1 (100 mg Fe) were demonstrated inadequate and inconsistent signal intensity. The quality of T2-weighted images was poorly compromised by artifacts, therefore, image assessments were not analyzed. The 3 highest dose levels of 3x1 (200mg Fe=6g), 4x1 (300mg Fe=9g), & 5x1 (400mg Fe=12g OMR) appeared equivalent in signal intensity & bowel opacification on T1-weighted images of the upper abdomen.

At the completion of Part A, statistical analysis of the T1-weighted image assessments from subjects enrolled at dose levels 3x1 (200 mg Fe) and 5x1 (400mg Fe) was performed and the results compared between these dose levels and also with the results obtained for subjects enrolled at dose levels 1x1 and 2x1 (Total number of subjects were evaluated).

Dose Group	1x1	2x1	3x1	4x1	5x1
OMR (Gm)	3	3	6	9	12
Fe (mg)	100	100	200	300	400
Subjects (N=29)	4	4	10	4	7

Signal Intensity - Signal intensity of the GIT was scored using a 5-point scale from 0-3 (0,1,2,3), 3 representing the brightest image. On axial T1-weighted scans there was a trend toward higher scores for the stomach than the proximal bowel in both 3x1 and 5x1 dose groups. Similar but less increases in signal intensity were seen on the axial T2-weighted images.

Opacification - Opacification of the GIT was graded on a 4-point scale (0=none, 1=minimal, 2=moderate, 3=significant) and persentage opacification was estimated for T1 and T2 weighted images of the upper abdomen (pre-and post-OMR). Data indicated that all subjects had a significant increase in opacification post-OMR of the upper abdominal images.

Artifacts - There appeared to be an increased motion artifacts in comparison between pre-to post-OMR images. Artifacts were minimal on the post-OMR T1 weighted scans and moderate-severe on the T2-weighted images.

Reviewer's Comment - Because of the nature of scale used and the small sample size will make it more difficult to achieve statistical significance.

Safety Results

Vital Signs (systolic/diastolic BP, and pulse rate) were measured immediately prior to and 30-60 minutes and 24 hours after OMR ingestion. No significant change in mean values of vital signs was observed in either dose group. However, there were 11 (9 systolic, 3 diastolic) subjects that had blood pressure changes and 10 (7 decreases, 3 increses) subjects for pulse rate. These changes, however, were not clinically significant.

Laboratory Parameters - There were 17 of 64 subjects who had laboratory value changes either pre- or 24-hour post-OMR ingestion; 15 of these 17 subjects had clinically significant baseline value changes and the majority of those values remained clinically significant 24 hours post-OMR. No dose-related trends were observed in the latoratory parameters measured.

Iron metabolism parameters (serum iron, ferritin, % saturation, total iron binding capacity and transferrin) were measured prior to OMR ingestion and 24 hours post-OMR ingestion. Six subjects had abnormal low values for (2-serum iron, 4-% saturation, and 2 ferritin) subjects which remained low 24 hours post-OMR; in two subjects values normalized on follow-uo examination. There were 11 subjects who experienced a transition from a normal value for (6-serum iron, 6-% saturation, 1-TIBC, and 1-transferrin) to a clinically significant abnormal 24 hours post-OMR; these clinically laboratory changes were repeated for 8 of the 11 subjects and became normalized.

Reviewer's Comment - The reviewer believes that fluctuation of the iron metabolism is due to the fact that the serum iron of man undergoes a regular diurnal variation.

Adverse Event - With respect to drug tolerance, no serious adverse effects were encountered in the subjects studied. Forty-nine (49) of 64 (76%) subjects reported at least one adverse effect. The most frequently adverse events of the digestive system are the following: Diarrhea (22%), Loose stool (17%), Nausea (7%), Abdominal pain (7%) and Headache (3%). Additionally, isolated occurrences, such as dizziness, insomnia, drowsiness, malaise, hematuria and constipation were also recorded during the study (see Table below).

Dose Group	1x1	2x1	3x1	4x1	5x1	3x2	
OMR (Gm)	3	3	6	9	12	12	
Subjects (N=64)	4	4	30	4	7	15	
Subject with ADRs	4	1	22	2	7	13	Total(%)
Cramping	1	0	2	0	0	2	5(>7)
Dark stool	3	0	17	2	6	10	38(<60)
Diarrhea	1	0	4	1	2	6	14(<22)
Loose stool	0	1	5	1	1	1	9(14)
Nausea	2	0	3	0	1	1	7(<11)
Pain	0	0	1	0	0	1	2
Green stool	0	0	1	0	0	0	1
Soft stool	0	0	1	0	0	0	1
Vomiting	1	0	0	0	0	0	1
Headache	0	0	2	0	0	0	2
Dizziness	0	0	1	0	0	0	1
Drowiness	0	0	1	0	0	0	1
Hypertension	0	0	1	0	0	0	1
Hematuria	0	0	2	0	0	0	2
Others	1	0	5	0	1	3	10
Total	9	1	46	4	11	24	95

Reviewer's Comment

As shown in the tabulation above, the overall digestive systems adverse events occurred in a dose-related manner, with the highest dose of 400mg Fe-OMR incidence of adverse events.

6.1 Non-U.S. Phase 1 study (English translation from original published article in Japanese)

Otsuka Pharmaceutic Company has completed Phase 1 clinical trial in Japan to determine the effective dose range of OMR in the Japanese population. A total of 91 patients with disorders of the abdomen scheduled to undergo routine MR imaging were evaluated at 5 different institutions.

Three dose levels of OMR were administered in a constant volume of 300 mL; 1.5g (50mg Fe), 3g (100mg Fe) and 6g (200mg Fe). Pre-& post-oral administration of OMR, patients were evaluated by MRI of the upper abdomen to evaluate delineation of the pancreas, and for changes in hematology, serum chemistry, and urinalysis. There were no significant changes attributable to OMR in the laboratory parameters following OMR administration. Only 2 patients reported black stool and one patient reported diarrhea following ingestion of OMR at the 6g/300 mL dose level. The MRI results indicated that 1.5g OMR was insufficient to provide desired contrast. The contrast enhancement of the GIT and the delineation of the pancreatic margins were signicantly improved compared to pre-contrast scan in the patients who received either 3g or 6g OMR.

Reviewer's Comment - It is interesting to note that only 2 patients who experienced adverse events of black stool and diarrhea as compared with U.S. Phase 1 trial that had 76% (49/64) subjects reported at least one adverse effect. In this trial, no specific information was provided concerning differentiation of organs from images.

6.2 Non-U.S. Phase II/III study (English translation from original published article in Japanese)

This was a multicenter, open-label randomized, dose comparison study conducted in Japan. A total of 169 patients (22 study centers) was studied. The patients were between 16-86 years of age (mean 58.3 years) and consisted of 105 males and 64 females. Patients were randomized to receive a single dose of either (100mg Fe/300 mL=3g OMR) or (200mg Fe/300mL = 6g OMR).

Efficacy

Assessments were performed for 169 patients (129 in the 100mg Fe group and 40 in the 200mg Fe group). MR image was performed with 0.2T, 0.5T, 1.0T, and 1.5T magnats to obtain T1-weighted spin echo (ES) images prior to and 20 minutes after ingestion of 600mg FAC (100mg Fe) or 1200mg FAC (200mg Fe) per 300mL water. Both investigator and a 7 member panel graded images for contrast efficacy (based on pre- and post-image scans) according to 5-point scales.

Evaluation of imaging effect

In the 100mg Fe group, scores of 3+ and 2+ were obtained from 17.1% and 48.8% of the patients, respectively, accounting for a total of 65.9% with scores of 2+. In the 200mg Fe group, scores of 3+ and 2+ were obtained from 50.0% and 30.0% of the patients, respectively, for a total of 80.0% with scores of 2+. The percentage of patients with scores of 2+ and above in the 2 groups was significantly different but not by Fisher's direct probability test.

All in all, OMR yielded good scores in contrast effect (90.5%), imaging effect(69.2%) and usefulness (81.7%). Furthermore, the usefulness by organ was scored 2+ and above as follows; stomach (85.4%), pancreas (81.4%), liver (77.8%) and gallbladder (75.0%).

Adverse effects - Only one patient (0.8%) of the 100mg Fe group had diarrhea but none in the 200mg Fe group. No significant alterations in any of the laboratory parameters were observed after ingestion of OMR.

Reviewer's Comment

The ages of the patients, however, in the two groups were significantly different at $p<0.05$ by U-test, but the strength of the static magnetic field was not significantly different between the two groups.

Again, it is hard to believe that in such large sample size enrolled only one patient had adverse effect of mild diarrhea.

Because of almost no adverse effects occurred in both Phase 1 and Phase 1I/III Japanese clinical trials. Therefore, these clinical results would be improper to pooled data together with the U.S. trials.

7.0 U. S. CLINICAL TRIALS

7.1 Pivotal Study A (Protocol #901-03A)

Principal Investigators - This was a Phase-II/III, open-label, multicenter, randomized clinical trial conducted by the following investigators at their respective study sites:

Number of Pts Enrolled	Study Site	200 mg Fe (6g OMR) 78	400 mg Fe (12g OMR) 82	Total 160
James G. Bova, D.O. (Ohio State University)	01A	15	16	31
Daniel Johnson, M.D. (Mayo Clinic)	02A	15	15	30
Herbert Kressel, M. D. (University of PA)	03A	6	6	12
Simon K. Lo, M.D. (Harbor UCLA Med. Ctr.)	04A	19	19	38
Albert A. Moss, M.D. (Unvi. of Washington)	05A	9	10	19
Gary Glazer, M.D. (Standford Univ. CA)	06A	14	16	30
Evaluable for Safety				
Patients Receiving Study Drug(1)		76	79	155
Pts with Pre-/Post-OMR Assessment(2)		75	76	151
Evaluable for Efficacy				
Investigator Assessment(3)		75	78	153
Blinded Review Assessment(4)		57	58	115
Fast Scan T1 Images(5)		46	49	95
Fast Scan T2 Images(5)		15	17	32

Note:

(1) Seven patients had no post-OMR imaging(2 vomited following OMR ingestion and 5 did not receive study drug.

(2) Thirth-eight (38) pts (17 6g group & 21 12g group) did not have blinded contrast assessment. Also, 7 pts did not undergo post-OMR imaging.

(3) Performed at the option of the investigator.

(4) All patients who received study drug were included in the safety analysis, except 5 patients who did not receive the study drug.

(5) Four patients did not have a day 2 laboratory assessment.

Study Objectives

To demonstrate the effectiveness of OMR as a contrast agent to visualize the gastrointestinal tract during MRI of the upper abdomen. To obtain additional safety data for the two dose levels studied.

Study Population

Demography - Six (6) study sites enrolled a total of 160 in- and out-patients with known or suspected upper abdominal disease.

	Demographic Information	
	200 mg Fe (6g-OMR)	400 mg Fe (12g-OMR)
Number of Pts Enrolled (N=160)	78	82
Age (years)		
Mean ± S.E.	55.5 ± 1.8	54.4 ± 1.6
Range		
<35	9	7
35-49	16	18
50-64	27	35
>65	26	22
Gender		
Male	40	49
Female	26	22
Race		
Caucasian	64	56
Black	6	8
Asian	2	6
Hispanic	6	6
Native American	0	1
Other	0	5
Height (in)		
Mean ± S.E.	66.5 ± 1.8	67.3 ± 0.5
Range		

Weight (lbs)		
Mean ± S.E.	152.7 ± 4.0	154.8 ± 4.0
Range		
<100	1	0
100-149	37	39
150-199	34	34
>200	5	8
not recorded	1	1

Two randomized dose groups were comparable with respect to demographic parameters. However, race was unevenly distributed.

Dose Information - Each patient was assigned a unique identification number upon enrollment and was then randomized into two dosing groups. Each patient was given a single dose of 600 mL of OMR solution. The OMR solution was prepared immediately before use by dissolving the centents of the appropriate number of OMR packets in 600 mL of tap water. Patients were instructed to drink the OMR dose in a bolus as quickly as possible. The following OMR dose levels were evaluated;

Two packets of OMR (6g) in 600 mL water (1200 mg FAC)

Four packets of OMR (12g) in 600 mL water (2400 mg FAC)

Concomitant Medications - As noticed, treatment with enteric or contrast agents, either intravenous or oral treatment with glucagon, scopolamine, or other anti-peristaltic agents within 24 hours prior to OMR and/or concomitant with the study MRI were not allowed. Medications & nutritional supplements, especially those containing iron, were not to be used on the day of the study.

Protocol Variations - There were 9 (#112A, #606A, #113A, 508A, #128A, #432A, #504A, #424A, #507) protocol variances. These 9 patients were excluded from the both efficacy & safety analyses. Other patient #502A who assigned to the 200 mg Fe group, was also excluded from the blinded investigator efficacy analysis because correct films were not available for review.

Efficacy Results

One hundred fifty-three (153) patients (75 in the 200 mg Fe group and 78 in the 400 mg Fe group) was studied by MRI before and after ingestion OMR. One hundred sixteen (116) of 153 patients in both dose groups were imaged with 1.5 tesla and 37 patients were imaged with 0.5 Tesla. Both dose groups had comparable mean times to imaging after OMR ingestion.

Image Quality and Artifacts - Both pre-and post-OMR images for each patient side-by-side, the investigator evaluated the adequacy of each image rated by 5-point scales,(yes, poor, good, excellent). The investigator was asked to observe artifacts present (yes, no) and if present, graded the effect of OMR on artifact as (none, minimal, moderate, severe).

Comparative T1-W Image Assessment:
OMR Image Quality and Effect on Artifacts

Assessment by On Site Investigator	200 mg Fe (6g OMR)	400 mg Fe (12g OMR)
Number of Pts Assessed (N=153)	75	78
Excellent	28 (37%)	38 (49%)
Good	43 (57%)	40 (51%)
Poor	4 (5%)	0
Unsatisfactory	0	0
Effect of OMR on Artifacts		
None	11 (15%)	13 (17%)
Minimal increase	40 (53%)	36 (47%)
Moderate increase	23 (31%)	24 (31%)
Severe increase	1 (1%)	4 (5%)
Not reported	0	1

	200 mg Fe (6g OMR)	400 mg Fe (12g OMR)
Assessment by Blinded Reader	Pre / Post	Pre / Post
Number of Pts Assessed (N=115)	57	58
Excellent	30 26	31 26
Good	21 24	23 27
Poor	6 7	4 5
Unsatisfactory	0 0	0 0
Wintin-group p-value	0.329	0.208
Effect of Artifacts on Post-OMR		
None	38 24	41 28
Minimal increase	13 20	10 20
Moderate increase	6 9	5 9
Severe increase	0 3	1 1
Not reported	0 1	1 0
Within-group value	0.001	0.021

On-site Investigator graded all images as adequate quality for radiologic interpretation. One hundred forty-nine (97%) of images were graded excellent and good quality. There was a about 10% greater image quality in the 400 mg Fe group compared to the single dose of 200 mg Fe group. As for artifacts appear comparable in both dose groups.

Based on the blinded review data, the quality of pre- and post-OMR images were similar and no significant differences between dose groups (91% of pre-OMR vs 90% for the post-OMR images). Artifacts, there were no significant differences between dose groups for post-OMR images. But both dose groups revealed statistically significant increases in artifacts from pre-to- post-OMR images.

Bowel Marking - (Image assessment by investigator)

Four (4) contrast parameters were evaluated; namely: signal intensity, opacification, signal homogeneity, and distension. Paired images for each patient (pre- and post-OMR) were assessed by the investigator, & the blinded reader (off-site Radiologist) judged each image independently and in random order (The following Table was adapted from Volume 29. p27 & p32).

Comparative T1-W Image Assessment:
Persent Images Showing Significant or Moderate
Improvement in Bowel Marking with

On-side Reader Assessment	200 mg Fe (6g OMR)	400 mg Fe (12g OMR)	Between Group
Number of Pts Assessed (N=153)	75	78	P-value*
Signal Intensity			
Stomach	84%(61/73)	92%(72/78)	0.132
Duodenum	56%(41/73)	68%(52/76)	0.132
Jejunum	49%(35/72)	65%(48/74)	0.066
Overall**	96%(72/75)	95%(74/78)	1.000
Opacification			
Stomach	85%(62/73)	95%(74/78)	0.056
Duodenum	62%(45/73)	71%(54/76)	0.231
Jejunum	49%(35/71)	68%(50/74)	0.029
Overall**	93%(70/75)	97%(76/78)	0.270

Signal Homogeneity			
Stomach	95%(69/73)	100%(78/78)	0.052
Duodenum	64%(47/73)	67%(51/76)	0.732
Jejunum	49%(35/72)	61%(45/74)	0.183
Overall**	99%(74/75)	100%(78/78)	0.490
Distention			
Stomach	89%(65/73)	91%(71/78)	0.788
Duodenum	45%(33/73)	55%(42/76)	0.253
Jejunum	30%(21/71)	42%(31/74)	0.166
Overall**	96%(72/75)	94%(73/78)	0.720

* Based on Fisher's exact test (two-tailed)

** Significant or moderate improvement in at least one body organ

Off-side (Blinded) Reader Assessment		200 mg Fe (6g OMR)	400 mg Fe (12g OMR)	Between Group
Number of Pts Assessed (N=115)		57	58	P-value*
Signal Intensity				
Stomach	%improved	93%(53/57)	98%(57/58)	0.053
	p-value***	<0.001	<0.001	
Duodenum		88%(50/57)	98%(56/57)	0.002
	" "	<0.001	<0.001	
Jejunum		67%(38/57)	77%(44/57)	0.134
	" "	<0.001	<0.001	
Opacification				
Stomach		91%(52/57)	98%(57/58)	0.053
	" "	<0.001	<0.001	
Duodenum		86%(49/57)	98%(57/58)	0.001
	" "	<0.001	<0.001	
Jejunum		70%(40/57)	76%(44/58)	0.269
	" "	<0.001	<0.001	

Signal Homogeneity				
Stomach	%improved	91%(52/57)	98%(56/57)	0.134
	p-value***	<0.001	<0.001	
Duodenum		86%(49/57)	98%(57/58)	0.004
	" "	<0.001	<0.001	
Jejunum		68%(39/57)	78%(45/58)	0.189
	" "	<0.001	<0.001	
Distention				
Stomach		93%(53/57)	98%(57/58)	0.598
	" "	<0.001	<0.001	
Duodenum		68%(39/57)	81%(47/58)	0.151
	" "	<0.001	<0.001	
Jejunum		35%(20/57)	47%(27/58)	0.224
	" "	<0.001	<0.001	

* Between group comparison of changes from pre-to post-OMR

** Score improved >1 unit

*** Changes from pre-to post-OMR evaluated (Wilcoxon signed-rank)

On-site reader - The data indicates that greater than 90% of post-OMR images in all 4 parameters were evaluated. There were no significant differences between dose groups. However, for individual organs the improvement in opacification of the jejunum was significantly greater in the 400 mg Fe group than in the 200 mg Fe group.

Off-site reader - The table above summarizes the changes in blinded reader ratings and percent of images noted at least one unit improvement from pre-to-post-OMR in blinded reader assessments of contrast parameters. Overall, there were statistically significant ($p<0.001$) increases from pre- to post-OMR scores for contrast parameters. The overall evaluation of blinded contrast review were significantly greater in the 400 mg Fe OMR group than in the 200 mg Fe OMR group.

Organ Delineation (ref. vol. 29-30 Tables 12 & 16)

On-site reader - Based on the data submitted, the improvement in delineation of the stomach wall and jejunum was significantly greater for the higher dose (400 mg Fe) group compared to the lower dose (200 mg Fe) group.

Off-site reader - The data indicates that overall evaluation of the organ delineation showed statistical improvements in mean scores from pre-to post-OMR and similar results in two dose groups. Over 90% of post-OMR images showed improved delineation of the stomach, less than half of improved delineation of the jejunum and less than 20% improved delineation of the bowel wall.

Intent-To-Treat - Blinded Reader Ratings of Contrast Efficacy

Image Quality and Artifacts - The table below summarizes the blinded reader ratings of image quality & artifacts, assuming worst case assessments for the 38 patients without blinded contrast reviews.

Comparative T1-W Image Assessment by Blinded Reviewer

OMR Image Quality and Effect on Artifacts

(Intent-to-Treat Analysis)

	200mg Fe OMR		400mg Fe OMR	
	Pre	Post	Pre	Post
Number of Pts Assessed (N=153)	75	75	78	78
Image Quality				
Excellent	30	26	31	26
Good	21	24	23	27
Poor	24	25	24	25
Unsatisfactory	0	0	0	0
Effect of OMR on Artifacts				
None	38	24	41	28
Minimal increase	13	20	10	20
Moderate increase	6	9	5	9
Severe increase	18	21	21	21
Not rated	0	1	1	0

In this intent-to-treat analysis, all of the pre-and post-OMR images were graded as adequate (good/excellent) quality of 69% in the pre-OMR compared to 67% for the post-OMR images. There were essentially no significant differences between pre- and post-OMR image scores and comparable between dose groups. Artifacts, however, revealed no significant differences between two dose groups.

Bowel Marking/Delineation

The mean changes in blinded reader ratings and percent of images show at least one unit improvement from pre-to-post-OMR in blinded reader assessments of signal intensity, opacifcation, homogeneity, GIT distension, and delineation assuming worst case assessments for the 38 patients without blinded contrast reviews. The following Table was adapted from volume 29. p37-8.

Comparative T1-W Image Assessment by Blinded Reader:
Mean Change in Scores & % Images Showing Improvement
in Bowel Marking with OMR-intent-to-treat Analysis

Number of Pts Assessed (N=153)		200mg Fe OMR 75	400mg Fe OMR 78	Between Group P-value*
Signal Intensity				
Stomach	% improved	71%(53)	73%(57)	0.409
	Mean ± S.E.	2.0±0.2	2.2±0.2	
	p-value***	<0.001	<0.001	
Duodenum	" "	67%(50)	72%(56)	0.083
		1.5±0.1	1.8±0.1	
		<0.001	<0.001	
Jejunum	" "	51%(38)	56%(44)	0.296
		1.0±0.1	1.1±0.1	
		<0.001	<0.001	
Opacification				
Stomach	" "	69%(52)	73%(57)	0.405
		2.0±0.2	2.2±0.2	
		<0.001	<0.001	
Duodenum	" "	65%(49)	73%(57)	0.008
		1.2±0.1	1.8±0.1	
		<0.001	<0.001	
Jejunum	" "	53%(40)	56%(44)	0.506
		0.9±0.1	1.0±0.1	
		<0.001	<0.001	

Signal Homogeneity				
Stomach	"	"	69%(52)	73%(56)	0.438
			1.9±0.2	2.1±0.2	
			<0.001	<0.001	
Duodenum	"	"	65%(49)	73%(57)	0.046
			1.2±0.1	1.5±0.1	
			<0.001	<0.001	
Jejunum	"	"	52%(39)	58%(45)	0.356
			0.6±0.1	0.7±0.1	
			<0.001	<0.001	
Distention					
Stomach	"	"	71%(53)	73%(57)	0.833
			1.2±0.1	1.2±0.1	
			<0.001	<0.001	
Duodenum	"	"	52%(39)	60%(47)	0.220
			0.6±0.1	0.8±0.1	
			<0.001	<0.001	
Jejunum	"	"	27%(20)	35%(27)	0.313
			0.3±0.1	0.4±0.1	
			<0.001	<0.001	
Delineation of (GI tract)					
Stomach	"	"	65%(49)	73%(57)	0.228
			1.5±0.2	1.7±0.1	
			<0.001	<0.001	
Stomach wall	"	"	64%(48)	68%(53)	0.689
			1.5±0.2	1.5±0.1	
			<0.001	<0.001	
Duodenum	"	"	56%(42)	60%(47)	0.144
			0.9±0.1	1.2±0.1	
			<0.001	<0.001	
Jejunum	"	"	32%(24)	38%(30)	0.434
			0.4±0.1	0.5±0.1	
			<0.001	<0.001	
Bowel wall	"	"	11%(8)	14%(11)	0.657
			0.2±0.1	0.2±0.1	
			<0.008	<0.001	

Delineation (pancreatic magins)				
Head	"	"	43%(32)	45%(35)	0.169
			0.6±0.1	0.8±0.1	
			<0.001	<0.001	
Body	"	"	43%(32)	33%(26)	0.294
			0.7±0.1	0.5±0.2	
			<0.001	<0.001	
Tail	"	"	37%(28)	32%(25)	0.735
			0.4±0.1	0.4±0.1	
			<0.001	<0.001	

* Assumes worst case assessments for 38 pts. without blinded contrast reviews; % improved indicates > 1 unit improvement.

** Evaluated using Wilcoxon rank-sun test.

*** Evaluated using Wilcoxon signed-rank test.

All in all, there were statistically significant ($p<0.001$) increases from pre-to-post-OMR image scores for bowel marking parameters. Approximately >70% of post-OMR image scores for signal intensity, opacification, signal homogeneity and distension of the stomach and duodenum. There were better improvement in opacification, and signal homogeneity of the duodenum in the high dose group compared to the low dose group.

Organ delineation - There were also statistically significant improvements in mean scores from pre-to-post-OMR, and similar results for the two dose groups.

Image Quality and Artifacts - The investigator and blinded reader ratings of contrast efficacy were compared using the results of the intent-to-treat analysis, in which worst possible image ratings were assumed for the 38 patients without blinded contrast reviews (see Table below).

Comparative T1-W Image Assessment

OMR Image Quality and Effect on Artifacts

Intent-to-treat Analysis

	200 mg Fe		400 mg Fe		Pooled	
	On-site / Off-site		On-site / Off-site		On-site / Off-site	
No. of Patients Assessed	75	75	78	78	153	153
Image Quality						
Excellent	28	26	38	26	66	52
Good	43	24	40	27	83	51
Poor	4	25	0	25	4	50
Unsatisfactory	0	0	0	0	0	0
Effect on Artifacts						
None	11	24	13	28	24	52
Minimal	40	20	36	20	76	40
Moderate	23	9	24	9	47	18
Severe	1	21	4	21	5	42
Not rated	0	1	1	0	1	1

The overall evaluation of the image quality was adequate (good/excellent) in 97% (149/153) scores of the investigator versus 67% (103/153) scores for the blinded reader. As for artifacts, there were 27%(42/153) patients that had severe artifacts in the off-site (blinded) reader as compared with only 3%(5/153) for the investigator score. The sponsor gave this explanation that "The discrepancy can be attributed at least in part, to assuming worst case scores for 25% (38/153) of images without blinded contrast reviews.

Bowel Marking/Delineation - A comparison of investigator and blinded reader intent-to-treat bowel marking assessments (The following Table was adapted from Vol. 29. p40).

	200mg Fe (6g-OMR)		400mg Fe (12g-OMR)	
	Investigator / Blinded		Investigator / Blinded	
No./Pts Assessed (N=153)	57**	75**	78**	78**
Signal Intensity				
Stomach	81%(61)	71%(53)	92%(72)	73%(57)
Duodenum	55%(41)	67%(50)	67%(52)	72%(56)
Jejunum	47%(35)	51%(38)	62%(48)	56%(44)
Opacification				
Stomach	83%(62)	69%(52)	95%(74)	73%(57)
Duodenum	60%(45)	65%(49)	69%(54)	73%(57)
Jejenum	47%(35)	53%(40)	64%(50)	56%(44)
Signal Homogeneity				
Stomach	92%(69)	69%(52)	100%(78)	72%(56)
Duodenum	63%(47)	65%(49)	65%(51)	73%(57)
Jejunum	47%(35)	52%(39)	58%(45)	58%(45)
Distention				
Stomach	87%(65)	71%(53)	91%(71)	73%(57)
Duodenum	44%(33)	52%(39)	54%(42)	60%(47)
Jejunum	28%(21)	27%(20)	40%(31)	35%(27)
Delineation(GI treat)				
Stomach	75%(56)	65%(49)	82%(64)	73%(57)
Stomach wall	85%(64)	64%(48)	97%(76)	68%(53)
Duodenum	51%(38)	56%(42)	64%(50)	60%(47)
Jejunum	33%(25)	32%(24)	50%(39)	38%(30)
Bowel wall	43%(32)	11%(8)	54%(42)	14%(11)
Delineation(pancreas)				
Head	31%(23)	43%(32)	38%(30)	45%(35)
Body	19%(14)	43%(32)	27%(21)	33%(26)
Tail	17%(13)	37%(28)	21%(16)	32%(25)

** Assumes worst possible image ratings for 38 patients not included in the blinded review and for the few patients with missing scores in the investigator review.

Data above also suggests somewhat lower scores for stomach of the bowel marking parameters by the blinded reader compared with the on-site reader. The discrepancy can be attributed to assuming worst possible image scores for 25% (38/153) of images without blinded contrast reviews. Data also suggests that more than 70% of images noted improvement in delineation of the stomach & stomach wall.

Fast Scan MRI Contrast Efficacy (Subset Analysis)

Image Quality and Artifacts - Images were evaluated for contrast efficacy by both investigator and blinded reader for 61 fast scan T1-weighted series (30 in the 200mg Fe group and 31 in the 400mg Fe group) and 17 fast scan T2-W series (10 in the 200mg Fe group and 7 in the 400mg Fe group).

Fast Scan T-1 weighted Imaging - (ref. Table 23. Vol. 29. p43)
The overall image quality was graded as adequate (excellent/good) in 93% (57/61) for the on-site assessment versus 84% (51/61) with the blinded reader. There were no statistically significant differences between on-site and off-site rating scores. As for artifacts, there were 5% (3/61) patients that had severe artifacts in the off-site assessment as compared with none for the on-site assessment.

Fast Scan T2 Weighted Imaging - The image quality was graded 82% (14/17) of the on-site assessment vs 70% (12/17) with the off-site assessment. There appear to be slightly better rating score with the T1-weighted images as compared to T2-weighted images. Pooled data for both on-site and off-site assessments of the image quality and artifacts were comparable and no dose effects noted.

Bowel Marking/Organ Delineation (ref. Tables 24,25. Vol. 29. p44,45)
A comparison of on-site and off-site ratings of bowel marking/delineation parameters for fast scan T1 and T2-weighted images showed the results were comparable in both assessments. OMR improved bowel marking parameters (signal intensity, signal homopgeneity, opacification and bowel distension) in most of the cases. The organ delineation prameters also yeilded similar improvement by both assessments. The results of this comparison (T1 & T2-w fast scans) do not reveal any statistically significant difference efficacy outcome.

Safety Results

Safety was assessed by measuring vital signs, blood chemical and hematological parameters and adverse events. Both vital signs and laboratory parameters were measured prior to 30-60 minutes, and 24 hours post-OMR ingestion. No consistent or clinically significant effects on vital signs or laboratory parameters were observed in either dose group. Several abnormalities in vital signs and laboratory parameters were observed in baseline measurements, consistnet with the underlying conditions of the patients (surgery, renal dialysis or blood transfusion).

Iron Metabolism - There was no evidence to suggest iron toxicity associated with OMR ingestion. Both scatter plots aand contingency tables indicated pre-to post-contrast fluctuations in serum iron and iron saturation; but these changes were consistent with reported diurnal variations in these parameters of up to 30% in individual subjects. `Cross-classification of serum iron and ferritin values failed to demonstrate iron toxicity related to OMR ingestion.

Adverse Events - A total of 30 adverse events, irrespective of drug relationship, were reported (according to Tables 27-8.p-49-0) in 21 of 76 (28%) patients who received 200mg Fe-OMR. By comparison, 54 adverse events were reported in 33 of 79 (42%) patients who received 400 mg Fe-OMR. The most frequently occurring adverse events were of the digestive system (28% with 200mg Fe versus 41% for 400mg Fe-OMR group) and body as whole (5% vs 10%) with mild to moderate intensity. Although the incidence of adverse events was greater in the 400mg Fe dose group than in the 200mg Fe dose group (42% versus 28%, respectively).

There were no serious or life-threatening adverse events encountered during the clinical trials. However, there were four patients (#129A, #255A, #419A, #425A) who died five days after the oral contrast (OMR) administered. These patients had a terminal diseases and their deaths were not related to OMR ingestion.

All adverse events reported are summarized in Table below by specific type and organ system.

Incidence of Adverse Events by Body System

	200mg Fe-OMR					400mg Fe-OMR				
Event Severity	1	2	3	4	Total	1	2	3	4	Total
Pts. enrolled (N=155)					76					79
Pts. with AE					21(28%)					33(42%)
Pts. with AE grade ≥2					8(11%)					12(15%)
Body as Whole:					4 (5%)					8(10%)
-fever	-	-	-	-	0	-	1	-	-	1
-headache	3	-	-	-	3	3	1	-	-	4
-pain	1	-	-	-	1	3	-	-	-	3
Cardiovascular:					3 (3%)					1(1%)
-hypotension	1	-	-	-	1	-	-	-	-	0
-tachycardia	2	-	-	-	2	1	-	-	-	1
Digestive:					21(17%)					32(41%)
-constipation	1	-	-	-	1	-	-	-	-	0
-diarrhea	6	2	1	-	9	17	4	2	-	23
-dyspepsia	-	1	-	-	1	-	-	-	-	0
-nausea	4	1	-	-	5	3	2	1	-	6
-abdominal pain	1	1	1	-	3	5	3	-	-	8
-vomiting	-	1	-	-	1	2	2	-	-	4
-flatulence	1	-	-	-	1	1	-	-	-	1
Nervous system:					1 (1%)					1 (1%)
-drowsiness	-	-	-	-	0	1	-	-	-	1
-insomnia	-	1	-	-	1	-	-	-	-	0
Respiratory system:					0 (0%)					2 (3%)
-coughing	-	-	-	-	0	-	1	-	-	1
-rhinitis	-	-	-	-	0	1	-	-	-	1
Urogenital system:					1 (1%)	-	-	-	-	0
dysmenorrhea	1	-	-	-	1	-	-	-	-	0
Total	21	7	2	-	30	37	14	3	-	54

Pivotal Study B (901-03B) - This was the same protocol as to pivotal A study.

Principal Investigators - This was a Phase-II/III, open-label, randomized, multicenter clinical trial conducted by the following investigators at their respective study sites:

	Site	200mg Fe OMR	400mg Fe OMR	Total
Number of Pts Enrolled		60	55	115
Robert Harris, D.O. Dartmouth Hitchcock NH	01B	10	9	19
Robert A. Halvorsen, M.D. San Francisco, CA	02B	3	3	6
Arthur Stillman, M.D. Univ. of Minnesota	04B	4	3	7
Richard Wheat, M.D. Alameda Redwood, CA	05B	10	9	19
Susan Wall, M.D. VAH San Francisco, CA	06B	16	14	30
Steven Bowman, M. D. Tampa Bay MC FL	07B	17	17	34
# Evaluable for Safety				
Patients Receiving Study Drug (1)		60	54	114
Pts with Pre-/Post-OMR Assessment (2)		59	54	113
# Evaluable for Efficacy				
Investigator Assessment (3)		60	54	114
Blinded Review Assessment (4)		53	50	103
Fast Scan T1 Images (5)		27	21	48
Fast Scan T2 Images (5)		22	24	46

Note:

(1) One pt. enrolled in the study and did not receive study drug. (2) One pt. did not have a day 2 laboratory assessment.

(3) One pt.refused to participate in the study.

(4) 8 pts. enrolled (5 in the 6g, 3 in the 12g group) did not undergo blinded contrast assessment.

(5) Performed at the option of the investigator.

Study Design

Demography - Six (6) study sites enrolled a total of 115 in- and out-patients with known or suspected upper abdominal disease.

	Demographic Information	
	200mg Fe OMR	400mg Fe OMR
Total Pts. Enrolled (N=115)	60	55
Age (years)		
Mean ± S.E.	60.3 ± 2.0	62.1 ± 1.8
Range		
<35	3	1
35-49	11	11
50-64	16	22
>65	30	21
Gender		
Male	44	34
Female	16	21
Race		
Caucasian	53	44
Black	4	7
Asian	1	3
Hispanic	2	1
Height (in)		
Mean ± S.E.	67.7 ± 0.5	67.2 ± 0.5
Range		
Weight (lbs)		
Mean ± S.E.	162.5 ± 4.0	163.5 ± 4.2
Range		
<100	0	1
100-149	21	17
150-199	30	29
>200	9	7
not recorded	0	1

No apparent difference between the dose group population was observed. However, race appears unevenly distributed.

Protocl Variations - One patient (#105B) refused study drug and had no pre- or post-OMR images. Therefore, this patient was excluded from the both efficacy and safety analysis. One patient (#109B) failed to have post-OMR laboratory evaluations, and the patient was excluded from the safety analysis. In addition, 12 patients were excluded from the blinded contrast review because their film images were judged to be of inadequate quality.

Efficacy Results

Image Quality and Artifacts - This was graded by the investigator and blinded readers (ref. Vol. 33. Tables 9 and 14).

On-site reader rated all the images as adequate quality (good /excellent) for 90% (103/114) images. However, there were no significant differences between 200mg Fe and 400 mg Fe dose groups (46% vs 44%, respectively). Effect on OMR that had none/minimal effect on artifacts for 76% (87/114) of the scans.

The blinded reader graded as adequate quality (good/excellent) for pre-OMR 76% (81/103) versus 70%(72/103) for the post-OMR images. The quality of (pre-and post) OMR images were graded better scores (82%, 82%) in the higher dose group (400mg Fe) compared with the lower dose group (200mg Fe). Effect on OMR had none or minimal effect on artifacts for 59% scans. However, both dose groups showed a statistically significant increases in artifacts from pre-to post-OMR images.

Bowel Marking - This was graded by investigator and blinded readers (ref. Tables 10,12,15,& 16).

On-site reader graded overall >90% for post-OMR upper abdominal MR images improvement in the intraluminal signal intensity, bowel opacification, signal homogeneity, & GIT distention parameters. There were no significant differences between these parameters with exception of signal homogeneity. Overall score was significantly higher with the 400 mg Fe-OMR dose compared with the lower dose group, reflecting somewhat higher percentages of improvement in the stomach (91% vs 83%), duodenum (44% vs 31%) and jejunum (39% vs 29%) respectively. Organ delineation, however, also showed similar results. The improvement in delineation of the stomach wall and jejunum was moderately greater with the higher dose as compared to the lower dose group. The overall improvement of post-OMR images was 96% vs 78% ($p=0.050$).

Blinded reader assessment - As shown in Table 15, p32. there were statistically significant ($p<0.001$) increases from pre-to post-OMR scores for signal intensity, opacification, homogeneity and distention of the stomach, duodenum and jejunum. Ninety percent(90%) of post-OMR T1-weighted images showed improved signal intensity, opacification and signal homogeneity of the stomach and 80% of score for the duodenum. The improvement in bowel marking parameters were comparable between the two dose groups. There were no statistcally significant differences in organ delineation between the two dose groups.

Intent-To-Treat Analysis - Blinded Reader Ratings of Contrast Efficacy

Image Quality and Artifacts - As summarized in the Spnsor's Table #17, p35), the 0ff-site reader ratings of image quality and artifacts, assuming worst case assessments for the 11 patients without blinded contrast reviews. In the intent-to-treat analysis, all of the pre-and post-OMR images were graded as adequate (good/excellent) quality of 71% in the pre-OMR compared with 64% for the post-OMR images. The quality of pre- and post-contrast scores appear to be slightly better ratings in the 400mg Fe dose group than in the 200mg Fe dose group (76%/76% vs 67%/53%, respectively). Artifacts, however, revealed a statistically significant increase in artifacts from pre-to post-OMR images for both dose groups.

Bowel Marking/Organ Delineation The mean changes in off-site reader ratings and percent of images show at least one unit improvement from pre-to post-OMR in blinded reader assessments of signal intensity, opacification, signal homogeneity, and gastrointestinal tract distension, assuming worst case assessments for the 11 patients without off-site contrast reviews (ref. Tables 18 & 19. p36 & 38).

All in all, there were statistically significant ($p<0.001$) increases from pre-to post-OMR image scores for bowel marking parameters. Approximately >90% of post-OMR image scores for signal intensity, opacification, and signal homogeneity of the stomach. Also, over 70% of post-OMR images revealed improved signal intensity, opacification and signal homogeneity of the duodenum and jejunum. As for organ delineation, there were also statistically significant improvements in mean scores from pre-to post-OMR.

The investigator and blinded reader ratings of contrast efficacy were compared using the results of intent-to-treat analysis, in which worst case assessements for the eleven patients without blinded contrast were reviewed.

Image Quality and Artifacts (ref. Table 20 Vol.33. p-39)

The post-contrast image quality (good/excellent) was graded 64% (73/114) for the blinded reader vs 90% (103/114) with the on-site reader. Artifacts of 55% (63/114) vs 76% (87/114) of post-OMR scans rated (none or minimal) artifacts, while severe artifacts showed 19% for the blinded reader vs 1% for the on-site reader.

Bowel Marking /Organ Delineation (ref. Tables 21& 22, p-40-1)

A comparison of on-site and off-site readers "intent-to-treat" bowel marking assessments showed no significant differences between two reader scores with respect to improvements in signal intensity, opacification, signal homogeneity and disstention of the stomach. The off-site reader graded higher scores compared with the on-site reader for the duodenum and jejunum of the four marking parameters. Organ delineation - The on-site reader graded over (75%) improvement score for the delineation of the stomach as compared (31%) with the blinded reader score.

Fast Scan MRI Contrast Efficacy (Subset Analysis)

Images were evaluated for contrast efficacy by both on-site and off-site readers for 42 fast scan T1-weighted series (23 in the 200mg Fe group and 19 in the 400mg Fe group) and 51 fast scan T2-Weighted series (25 in the 200mg Fe group & 26 in the 400mg Fe group). See Table #23. p43.

Fast scan T1-weighted imaging - The overall image quality was graded as adequate (good/excellent) in 83% (35/42) for the on-site assessment versus 55% (22/40) with the blinded reader.
Fast scan T2-weighted imaging - The image quality was graded 69% (35/51) for the on-site assessment versus 41% (21/51) with the blinded reader. Pooled data indicated that the on-site reader was graded somewhat better image score than with the blinded reader. As for artifacts, there were comparable ratings between fast scan T1 and T2-weighted images

Bowel Marking /Delineation (ref. Vol. 33. Tables 24-5. p-44-5)

A comparison of on-site and off-site ratings of bowel marking parameters for fast scan T1 and T2-weighted images showed the results were comparable in both assessments. OMR imporved bowel marking parameters (signal intensity, signal homogeneity, opacification and bowel distention) in most of the cases. The organ delineation parameters also yeilded similar improvement by both assessments.

Safety Results

Safety was assessed by measuring vital signs, blood chemiscal and hematological parameters and adverse events. Both vital ssigns and laboratory parameters were measured prior to 30-60 minutes, and 24 hours post-OMR ingestion. Although some individual variation was noticed, there were no cliniically significant changes or trends in change from baseline value in any of the vital signs and laboratory parameters following the ingestion of OMR.

Iron Metabolism - There were no significant changes in mean values for iron metabolism parameters following OMR ingestion , with exception, however, that pre-and post-OMR mean values for ferritin were abnormally higher in the 400mg Fe dose group compared with 200mg Fe dose group. There were also no significant shifts in iron metabolism parameters. Liver function tests (Sgot, Sgpt, GGT, Alk. phosphatase, Billirubin), however, that mean values were consistently higher in the lower dose group (200mg Fe) compared with the higher dose group (400mg Fe).

Both scatter gram and cross-classification tables showed number of patients had abnormally high pre-OMR values which remained high following OMR ingestion. These abnmorally liver function parameters were related to the patient's underlying disease.

Adverse Events - A total of 20 adverse events, irrespective of drug relationship, were reported (according to Tables 27-8.p-49-0) in 13 of 60 (22%) patients who received 200mg Fe-OMR. By comparison, 23 adverse events were reported in 16 of 54 (30%) patients who received 400 mg Fe OMR. The most frequently occurring adverse events were in the digestive system with (20% in 200mg Fe vs 35% for 400mg Fe-OMR group. No patient reported more than one adverse event and none of the adverse events were severe, or serious with exception of one sickle cell crisis patient who expired 49 days after receiving OMR. Data suggest a trend toward increased adverse events with the 400mg Fe (12g OMR) dose group than in the 200mg Fe (6g OMR) dose group.

Incidence of Adverse Events by Body System

	200mg Fe (6g OMR)					400mg Fe(12g OMR)				
Event Severity	1	2	3	4	Total	1	2	3	4	Total
Pts. Assessed (N=114)					60					54
Pts with AE					13(22%)					16(30%)
Pts with AE grade ≥2					5 (8%)					3(6%)
Body as Whole:					4 (7%)					1(2%)
headache	2	-	-	-	2	1	-	-	-	1
pain	2	-	-	-	2	-	-	-	-	0
Cardiovascular:	-	-	-	-	0	-	-	-	-	1 (2%)
sickle crsis	-	-	-	-	0	-	-	-	1	1
Digestive:					12(20%)					19(35%)
constipation	1	-	1	-	2	-	-	-	-	0
diarrhea	4	1	-	-	5	11	-	2	-	13
nausea	-	1	-	-	1	3	-	-	-	3
abdominal pain	1	-	-	-	1	2	-	-	-	2
rectal pain	-	-	-	-	0	-	-	1	-	1
vomiting	3	-	-	-	3	-	-	-	-	0
Nervous system:					2 (3%)					0
anxiety	-	-	1	-	1	-	-	-	-	0
convulsions	-	-	1	-	1	-	-	-	-	0
insomnia	-	-	1	-	1	-	-	-	-	0
Respiratory system:					1 (2%)					0
epistaxis	1	-	-	-	1	-	-	-	-	0
Skin:					0					1 (2%)
pruritis	-	-	-	-	0	1	-	-		1
Urogenital system:					0					1 (2%)
infection	-	-	-	-	0	1	-	-	-	1
Total	12	2	6	0	20	19	-	3	1	23

Pooled Data - Forty-three (43) adverse events were reported in 29 of the 114 patients (25%). The most frequently occurring adverse events were mild diarrhea (16%), nausea (>3%), vomiting (<3%), abdominal pain (<3%), and headache (<3%) of patients.

Serious/Lifethreatening and/or deaths - The sponsor listed three (#116B, #201B, #707B) patients as serious(1 recovered, 2 deaths). Patient (#201B) was a 63 year-old back female with end-stage of renal disease and with a history of hypertension and insulin-dependent diabetes mellitus. Eight days after completing imaging with OMR, the patient suffered from cardiopulmonary arrest associated with shock, hypoxia, pneumonitis and sepsis. She died 18 days after receving OMR. The other patient (#707B) was a 45 year-old black male with a number years history of sickle cell anemia with disease-related complications. No adverse events were reported within 24 hours following OMR ingestion. Five days after the patient was hospitalized with sickle cell crisis, he soon recovered and was discharged from the hospital 2 days later. Forty-two days later the patient was re-admitted to the hopspital because of reoccurrence of the sickle cell crisis. Shortly thereafter, the patient suffered cardiac arrest and died. These two deaths were unrelated to the drug.

8.0 INTEGRATED SUMMARY OF EFFECTIVENESS

This summary presents an overview of the efficacy of FerriSeltz™ (OMR) as an oral contrast agent to mark upper gastrointestinal tract in patients undergoing diagnostic magnetic resonance imaging (MRI). The proposed clinical dose levels are 200mg Fe (6g OMR) and 400mg Fe (12g OMR).

A total of 275 patients were enrolled in the two clinical trials (six investigators enrolled a total of 160 patients in Portocol 901-03A, and six investigators enrolled a total of 115 patients in Prototcl 901-03B). Both studies used identical protocols. Study patients were predominantly Caucasian (79%; 217/275) and predominantly male (61%; 167/275), but included a wide range of ages. T1-weighted spin echo MRI of the upper abdomen was performed on each patient before and after ingestion of a single or double dose of OMR. All MRI variables were consistent for the pre- and post-OMR imaging series, allowing each patient to serve as his/her own control.

Of the 275 patients enrolled, 267 received the study drug and complete post-OMR imaging; 6 patients did not receive study drug and 2 patients vomited following OMR ingestion. Investigating (on site) radiologists completed side-by-side assessments of pre-and post-OMR images for all 267 patients and 218 patients for blinded (off-site) radiologists. The contrast assessments were focused on the three primary effectiveness criteria: (a. the degree of bowel marking, b. delineation of the bowel from adjacent anatomic landmarks and organs, and c. artifact generation).

Comparison of investigator and blinded reviewer evaluations of contrast efficacy were performed on both an "intent-to-treat" basis, in which worst possible ratings (i.e., no improvement in post-contrast images) were assumed for the 49 patients without blinded contrast reviews, and by a comparison of the 218 patients with both investigator and blinded reviewer ratings.

Contrast Efficacy Data - A direct comparison of the investigator and blinded reviewer ratings of contrast efficacy was performed for the 218 patients with both readers.
By Readers Comparison (on-site vs off-site radiologists) - The overall image quality was graded 80% (175/218) for blinded assessment compared to 94% (206/218) with the on-site assessment. Artifacts (none or minimal) were graded 71% for both readers. However, severe artifacts graded 8% (17/218) vs >1% (3/218), respectively (The following Table 5.27, was adapted from Vol. 26. p-89).

Comparative T_1-W Image Assessment:
FerriSeltz ("OMR") Image Quality and Effect on Artifacts*—
Cases with Both Investigator and Blinded Reviews
Pooled Phase II/III Studies

	200 mg Fe (6 gm OMR)		400 mg Fe (12 gm OMR)	
	Investigator	Blinded Reviewer	Investigator	Blinded Reviewer
No. of Patients Assessed	110	110	108	108
Excellent	28	34	48	32
Good	73	47	57	62
Poor	8	28	3	13
Inadequate	0	1	0	0
Not rated	1	0	0	1
Presence of Artifacts on Post-OMR Images				
None	28	35	27	35
Minimal	52	38	47	46
Moderate	29	21	32	23
Severe	1	13	2	4
Not rated	0	3	0	0

Reviewer's Comments

* The sponsor failed to compare both low and high dose groups. Based upon the data presented, the optimal (good and excellent) image quality would be 92% (199/216) in the high dose group versus 83% (182/220) with the low dose group. Further-more, the severe artifacts would be 3% vs 6%, respectively.

* It is expected that imaging quality assessments were better graded for the on-site reader than with the off-site readers. Conversely, the high dose group showed 9% improvement of imaging quality than low dose group and only 3% of severe artifacts in the high dose group as compared to 6% in the low dose group. With respect to artifacts (none or minimal) , there were no differences between low & high dose groups.

* Clearly, the higher dose group yielded better imaging quality than in the lower dose group regardless of on-site and/or off-site readers assessment.

By Readers Comparison (Comparative T1-weighted image assessment)

A comparison of on-site and off-site reader bowel marking assessments revealed somewhat higher ratings for stomach, duodenum & jejunum marking parameters by the off-site reader compared with the on-site readers . There were no statistically significant differences between on-site vs off-site rating scores. The signal intensity, opacification and signal homogeniety of the stomach were graded over 90% scores by both readers. It is interesting to note that in the high dose group, the marking parameters of the stomach, duodenum, and jejunum generally improved higher ratings as compared with the low dose group. The delineation parameter also yielded similar results (as presented in the sponsor's Table 5.28-9. p 90-91).

Contrast Efficacy Data - (Intention-to-Treat Comparison of On-site and Off-site reader Assessments)

Comparison of on-site and off-site reader evaluations of contrast efficacy were performed on both an intent-to-treat basis, in which worst possible ratings (i.e., no improvement in post-OMR images) were assumed for the 46 patients without blinded contrast reviews.

By Readers Comparison - The overall results of the imaging quality (good and excellent) were graded 66% (176/267) for the off-site assessment compared to 94% (252/267) with the on-site assessment. Minimal or no artifacts showed 58% (155/267) vs 70% (187/267) and severe artifacts graded as 24% (64/267) vs 2% (6(/267), respectively (The following Table 5.30. adapted from Vol. 26. p 92).

Comparative T_1-W Image Assessment:
FerriSeltz ("OMR") Image Quality and Effect on Artifacts—
Intent-to-Treat Analysis*
Pooled Phase II/III Studies

	200 mg Fe (6 gm OMR)		400 mg Fe (12 gm OMR)	
	Investigator	Blinded Reviewer	Investigator	Blinded Reviewer
Number of Patients Assessed	135	135*	132	132*
Quality of Images for Radiologic Assessment:				
Excellent	39	34	60	32
Good	85	48	68	62
Poor	10	51	4	37
Inadequate	0	2	0	0
No rated	1	0	0	1
Presence of Artifacts on Post-OMR Images (blinded reviewer)				
None	34	35	30	35
Minimal	65	39	58	46
Moderate	34	21	39	23
Severe	2	36	4	28
Not rated	0	4	1	0

*** Assumes no improvement in post-contrast images for 46 patients without blinded contrast reviews**

Reviewer's Comments

*** The sponsor provided no dose comparison (200mg Fe vs 400mg Fe-OMR). Based upon the data presented above, the optimal (good and excellent) image quality should be 84% (222/264) for high dose group compared to 76% (206/270) with the low dose group. With respect to none or minimal artifacts shown, there were no differences between the dose groups (64% for each dose group). Severe artifacts should be graded as 12% versus 14%, respectively.**

*** Clearly, by dose comparison however, the higher dose group yielded better improvement than in the lower dose group regardless of on-site or off-site reader assessments.**

By Readers Comparison - (Comparative T1-weighted image assessment)

A comparison of on-site and off-site reader "intent-to-treat" bowel marking assessments, revealed somewhat lower ratings for stomach, and higher ratings for duodenum & jejunum marking parameters by the off-site reader compared with the on-site readers . There were no statistically significant differences between the on-site versus off-site rating scores. The signal intensity, opacification and signal homogeneity of the stomach were graded over 75% scores by both readers. In the delineation parameters also yeilded similar improvements in the organ delineation (stomach, stomach wall, duodenum, jejunum and bowel wall) by both assessments (Table 5.31-2 presented in the Vol. 26. p 93-4).

Reviewer's Comment - Again, in the high dose group (400mg Fe-OMR), the overall bowel marking parameters appear to be better rating scores of the stomach, duodenum and jejunum as compared with the low dose group (200mg Fe-OMR). The organ delineation parameters also yielded similar results by both assessments. Overall, there was somewhat improvement in the rating scores for the high dose group than with the low dose group.

Retrospective Analysis of Clinical Utility

In the U.S. Phase-II/III pivotal clinical trials, while viewing pre-and post-contrast images side-by-side, each investigator indicated on the CRF whether OMR provided additional information that aided in diagnosis or patient management. The investigators summarized that OMR provided additional information that aided in diagnosis in 44% (116/265) of cases and in change patient's management and/or surgical approach in 12% (32/265) of cases.

Clinical Diagnosis (Gold Standard) - A clinical "gold standard" diagnosis was established for each patient, based on a review of all available confirmatory diagnostic data contained in hospital records. These data included discharge summaries, copies of laboratory tests, and reports of diagnostic procedures, including CT, ultrasound, endoscopy, and biopsy. The stomach, duodenum, and pancreas were considered abnormal only if data confirmed the presence of mass lesions or bowel wall thickness.

In 84% (223/264) of cases, gold standard diagnoses were assigned by a reviewing physician. In 16% (41/264) of the cases with missing or conflicting data, a panel of three external experts reviewed the available data and the study pre-contrast MR images in order to reach a consensus on the presence or absence of pathology in the stomach, duodenum, and pancreas. "Gold standard" diagnoses had three levels of certainty, depending on whether they were: (1) proven by surgical or biopsy results; (2) based on non-invasive diagnostic modalities other than the study pre-contrast MRI; or (3) based on available clinical findings and the study pre-contrast MRI, in the absence of biopsy or non-invasive testing. As summarized in the following Table 5.33, a final gold standard diagnosis was established for 264 patients (151 of the 160 patients enrolled in study A, and 113 of the 115 patients enrolled in Study B).

Basis of "Gold Standard" Diagnoses

	Biopsy or Surgery	Imaging Procedures	Clinical History & Study MRI	Total
Stomach:	70	131	60	261
Normal	58	128	59	245
Abnormal	12	3	1	16
Duodenum:	70	131	60	261
Normal	66	130	60	256
Abnormal	4	1	0	5
Pancreas:	70	133	60	263
Normal	42	118	59	219
Abnormal	28	15	1	44
Total Patients:				264
Study A	54	76	21	151
Study B	16	57	40	113

APPEARS THIS WAY
ON ORIGINAL

Study Criteria

Pre- and post-contrast scans from each of the patients for whom a clinical "gold standard" diagnosis could be established were randomized and then assessed independently by two radiologists expert in abdominal MRI. The blinded diagnostic reviewers assessed the stomach, duodenum, and pancreas in each image for the presence or absence of pathology, using a 5-point scale (1=definitely normal, 2=probably normal, 3=uncertain, 4=probably abnormal, 5=definitely abnormal). Ratings for each blinded diagnostic reviewer were then reclassified as normal (scores 1 or 2), abnormal (scores 4 or 5) or uncertain (scores of 3), and 3x3 tables constructed to compare pre- and post-contrast evaluations of the stomach, duodenum, and pancreas by each reviewer. For each blinded diagnostic reviewer and organ, 3x3 tables were constructed for gold standard normals and abnormals separately, and Stuart-Maxwell chi-square tests were then applied to evaluate the change in each reviewer's diagnostic judgment, allowing for shifts into or out of the "uncertain" category into the correct normal or abnormal categories.

As summarized, the Stuart-Maxwell statistical Table 5.34 reveales highly significant differences ($p<0.001$) between pre-and post-OMR ratings for patients with a "gold standard" normal diagnosis of the stomach, duodenum (both readers) and pancreas (reader #1), in the total study population as well as in 3 subgroups.

Diagnosis of the Stomach - As summarized, the McNemar statistical Table 5.35. shows that OMR had a statistically significant ($p<0.001$) on the diagnostic accuracy & specificity for both blinded readers in all 6 populations analyzed. While blinded reader (#1) achieved 87% accuracy and 90% specificity, blinded reader (#2) obtained 75% accuracy and 77% specificity for the stomach.

Diagnosis of the Duodenum - As summarized, the McNemar statistical Table 5.36. shows that OMR had a statistically significant ($p<0.001$) on the diagnostic accuracy and specificity for both blinded readers in all 6 populations analyzed. While blinded reader (#1) achieved 86% accuracy and 87% specificity, blinded reader (#2) obtained 56% accuracy and 56% specificity for the duodenum. Too few patients had duodenal abnormalities in this study to allow for reliable estimates of sensitivity.

Diagnosis of the Pancreas - As summarized, the McNemar statistical Table 5.37. shows that OMR had a statistically significant ($p<0.001$) on the diagnostic accuracy & specificity achieved by blinded reader (#1) in 5 of the 6 populations analyzed. While blinded reader (#1) achieved more improvement in accuracy (77% post- vs 67% pre-OMR) and specificity (82% post- vs 70% pre-OMR) of the pancreas, both blinded readers achieved comparablity in accuracy (67% vs, 64%), specificity (70% vs 68%), and sensitivity (50% vs 48%) for pre-contrast images.

Additional Information that aided in Diagnosis or Patient Management

The investigators presented that OMR provided information that aided for diagnosis in 44% (116/265) of cases and which change in diagnosis, patient management, or surgical approach in 12% (32/265) of cases. Twenty-three (23) of the 24 cases summarized the use of OMR which enabled one or both of the blinded readers to have increased confidence in excluding pathology in the upper gastrointestinal tract in patients undergoing T1-weighted MRI. OMR enabled the blinded readers to correctly identify the normal findings of the stomach and duodenum in 19 patients undergoing MRI to evaluate the liver or pancreas, in three patients for gastric masses, and one patient with bowel obstruction. In 11 of the cases demonstrated, the use of OMR enabled a blinded reader to correctly identify the presence of an abnormality in the stomach, duodenum, or pancreas (see case reports as follows).

Table 5.38. **Case Studies: Examples Where FerriSeltz ("OMR") Provided Additional Radiologic Information that Aided in Diagnosis or Patient Management**

Study-Case No.	Reason for MRI	Pre-Contrast MRI	Post-Contrast MRI
A-118	Evaluate liver and upper GI tract in patient with hepatoma and possible diverticulum	Both blinded reviewers rated stomach and duodenum "uncertain" but noted "liver lesion"	Both blinded reviewers correctly identified "normal" stomach and duodenum– diverticulum in jejunum, not duodenum
A-119	Evaluate possible mass at porta hepatis	Both blinded reviewers rated stomach and duodenum "uncertain" and reviewer #1 rated pancreas "uncertain"	Both blinded reviewers correctly identified "normal" stomach, duodenum, and pancreas –liver mass was not invading stomach, which aided in surgical decision
A-124	Evaluate liver for evidence of transplant rejection vs. recurrence of hepatoma	Both blinded reviewers rated stomach and duodenum "uncertain" and reviewer #1 rated pancreas "uncertain"	Both blinded reviewers correctly identified "normal" stomach and pancreas and reviewer #1 correctly identified "normal" duodenum. Investigator noted fibrosis at edge of liver
A-131	Evaluate abdomen and liver to assess colon cancer metastasis	Blinded reviewer #1 rated pancreas "uncertain" and blinded reviewer #2 rated stomach and duodenum "uncertain"	Both blinded reviewers correctly identified "normal" stomach, duodenum, and pancreas; OMR improved visualization of liver mets and extrahepatic lymph nodes
A-201	Evaluate patient with gastrinoma and liver mets presenting with hepatomegaly to determine possibility for repeat chemotherapy	Both blinded reviewers rated stomach "uncertain"	Both blinded reviewers correctly identifed "abnormal" stomach, with marked gastric wall thickening and fold enlargement

Case Studies: Examples Where FerriSeltz ("OMR") Provided Additional Radiologic Information that Aided in Diagnosis or Patient Management, continued

Study-Case No.	Reason for MRI	Pre-Contrast MRI	Post-Contrast MRI
A-203	Evaluate mass in left flank to determine origin and select medical or surgical management	Blinded reviewer #2 rated stomach and duodenum "uncertain"	Both blinded reviewers correctly identified "normal" duodenum and "abnormal" stomach and pancreas– OMR enabled visualization of a large mass and localized it as arising from the upper pole of the left kidney and involving the tail of the pancreas and greater curvature of the stomach
A-208	Evaluate possible mass in head of pancreas in patient presenting with tenderness in left upper quadrant	Blinded reviewer #1 rated duodenum and pancreas "uncertain" and blinded reviewer #2 rated stomach and duodenum "uncertain"	Both blinded reviewers correctly identified "normal" stomach and duodenum and blinded reviewer #1 correctly identified "abnormal" pancreas (mass in head)
A-215	Confirm diagnosis and select appropriate therapy in patient with pancreatic cancer presenting with jaundice and tenderness in right upper quandrant	Both blinded reviewers rated stomach "uncertain" and blinded reviewer #2 also rated duodenum and pancreas "uncertain"	Both blinded reviewers correctly identified "normal " stomach and "abnormal" pancreas, confirming mass in head of pancreas and eliminating extension into the stomach
A-218	Evaluate patient with inoperable pancreatic cancer for possible radiation therapy	Blinded reviewer #2 rated stomach "uncertain", duodenum "abnormal", and pancreas "normal"	Blinded reviewer #2 correctly identified "normal" stomach and "abnormal" pancreas, confirming mass in head of pancreas, and rated duodenum "uncertain"
A-220	Evaluate patient with von Hippel Lindau syndrome and pancreatic cysts	Both blinded reviewers rated "uncertain" and blinded reviewer #2 also rated stomach "uncertain"	Both blinded reviewers correctly identified "normal" stomach and "abnormal" pancreas; blinded reviewer #1 also correctly identified "normal" duodenum

Case Studies: Examples Where FerriSeltz ("OMR") Provided Additional Radiologic Information that Aided in Diagnosis or Patient Management, continued

Study-Case No.	Reason for MRI	Pre-Contrast MRI	Post-Contrast MRI
A-253	Evaluate patient with pancreatitis presenting with post-prandial pain	Blinded reviewer #2 rated stomach and duodenum "uncertain"	Both blinded reviewers correctly identified "normal" stomach and duodenum and "abnormal" pancreas; OMR enabled clear delineation of the duodenum as separate from the cystic mass in the head of the pancreas
A-255	Evaluate patient with pancreatic cancer with liver mets prior to 3rd course of chemotherapy	Both blinded reviewers rated stomach and duodenum "uncertain" and blinded reviewer #1 rated pancreas "normal"	Both blinded reviewers correctly identified "normal" duodenum and blinded reviewer #1 also correctly identified "normal" stomach and "abnormal" pancreas; OMR helped delineate the pancreatic tail mass from the stomach and
A-260	Evaluate patient to differentiate between metastatic pancreatic cancer (original dx) and neuroendocrine tumor	Blinded reviewer #2 rated stomach and duodenum "uncertain"	Both blinded reviewers correctly identified "normal" duodenum and "abnormal" stomach and pancreas; OMR enabled clear delineation of the stomach from the pancreatic mass which was displacing the stomach
A-306	Evaluate patent with pancreatic cancer for potential chemotherapy	Both blinded reviewers rated stomach and duodenum "uncertain" and blinded reviewer #1 also rated pancreas "uncertain"	Both blinded reviewers correctly identifid "normal" stomach and "abnormal" pancreas' OMR enhanced delineation of organs

Case Studies: Examples Where FerriSeltz ("OMR") Provided Additional Radiologic Information that Aided in Diagnosis or Patient Management, continued

Study-Case No.	Reason for MRI	Pre-Contrast MRI	Post-Contrast MRI
A-405	Evaluate jaundiced patient with metastatic ovarian cancer for liver mets vs. biliary obstruction	Blinded reviewer #1 rated stomach and pancreas "uncertain" and blinded reviewer #2 rated stomach and duodenum "uncertain"	Both blinded reviewers correctly identified "normal" stomach, duodenum, and pancreas; OMR helped visualize malignant ascites in peritoneum
A-410	Evaluate patient with pancreas cancer presenting with mild distention and tenderness in abdomen	Blinded reviewer #1 rated stomach, duodenum and pancreas "uncertain" and blinded reviewer #2 rated duodenum "uncertain" and pancreas "normal"	Both blinded reviewers correctly identified "normal" stomach; blinded reviewer #1 correctly identified "normal" duodenum; and blinded reviewer #2 correctly identified "abnormal" pancreas; Investigator noted that OMR enhanced delineation of the duodenum
A-420	Evaluate patient with pancreatitis and abnormal liver function tests	Blinded reviewer #1 rated duodenum "uncertain" and blinded reviewer #2 rated stomach and duodenum "uncertain"	Both blinded reviewers correctly identified "normal" stomach and pancreas. and blinded reviewer #1 also correctly identified "normal" duodenum; OMR helped delineate and identify the duodenum and inflammation of the abdominal wall and right upper quandrant of the abdominal cavity
A-423	Evaluate patient with pancreatitis presenting with mild upper abdominal fullness and weight loss	Both blinded reviewers rated duodenum "uncertain" and correctly identified "abnormal" pancreas	Blinded reviewer #1 correctly identified "normal" duodenum, but blinded reviewer #2 still rated duodenum "uncertain"; Investigator noted that OMR improved delineation of stomach and duodenum

Case Studies: Examples Where FerriSeltz ("OMR") Provided Additional Radiologic Information that Aided in Diagnosis or Patient Management, continued

Study-Case No.	Reason for MRI	Pre-Contrast MRI	Post-Contrast MRI
A-429	Evaluate gastric pathology in patient presenting with melena, weakness, and iron-deficiency anemia	Blinded reviewer #2 rated stomach, duodenum and pancreas "uncertain"	Blinded reviewer #2 correctly identified "abnormal" stomach and "normal" duodenum and pancreas; OMR helped visualize infiltrating tumor in the antrum of stomach
A-506	Evaluate patient with breast cancer, presenting with ascites and bowel obstruction, for possible abdominal mets	Blinded reviewer #2 rated duodenum and pancreas "uncertain"	Blinded reviewer #2 correctly identified "normal" stomach, duodenum and pancreas; Investigator noted that OMR helped differentiate the bowel from mesenteric tumor
B-102	Evaluate pancreas and liver to diagnose cause of obstructive jaundice	Blinded reviewer #2 rated stomach and duodenum "uncertain", but correctly identified "abnormal" pancreas	Blinded reviewer #2 correctly identified "normal" stomach and duodenum and "abnormal" pancreas
B-403	Verify diagosis of pancreatic cancer	Both blinded reviewers rated duodenum "uncertain" and blinded reviewer #2 also rated stomach "uncertain"	Both blinded reviewers correctly identified "normal" stomach and duodenum and "abnormal" pancreas (mass in head)
B-619	Evaluate liver lesions and abdominal cavity in patient with hepatic and renal cysts presenting with pain in upper quadrant	Both blinded reviewers rate stomach and duodenum "uncertain"	Both blinded reviewers correctly identified "normal" stomach, duodenum and pancreas; Investigator noted liver cyst and thickened esophageal wall, but no stomach involvement
B-626	Evaluate stomach in patient with gastric mass presenting with loss of appetite	Both blinded reviewers raed stomach and duodenum "uncertain" and blinded reviewer #2 also rated pancreas "uncertain"	Both blinded reviewers correctly identified "abnormal" stomach and "normal" duodenum and pancreas

Analysis Of Dose-Response - As presented in the Table below, the overall trend toward higher ratings of the contrast efficacy in 400mg Fe/12g is compared with the 200mg Fe/6g OMR group.

Comparative T_1-W Image Assessments:

Percent Images Showing Improvement in Bowel Marking with FerriSeltz™ ("OMR"):

Comparison of High and Low Doses

	Investigators			Blinded Reviewers		
	200mg Fe (6 g OMR)	400 mg Fe (12 g OMR)	Between Group p-value	200 mg Fe (6 g OMR)	400 mg Fe (12 g OMR)	Between Group p-value
No. Patients Assessed	135	132		110	108	
Signal Intensity						
Stomach	86%(113/131)	91%(120/132)	0.251	96%(106/110)	98%(104/106)	0.683
Duodenum	52% (68/131)	62% (80/130)	0.134	87% (96/110)	94%(100/106)	0.100
Jejunum	42% (55/131)	59% (75/128)	0.009	71% (78/110)	79% (84/107)	0.215
Opacification						
Stomach	86%(113/131)	93%(123/132)	0.071	95%(104/109)	98%(104/106)	0.446
Duodenum	53% (70/131)	63% (82/130)	0.132	83% (90/109)	89% (94/106)	0.295
Jejunum	39% (51/130)	58% (74/128)	0.004	75% (82/109)	79% (84/107)	0.630
Signal Homogeneity						
Stomach	89%(117/131)	96%(127/132)	0.034	95%(105/110)	98%(104/106)	0.446
Duodenum	50% (65/131)	58% (75/130)	0.215	83% (91/110)	90% (96/107)	0.169
Jejunum	40% (52/131)	52% (66/128)	0.062	76% (83/109)	79% (85/108)	0.746
Distention						
Stomach	89%(117/131)	89%(118/132)	1.000	86% (95/110)	93% (99/107)	0.186
Duodenum	40% (53/131)	48% (63/130)	0.214	58% (64/110)	65% (70/107)	0.328
Jejunum	28% (37/130)	40% (51/128)	0.066	39% (43/110)	45% (49/108)	0.411
Delineation of GI Tract						
Stomach	76%(100/131)	83%(109/131)	0.218	59% (65/110)	73% (77/106)	0.045
Stomach wall	73% (96/131)	89%(117/131)	0.001	65% (72/110)	76% (81/106)	0.099
Duodenum	45% (59/131)	58% (75/129)	0.036	45% (50/110)	58% (62/107)	0.078
Jejunum	26% (34/131)	48% (61/127)	<0.001	44% (48/109)	54% (58/108)	0.175
Bowel wall	29% (38/133)	41% (53/128)	0.038	21% (23/110)	24% (26/107)	0.627

*** Based on Fisher's Exact test (2-tailed)**

Subsets Analysis of the Overall Population - There were no consistent differences in contrast efficacy for demographic parameters.

Comparative T_1-W Image Assessment:

Percent Images Showing Significant or Moderate Improvement in Bowel Marking•**

Effects of Sex, Race, and Age

Pooled Phase II/III Studies

Investigator Ratings

	Total	Male	Female	Between Group p-value*	White	Other	Between Group p-value*	<65yr	≥65yr	Between Group p-value*
# Subjects	267	164	103		210	57		170	97	
Signal Intensity										
Stomach		86%	89%	0.458	87%	88%	1.000	87%	88%	1.000
Duodenum		52%	60%	0.255	54%	61%	0.368	59%	48%	0.096
Jejunum		49%	48%	0.802	44%	65%	0.007	54%	39%	0.022
Opacification										
Stomach		85%	94%	0.019	88%	91%	0.641	91%	84%	0.074
Duodenum		56%	58%	0.800	53%	70%	0.024	62%	48%	0.040
Jejunum		48%	46%	0.802	42%	63%	0.007	51%	39%	0.074
Signal Homogeneity										
Stomach		88%	96%	0.042	91%	93%	0.793	94%	88%	0.115
Duodenum		52%	52%	1.000	50%	61%	0.137	55%	48%	0.373
Jejunum		43%	46%	0.800	39%	65%	<0.001	47%	39%	0.249
Distention										
Stomach		85%	92%	0.121	87%	91%	0.495	89%	87%	0.696
Duodenum		42%	46%	0.613	42%	47%	0.548	47%	37%	0.125
Jejunum		35%	30%	0.504	32%	37%	0.526	37%	26%	0.078
Delineation of GI Tract										
Stomach		77%	81%	0.543	80%	74%	0.367	79%	76%	0.644
Stomach wall		77%	83%	0.274	79%	84%	0.453	85%	70%	0.004
Duodenum		49%	52%	0.616	47%	63%	0.036	55%	41%	0.031
Jejunum		38%	41%	0.702	31%	53%	0.008	43%	23%	<0.001
Bowel wall		36%	31%	0.429	31%	46%	0.042	37%	29%	0.183

Comparative T_1-W Image Assessment:

Percent Images Showing Significant or Moderate Improvement in Bowel Marking•**

Effects of Sex, Race, and Age

Pooled Phase II/III Studies

Blinded Reviewer Ratings

	Total	Male	Female	Between Group p-value*	White	Other	Between Group p-value*	<65yr	≥65yr	Between Group p-value*
# Subjects	218	134	84		171	47		144	74	
Signal Intensity										
Stomach		96%	98%	0.714	97%	94%	0.374	97%	95%	0.448
Duodenum		92%	87%	0.256	89%	91%	0.791	93%	84%	0.055
Jejunum		78%	69%	0.202	75%	72%	0.710	77%	69%	0.195
Opacification										
Stomach		94%	98%	0.323	96%	94%	0.452	98%	92%	0.092
Duodenum		86%	82%	0.566	84%	87%	0.654	89%	76%	0.017
Jejunum		81%	69%	0.072	77%	72%	0.562	80%	69%	0.093
Signal Homogeneity										
Stomach		95%	98%	0.488	96%	94%	0.409	97%	93%	0.172
Duodenum		88%	82%	0.237	84%	91%	0.246	90%	78%	0.039
Jejunum		81%	71%	0.137	78%	72%	0.434	79%	73%	0.312
Distention										
Stomach		86%	94%	0.075	89%	89%	1.000	89%	89%	1.000
Duodenum		60%	63%	0.775	59%	70%	0.180	64%	57%	0.309
Jejunum		46%	36%	0.159	40%	49%	0.320	43%	41%	0.773
Delineation of GI Tract										
Stomach		59%	75%	0.019	62%	77%	0.083	69%	57%	0.072
Stomach wall		64%	80%	0.015	69%	74%	0.590	71%	69%	0.876
Duodenum		46%	61%	0.037	47%	66%	0.032	59%	36%	0.002
Jejunum		51%	44%	0.330	48%	51%	0.744	47%	51%	0.571
Bowel wall		22%	24%	0.741	23%	21%	1.000	22%	24%	0.732

* **Based on Fisher's Exact test (2-tailed)**

Image Quality Assessment by the On-site Radiologists - The overall image quality (good/excellent) was graded 57% (93/164) for male versus 94% (97/103) with the female population, 46% (97/210) for Caucasian versus 150% (86/57) with the non-caucasian, and 56% (96/170) for less than 65 versus 95% (92/97) with greater than 65 years of age group. Artifacts (none/minimal) were graded 45% (74/164) vs 62% (64/103), 33% (71/210) vs 120% (68/57), and 39% (66/170) vs 80% (78/97), respectively.

Image Quality Assessment by the Off-site Radiologists - The overall image quality (good/excellent) was graded 55% (73/134) for male versus 110% (92/84) with the female population, 48%(82/171) for Caucasian vs 160% (75/47) with the non-caucasian, and 55% (79/144) for less than 65 versus 112% (83/74) with greater than 65 years of age group. Artifacts (none/minimal) were graded 45% (60/134) vs 103% (87/84), 43% (73/171) vs 125%(59/47), & 49%(71/144) vs 94%(70/74), respectively. Data indicates that the image quality ratings were statistically significant with the females population, non-caucasion and >65 years of age compared with males, caucasion and < 65 years of age by both on-site and off-site Radiologists. The artifacts however, yielded similar results (see Tables below):

A. Investigator Ratings

	Total	Male	Female	Between Group p-value*	White	Other	Between Group p-value*	<65yr	≥65yr	Between Group p-value*
# Subjects	267	164	103		210	57		170	97	
Excellent		30%	49%	0.001	41%	23%	0.001	40%	32%	0.093
Good		63%	48%		56%	63%		56%	60%	
Poor		7%	3%		3%	14%		4%	8%	
Inadequate		0	0		0	0		0	0	
Not rated		0	1%		<1%	0		1%	0	
Effect of OMR on Artifacts										
None		26%	20%	0.076	25%	21%	0.596	22%	27%	0.071
Minimal		48%	44%		46%	47%		44%	51%	
Moderate		24%	33%		27%	30%		32%	20%	
Severe		2%	3%		2%	2%		2%	2%	
Not rated		1%	0		<1%	0		0	1%	

B. Blinded Reviewer Ratings										
				Between Group			Between Group			Between Group
	Total	Male	Female	p-value*	White	Other	p-value*	<65yr	≥65yr	p-value*
# Subjects	218	134	84		171	47		144	74	
Quality of Post-OMR Images for Radiologic Assessment										
Excellent		22%	44%	<0.001	32%	26%	0.345	35%	22%	0.249
Good		51%	48%		50%	49%		44%	61%	
Poor		26%	7%		18%	23%		19%	18%	
Inadequate		1%	0		1%	0		1%	0	
Not rated		1%	1%		0	2%		1%	1%	
Presence of Artifacts in Post-OMR Images										
None		25%	43%	<0.001	30%	38%	0.530	37%	23%	0.212
Minimal		35%	44%		43%	21%		34%	47%	
Moderate		27%	10%		18%	28%		22%	18%	
Severe		11%	2%		6%	13%		7%	9%	
Not rated		1%	1%		2%	0		1%	3%	

* Based on Wilcoxon rank sum test

A Comparison of Field Strength (high 1.5T and low .35-.5T range)

As summarized in the Table below, there are no significant differences between the two readers. According to on-site radiologist ratings, however, there were statistically significant (H vs L) $p<0.001$ of the signal intensity, signal homogeneity and delineation of the stomach and stomach wall.

The overall image quality ratings appears to be better scored with the low field strength than in the high field strength for both readers. As for on-site reader assessment, however, there was a statistically of 25% (48/190) significance in the high field vs 12% (9/77) with the low field strength, ($p<0.001$) of the excellent scores. The off-site reader assessment yielded similar results of 28% versus 16%.

Comparative T_1-W Image Assessment:

Percent Images Showing Significant or Moderate Improvement in Bowel Marking•**

Effects of Field Strength

Pooled Phase II/III Studies

	Investigator Ratings				Blinded Reviewer Ratings			
	Total	High Field (1.5T)	Low Field (.35-.5T)	Between Group p-value*	Total	High Field (1.5T)	Low Field (.35-.5T)	Between Group p-value*
# Subjects	**267**	**190**	**77**		**218**	**142**	**76**	
Signal Intensity								
Stomach		**92%**	**75%**	**<0.001**		**96%**	**96%**	**1.000**
Duodenum		**58%**	**49%**	**0.223**		**91%**	**88%**	**0.638**
Jejunum		**47%**	**53%**	**0.348**		**75%**	**72%**	**0.630**
Opacification								
Stomach		**92%**	**81%**	**0.019**		**96%**	**95%**	**0.742**
Duodenum		**57%**	**56%**	**0.892**		**87%**	**80%**	**0.242**
Jejunum		**44%**	**53%**	**0.223**		**77%**	**74%**	**0.617**
Signal Homogeneity								
Stomach		**95%**	**82%**	**0.001**		**96%**	**96%**	**1.000**
Duodenum		**52%**	**53%**	**0.893**		**88%**	**82%**	**0.224**
Jejunum		**42%**	**51%**	**0.221**		**77%**	**76%**	**0.867**
Distention								
Stomach		**91%**	**81%**	**0.022**		**92%**	**83%**	**0.042**
Duodenum		**45%**	**40%**	**0.586**		**68%**	**50%**	**0.013**
Jejunum		**34%**	**31%**	**0.774**		**44%**	**38%**	**0.392**
Delineation of GI Tract								
Stomach		**84%**	**64%**	**<0.001**		**68%**	**59%**	**0.184**
Stomach wall		**87%**	**62%**	**<0.001**		**74%**	**63%**	**0.120**
Duodenum		**51%**	**49%**	**0.373**		**53%**	**49%**	**0.573**
Jejunum		**34%**	**39%**	**0.483**		**51%**	**45%**	**0.477**
Bowel wall		**33%**	**36%**	**0.670**		**25%**	**17%**	**0.173**

*** Based on Fisher's Exact test (2-tailed)**

Comparative T_1-W Image Assessment:

FerriSeltz™ ("OMR") Image Quality and Effect on Artifacts—

Effects of Field Strength

Pooled Phase II/III Studies

	Investigator Ratings				Blinded Reviewer Ratings			
	Total	High Field (1.5T)	Low Field (.35-.5T)	Between Group p-value*	Total	High Field (1.5T)	Low Field (.35-.5T)	Between Group p-value*
# Subjects	267	190	77		218	142	76	
Excellent		48%	9%	<0.001		40%	12%	<0.001
Good		48%	79%			44%	62%	
Poor		3%	12%			16%	25%	
Inadequate		-0-	-0-			-0-	3%	
Not rated		1%	-0-			-0-	-0-	
Presence of Artifacts in Post-OMR Images								
None		25%	22%	0.427		35%	28%	0.197
Minimal		47%	44%			39%	37%	
Moderate		25%	32%			18%	24%	
Severe		3%	1%			7%	9%	
Not rated		1%	-0-			1%	3%	

* Based on Wilcoxon rank sum test

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9.0 INTEGRATED SUMMARY OF SAFETY

This summary presents an overview of the safety of FerriSeltz™ (OMR) as an oral contrast agent to mark the upper gastrointestinal tract in patients undergoing diagnostic magnetic resonance imaging (MRI). The proposed clinical dose levels were of 200 mg Fe/600mL (6g OMR) and 400mg Fe/600mL (12g OMR).

Three studies were conducted in the U. S.; One Phase-1 study (protocol 901-01) and two Phase-II/III studies (protocol 901-03A and 901-03B). Two additional non-U.S. clinical studies were conducted in the Far East(Japan); one Phase-1 dose-finding study of OMR in patient with abdominal disease, and other one Phase-II/IIIA study for efficacy evaluation of OMR in patients undergoing MRI of the upper abdomen. A total of 339 patients (64 Phase-1, 275 Phase-II/III) were dosed in the three U.S. clinical trials and 260 patients (91 Phase-1, 169 Phase-II/III) were dosed in the non-U.S. trials. Additional multicenter studies were conducted in Japan with a total of 454 subjects in 11 English translations from the original Japanese published articles with no raw data provided.

Low dose group (200mg Fe-OMR) was given to 138 patients (84 males and 54 females) ranging in age from (mean 60.0 years) and weighing from (mean 157.0 lbs).

High dose group (400mg Fe-OMR) was given to 137 patients (83 males and 54 females) ranging in age from (mean 57.5 years) and weighing from mean 158.3 lbs).
These two groups comparable with respect to the demographic parameters. Race however, was unevenly distributed.

Of the 275 patients enrolled, 98% (269) of the patients received the study drug, which was evaluated for its safety (138 in the 200mg Fe group and 133 in the 400mg Fe group). A total of 267 patients (135 in the 200mg Fe group and 132 in the 400mg Fe group) had investigator assessments of contrast efficacy. There were 218 of 267 (81%) patients which were included in the blinded reader assessment. Fast Scan T1 images were acquired for 143 patients and 78 patients for T2 weighted images (see Table below).

Total Number of Patients Enrolled (Pooled A and B)

	200mg Fe (6g-OMR)		400mg Fe (12g -OMR)		Sub-Total	Grand Total
Total Pts Enrolled	78	60	82	55	160/115	275
Site	A	B	A	B	AA/BB	
01A / O1B	15	10	16	9	31 / 19	50
O2A / O2B	15	3	15	3	30 / 6	36
O3A / O3B	6	4	6	3	12 / 7	19
O4A / O4B	19	10	19	19	38 / 29	67
O5A / O5B	9	16	10	14	19 / 30	49
O6A / O6B	14	17	16	17	30 / 34	64

Patients Evaluable for Safety and Efficacy (Pooled A and B)

	200mg Fe (6g-OMR)		400mg Fe (12g -OMR)		Sub-Total	Grand Total
Total Pts Enrolled	78	60	82	55	138/137	275
Site	A	B	A	B	AB / AB	
Pts. Received Study Drug(1)	76	60	79	54	136 / 133	269
Pts./w Pre-/Post-OMR(2)	75	59	76	54	134 / 130	264
Investigator Assessment(3)	75	60	78	54	135 / 132	267
Blinded Reader Assessment(4)	57	53	58	50	110 / 108	218
Fast Scan T1-W Images(5)	46	27	49	21	73 / 70	143
Fast Scan T2-W Images(5)	15	22	17	24	37 / 41	78

Study-A : 1) 7 patients had no post-OMR imaging(2 vomited following OMR ingestion & 5 did not receive study drug). 2) 38 patients(17, 6g group and 21, 12g group) did not have blinded contrast assessment, and 7 patients who did not undergo post-OMR imaging. 3) Performed at the option of the investigator. 4) All patients who received study drug were included in the safety analysis, except 5 (113A, 128A, 432A, 504A, 508A,) did not receive study drug. 5) 4 patients did not have a day 2 laboratory assessment.

Study-B: 1) One patient enrolled in the study and did not receive study drug. 2) One patient did not have a day 2 laboratory assessment. 3) One patient refused to participate in the study. 4) 8 patients enrolled (5 in the 6g group, 3 in the 12g group) did not undergo blinded contrast assessment. 5) Performed at the option of the investigator.

Demographics Data and Other Characteristics

Demography - Twelve (12) study sites enrolled a total of 275 patients with known or suspected upper abdomenal disease (data pooled by dose):

	Pooled Phase II/III Studies		
	200 mg Fe (6 gm OMR)	400 mg Fe (12 gm OMR)	Total
Number of Patients Enrolled	138	137	275
Age (years)			
Mean ± S.E.	60.0 ± 1.4	57.5 ± 1.20	58.8 ± 0.90
Range:			
<35	12	8	20
35 - 49	27	29	56
50 - 64	43	57	100
≥65	56	43	99
Sex			
Male	84	83	167
Female	54	54	108
Race			
Caucasian	117	100	217
Black	10	15	25
Hispanic	8	7	15
Asian	3	9	12
Other	0	6	6
Height (inches)			
Mean ± S.E.	67.0 ± 0.32	67.3 ± 0.34	67.1 ± 0.23
Range			
Weight (pounds)			
Mean ± S.E.	157.0 ± 2.84	158.3 ± 2.94	157.6 ± 2.04
Range			
<100	1	1	2
100 - 149	58	56	114
150 - 199	64	63	127
200+	14	15	29
Not reported	1	2	3

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No apparent difference between the dose group was noted. However, race was unevenly distributed.

As summarized in Table below, the two randomized dose groups were comparable in terms of diagnosis of enrollment. Overall, 37% of patients enrolled were undergoing diagnostic MRI to evaluate possible but unconfirmed disease (27%) with unknown diagnosis and 10% with possible recurrent or metastatic disease). About 1/4 of patients were undergoing diagnostic MRI for evaluation of liver disease.

	Pooled Phase II/III Studies		
	200 mg Fe (6 gm OMR)	400 mg Fe (12 gm OMR)	Total
Number of Patients Enrolled	138	137	275
Diagnosis at Enrollment:*			
Pancreatic	23 (17%)	23 (17%)	46 (17%)
Adenocarcinoma	3	5	8
Neuroendocrine	3	1	4
Masses (pathology unknown)	12	7	19
Pancreatitis	5	8	13
Pancreatic cyst	0	2	2
Gastrointestinal	13 (9%)	13 (9%)	26 (9%)
Adenocarcinoma	7	8	15
Neuroendocrine	2	0	2
Masses (pathology unknown)	3	2	5
Other	1	3	4
Hepatic	34 (25%)	28 (20%)	62 (23%)
Adenocarcinoma	6	1	7
Hepatic metastatic disease	10	11	21
Masses (pathology unknown)	9	10	19
Other	9	6	15
Other abdominal metastatic disease	4 (3%)	1 (1%)	5 (2%)
Possible recurrent/metastatic disease	13 (9%)	15 (11%)	28 (10%)
Other organ systems	12 (9%)	21 (15%)	33 (12%)
Neoplastic disease	2	8	10
Masses (pathology unknown)	5	4	9
Miscellaneous	5	9	14
Unknown	39 (28%)	86 (26%)	75 (27%)

U.S. Phase-1 Study

A total of 64 normal healthy volunteers were enrolled. All 64 subjects were evaluated for safety (59 male and 5 female subjects). The majority of the subjects were Caucasian, 4 Asian and one Hispanic.

With respect to drug tolerance, no serious adverse effects were encountered in the subjects studied. Forty-nine(49) of 64 (76%) subjects reported at least one adverse effect. The most frequently occurring adverse effects were diarrhea (<22%), loose bowel (<17%), nausea (>7%), abdominal pain (7%), and headache (3%). Additionally, isolated occurrences, such as dizziness, insomnia, drowsiness, malaise, hematuria and constipation were also recorded during the study.

U.S. Phase-II/III Clinical Trials

A total of 275 patients was studied. Of the 269 patients who received the study drug and who were included in the safety analysis, 6 patients did not receive the study drug (113A, 128A, 432A, 504A, 508A, and 105B). Thirty-five (35) of 136 (26%) patients who received 200mg Fe-OMR group and 49 of 133 (37%) patients who received 400mg Fe OMR group experienced a total of 53 and 75 adverse events, respectively. The most frequently occurring adverse effects were diarrhea (10% in 200mg Fe vs 27% in the 400mg Fe group), abdominal pain (3% in the 200mg Fe vs 8% in the 400mg Fe group), nausea (4% in the 200mg Fe vs 7% in the 400mg Fe group), vomiting 2% for each drug group and headache also had 4% of each drug group. Overall, the incidence of adverse effects were much greater in the 400mg Fe-OMR group than in the low dose group (200mg Fe OMR group). In the 400mg Fe group, there were 37% of patients who experienced a clinical adverse event, 35% of patients who experienced digestive system events (diarrhea, abdominal pain, nausea & vomiting) and body as whole (headache and pain). There was no significance between dose groups in the incidence of moderate or severe adverse effects.

In the U.S. dose comparison concurrent controlled studies, there was a trend toward a higher incidence of clinical adverse effects in the 400mg Fe compared with the 200mg Fe group, it did not reach statistical significance (37% vs 26%, p=0.065). see Table below

Incidence of Adverse Events by Body System:
Pooled Phase II.III Studies

Event Severity	Total Adverse Events 200mg Fe (6g OMR)	400mg Fe (12g OMR)	Between Group p-value*	Moderate or Severe Events*** 200mg Fe (6g OMR)	400mg Fe (12g OMR)	Between Group p-value*
Patients Assessed	136	133		136	133	
Patients with AE	35 (26%)	49 (37%)	0.065	13 (10%)	15 (11%)	0.693
Adverse Events by Body System:						
Body as Whole:	8 (6%)	9 (7%)	0.807	3 (2%)	2 (2%)	1.000
— fever	-0-	1 (1%)		-0-	1 (1%)	
— headache	5 (4%)	5 (4%)		1 (1%)	1 (1%)	
— pain	3 (2%)	3 (2%)		2 (1%)	-0-	
Cardiovascular:	2 (1%)	2 (2%)	1.000	-0-	1 (1%)	0.494
— hypotension	1 (1%)	-0-		-0-	-0-	
— sickle crisis	-0-	1 (1%)		-0-	1 (1%)	
— tachycardia	2 (1%)	1 (1%)		-0-	-0-	
Digestive:	27 (20%)	46 (35%)	0.089	9 (7%)	11 (8%)	0.648
— constipation	3 (2%)	-0-		1 (1%)	-0-	
— diarrhea	14 (10%)	36 (27%)		4 (3%)	7 (5%)	
— dyspepsia	1 (1%)	-0-		-0-	-0-	
— flatulence	1 (1%)	1 (1%)		-0-	-0-	
— nausea	6 (4%)	9 (7%)		2 (1%)	3 (2%)	
— pain, abdominal	4 (3%)	10 (8%)		2 (1%)	3 (2%)	
— pain, rectal	-0-	1 (1%)		-0-	1 (1%)	
— vomiting	3 (2%)	3 (2%)		1 (1%)	2 (2%)	
Nervous system:	3 (2%)	-0-	0.247	3 (2%)	-0-	0.247
— anxiety	1 (1%)	-0-		1 (1%)	-0-	
— convulsion s	1 (1%)	-0-		1 (1%)	-0-	
— insomnia	2 (1%)	-0-		2 (1%)	-0-	
Respiratory system:	1 (1%)	2 (2%)	0.619	-0-	1 (1%)	0.494
— coughing	-0-	1 (1%)		-0-	1 (1%)	
— epistaxis	1 (1%)	-0-		-0-	-0-	
— rhinitis	-0-	1 (1%)		-0-	-0-	
Skin:	-0-	1 (1%)	0.494	-0-	-0-	
— pruritis	-0-	1(1%)		-0-	-0-	
Urogenital system:	1 (1%)	1 (1%)	1.000	-0-	-0-	
— dysmenorrhea	1 (1%)	-0-		-0-	-0-	
— I nfection (UTI)	-0-	1 (1%)		-0-	-0-	

As shown in the Table below, the incidence of adverse effects appear to be greater in the female group especially the body as a whole, and the digestive tract than in the male population. There appears to be a higher percentage rate of adverse effects for the caucasian race in comparison with non-caucasian group. In the age group, however, the age group <65 tends to have more adverse effects than in the older age group of >65 years.

Incidence of Adverse Events by Body System and Patient Demographics: Pooled Phase II/III Studies

	Total	Male	Female	White	Non-white	<65 yr	≥65 yr
# Patients	269	164	105	212	57	170	99
% Patients w/AE	31%	28%	35%	33%	25%	36%	21%
Body as Whole:	6%	5%	8%	7%	5%	7%	5%
• fever	<1%	<1%	0	0	2%	1%	0
• headache	4%	2%	6%	4%	4%	4%	3%
• pain	2%	2%	2%	3%	0	2%	2%
Cardiovascular:	1%	2%	1%	1%	2%	1%	1%
• hypotension	<1%	<1%	0	<1%	0	0	1%
• sickle crisis	<1%	<1%	0	0	2%	1%	0
• tachycardia	1%	1%	1%	1%	0	1%	1%
Digestive system:	27%	24%	31%	29%	19%	33%	17%
• constipation	1%	2%	0	<1%	4%	1%	1%
• diarrhea	19%	15%	24%	20%	12%	21%	14%
• dyspepsia	<1%	0	1%	<1%	0	<1%	0
• flatulence	1%	0	2%	1%	0	1%	0
• nausea	6%	3%	10%	6%	4%	7%	3%
• pain, abdominal	5%	5%	5%	5%	5%	6%	3%
• pain, rectal	<1%	1%	0	0	2%	1%	0
• vomiting	2%	2%	3%	2%	2%	2%	3%
Nervous system:	1%	1%	1%	1%	2%	1%	1%
• anxiety	<1%	0	1%	<1%	0	1%	0
• convulsions	<1%	0	1%	<1%	0	1%	0
• insomnia	1%	1%	0	<1%	2%	1%	1%
Respiratory system:	1%	1%	2%	1%	0	1%	1%
• coughing	<1%	0	1%	<1%	0	0	1%
• epistaxis	<1%	0	1%	<1%	0	1%	0
• rhinitis	<1%	1%	0	<1%	0	1%	0
Skin:	<1%	0	1%	<1%	0	1%	0
• pruritis	<1%	0	1%	<1%	0	1%	0
Urogenital system:	1%	0	2%	<1%	2%	1%	1%
• dysmenorrhea	<1%	0	1%	0	0	1%	0
• urinary infection	<1%	0	1%	<1%	2%	0	1%

* A patient may appear more than once within a body system

Subset Analysis of Adverse Effects

Age group (<65 vs >65 years of age)

As summarized in the Tables below the data shows less than 65 years of age tends to have greater adverse effects compared with the older age group for both sex. There were higher percentage rates for adverse effects toward 400mg Fe than in the low dose (200mg Fe OMR) group.

Body Size (<150 lbs vs >150 lbs)

In the female group, there were higher percentage rates for adverse effects in the <150 lbs compared with >150 lbs for both low and high dose groups. In the male population, however, there appeared to be greater adverse effects toward >150 lbs compared with <150 lbs for both low and high dose groups.

Race (Caucasian vs non-caucasian)

Race however, appeared to have a higher percentage rate of adverse effects for the caucasian group than in the non-caucasian group for both low and high dose groups. There was no difference between sex, however. The majority of the adverse events were mild in intensity.

Serious Adverse Events

These events were initially reported in an IND safety (15-Day) reports. There were no life-threatening or serious (death) adverse events encountered during the clinical trials. However, there were 8 patients (129A, 255A, 419A, 425A, 201B, 203B, 511B, 707B) who died witin 5 days to 2 months after the oral contrast (OMR) administration. These patients had pre-existant advanced terminal diseases and their deaths were not related to OMR ingestion. The clinical records & the outcome described are in Vol. 26. p 260136-8).

Adverse Events from Non-U.S. Clinical Trial (European Clinical Experience)

The Otsuka Pharmaceutical Company has been conducting clinical trials of OMR in Belgium and U.K. among terminal patients. There were three serious or life-threatening adverse events presented as follows:

ADRs from European Clinical Experience

Date of Event	Adverse Event	Severity	Dose	Reason for MRI	Outcome
2/1/95	fever, arrhythmia, respiratory depression (12hr post)	life threat	6 g	Staging high grade malignant non-Hodgkins lymphoma (terminal case)	Death due to respiratory arrest after 4 days, attributed to pre-existing infection w/P. carinii
2/24/95	cerebro-vascular disorder (12 hr post)	life threat	6 g	Assess gland involvement in recurrent breast and ovarian carcinomas (terminal case)	Death after 11 days, not attributed to FerriSeltz
7/28/95	lung edema & dyspnea (12 hr post)	life threat	6 g	Assess abdomen	Recovered 1 hr after administration of lasix

Far East (Japan)

FerriSeltz™ has been marketed in Japan since September 1993. During the period from January 1, 1994 to October 1, 1995, 11 adverse drug experiences had been reported. All of these reported events were mild and resolved spontaneously. However, a 78-year odl female patient, developed a retroperitoneal hemorrhage with severe abdominal pain one hour following ingestion of OMR. She was diagnosedin having pancreatitis (see Table below);

ADRs from Japanese Marketing Experience

Date of Event	Adverse Event	Severity	Dose	Reason for MRI	Outcome
1/21/94	nausea	mild	3 g	Suspected pancreatic tumor	Resolved spontaneously
3/1/ 94	diarrhea		3 g	Suspected pancreatic tumor	Resolved spontaneously
4/20/94	vomiting	moderat e	3 g	Assess status of retroperitoneal tumor	Resolved spontaneously
6/14/94	diarrhea	mild	6 g	Postoperative status of ovariectomy for lymphoma	Resolved spontaneously
6/27/94	flatulence, vomiting	mild	3 g	Suspected biliary tumor	Resolved spontaneously
10/5/94	recurrence of retro-peritoneal hemorrhag e	life-threat	6 g	Suspected acute pancreatitis causing abdominal tumor & retroperitoneal swelling	Abdominal resection performed to aspirate the hematoma and restore hemostasis
10/20/94	abdominal pain	mild	3 g	Suspected pancreatic cancer	Resolved spontaneously
10/26/94	abdominal pain	mild	3 g	Suspected pancreatic cancer	Resolved spontaneously
10/28/94	nausea	mild	3 g	Suspected liver mets from breast cancer	Resolved spontaneously
617/95	nausea & vomiting	mild	3 g	Evaluate hepatoma & hepatic cirrhosis	Reoslved spontaneously
7/31/95	diarrhea	mild	3 g	Suspected duodenal ulcer	Resolved spontaneously

Safety profile was assessed by measuring vital signs, laboratory biochemical and hematological parameters, urinalysis, and adverse events. All of the value changes listed below under safety were transient with both dose groups (200mg Fe and 400mg Fe OMR), and none of the changes noted elicited medical intervention or concern.

Vital Signs

Supine systolic/diastolic blood pressure and pulse rate were measured prior to 30-60 minutes, and 24 hours post-OMR ingestion. There were no significant mean changes from baseline in any of these parameters at any time points. Significant individual patient changes from baseline for systolic/diastolic /PR (>20 mmHg and >15 bpm) were reviewed. The changes, most of which were decreases, appeared to be transient in nature. There were no significant differences between the drug groups (200mg Fe and 400mg Fe-OMR). Scatter plots were generated for study A and study B, but not for the pooled data for study A+B (see Table below).

Vital Sign Mean Values at Each Timepoint:
Pooled Phase II/III Studies

		200 mg Fe			400 mg Fe			Between-Group
Parameter	Timepoint	N	Mean	Range	N	Mean	Range	p-value*
Blood Pressure								
Systolic	Pre-OMR	136	128.5		133	131.2		0.250
(mm Hg)	30-60 min Post	134	130.9		132	134.3		0.164
	24±4 hr Post	134	125.9		132	128.7		0.256
Diastolic	Pre-OMR	136	77.5		132	78.4		0.533
(mm Hg)	30-60 min Post	134	78.4		131	79.1		0.630
	24±4 hr Post	134	76.1		132	75.8		0.705
Temperature								
(°F)	Pre-OMR	130	98.1		128	98.4		0.027
	30-60 min Post	129	98.0		124	98.2		0.086
	24±4 hr Post	128	97.9		127	98.1		0.031
Pulse	Pre-OMR	136	73.5		133	77.9		0.003
(bpm)	30-60 min Post	134	73.8		132	77.8		0.011
	24±4 hr Post	134	75.3		130	78.1		0.056

* Comparison of dose groups using ANOVA, adjusting for study center

Laboratory Parameters

Laboratory assessments were made prior to and 24 hours post-OMR ingestion for a total of 264 (151A/113B) patients. Iron metabolism, blood chemistry, hematology and urinary measurements were analysed separately. There were no consistent or clinically significant changes on vital signs and laboratory parameters.

Iron Metabolism Parameters

Mean values and mean changes from pre-to post-OMR were calculated for each dose group and paired t-tests used to test the significance of within -group changes. Following OMR ingestion, there were significant decreases in mean values of transferrin, and total iron binding capacity(TIBC) in two dose groups, although, mean values remained within normal reference range for these parameters. There were no significant shifts from within and outside normal ranges from iron metabolism parameters. However, thirty-three (33) patients had significant abnormalities in pre-study iron metabolism parameters mainly related to their underlying clinical disease. Other attributing factors primarly due to iron deficiency are gastric tumor (#429A), renal dialysis (#418A), acute liver failure (#516), during menstruation (#623A), persistent urinary tract infection (#116B), and blood loss during surgery (#403B). The remaining patients (#103A, #251A, #423A, #621A, #501B, #513B, #630B),) that had percentage change from pre-to post-contrast values were >20% and not clinically significant stated by the sponsor.

Dose Group Absolute Differences in Mean
Iron Metabolism Parameters: Pooled Phase II/II Studies

		Means (± S.E.)			Within
Parameter**	Dose Group	Pre-	24±4 hr Post-	Change (post - pre)	Group p-value*
Serum iron	200 mg Fe	76.5 (3.97)	78.8 (4.11)	1.17 (2.69)	0.663
(mcg/dL)	400 mg Fe	78.4 (4.13)	78.8 (4.58)	0.71 (3.46)	0.839
TIBC	*200 mg Fe*	*327.3 (6.35)*	*320.3 (5.84)*	*-6.58 (3.25)*	*0.045*
(mcg/dL)	*400 mg Fe*	*317.2 (6.46)*	*306.1 (6.94)*	*-9.72 (3.73)*	*0.010*
Ferritin	200 mg Fe	276.1 (37.83)	270.9 (36.62)	-1.28 (7.91)	0.866
(ng/mL)	400 mg Fe	452.7 (84.86)	428.0 (68.32)	-32.06 (24.48)	0.193
% Saturation	200 mg Fe	24.3 (1.41)	25.6 (1.48)	0.87 (0.87)	0.319
	400 mg Fe	25.7 (1.54)	26.2 (1.61)	1.04 (1.21)	0.390
Transferrin	*200 mg Fe*	*288.5 (5.75)*	*282.3 (5.56)*	*-5.64 (2.06)*	*0.007*
(mg/dL)	*400 mg Fe*	*277.9 (6.07)*	*268.3 (6.14)*	*-7.96 (2.34)*	*<0.001*

* Comparison of the change from pre- to post-OMR using paired t-test

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As tabulated in the Table below, the most of the changes (pre-to post-OMR) show a fluctuation of the iron metabolism, particularly of that in the serum iron and %saturation which are consistent with known diurnal variations of up to 30% in individual subjects. In the cross-classification of post-OMR serum iron and ferritin values there are four patients (#127A, #114B, #619B, and #628B) with clinically significant increases in serum iron (>220 mcg/dL) and ferritin (>400 ng/mL). These four patients had clinically significant increases of iron metabolism prior to ingestion of OMR. There was no suggestive evidence of iron toxicity noticed after ingestion of OMR.

Percentage Change in Iron Metabolism Parameters
(pre- to post-contrast): Pooled Phase II/III Studies

Parameter	# Pts	No Change (±20%)	Increase >20%	>40%	>60%	Decrease >20%	>40%	>60%
200 mg Fe (6 g FerriSeltz)								
Serum iron	132	59	43	31	20	30	10	4
TIBC	132	122	5	0	0	5	0	0
Ferritin	128	108	13	4	1	7	1	1
% Saturation	132	50	48	32	23	34	9	3
Transferrin	129	128	0	0	0	1	0	0
400 mg Fe (12 g FerriSeltz)								
Serum iron	129	58	32	20	13	39	16	3
TIBC	129	118	4	2	1	7	1	0
Ferritin	126	108	11	5	3	7	0	0
% Saturation	128	54	37	23	16	37	15	3
Transferrin	127	124	2	0	0	1	1	0

Cross-Classification of Post-Contrast Values for
Serum Iron and Ferritin: Pooled Phase II/III Studies
(post-contrast values in relation to threshold criteria)

		Ferritin (ng/dL) 200 mg Fe (6 g FerriSeltz) n = 132				400 mg Fe (12 g FerriSeltz) n= 128			
		<12	12-299	300-400	>400	<12	12-299	300-400	>400
Serum Iron (mcg/dL)	<50	5	22	5	6	2	20	5	16
	50-219	0	72	4	16	0	59	4	18
	220-400	0	1	0	1	0	1	0	3
	>400	0	0	0	0	0	0	0	0

Blood chemistry parameters measured prior to and 24 hours after OMR ingestion revealed that there were significant decreases in mean values of SGOT and potassium in the 200mg Fe dose group, and SGPT and calcium in the 400mg Fe dose group. But, mean values remained within the normal limits for these parameters.. There were no significant shifts from within normal range to outside normal range for blood chemistry parameters.

However, five patients presented with abnormally high pre-contrast liver function parameters which remained high, or in a few cases normalized following OMR ingestion: These abnormally high liver function parameters were mainly due to patient's pre-existing conditions (such as hepatitis, hepatoma, billary obstruction or liver metastatsis secondary to carcinoma.

Dose Group Absolute Differences in
Mean Blood Chemistry Parameters: Pooled Phase II/III Studies

		Means (± S.E.)			Within
Parameter**	DoseGroup	Pre-	24±4 hr Post-	Change (post - pre)	Group p-value*
AST (SGOT)	*200 mg Fe*	*44.2 (3.96)*	*42.1 (4.20)*	*-2.25 (0.97)*	*0.022*
(IU/L)	400 mg Fe	42.3 (3.81)	39.7 (3.39)	-2.57 (1.32)	0.054
ALT (SGPT)	200 mg Fe	55.7 (9.16)	53.4 (9.76)	-2.35 (1.94)	0.229
(IU/L)	*400 mg Fe*	*43.6 (6.06)*	*38.5 (4.07)*	*-5.05 (2.54)*	*0.049*
GGT	200 mg Fe	105.0 (12.72)	103.0 (12.72)	-1.86 (1.24)	0.136
(IU/L)	400 mg Fe	106.0 (18.36)	96.4 (15.84)	-9.60 (6.05)	0.115
Alkaline	200 mg Fe	191.4 (16.19)	190.8 (16.36)	-1.73 (1.56)	0.269
Phosphatase	400 mg Fe	194.9 (19.82)	183.3 (17.54)	-11.61 (6.19)	0.063
(IU/L)					
Bilirubin	200 mg Fe	1.2 (0.28)	1.2 (0.30)	0.005 (0.037)	0.903
(mg/dL)	400 mg Fe	1.2 (0.31)	1.2 (0.30)	-0.14 (0.143)	0.316
BUN	200 mg Fe	18.6 (1.21)	18.6 (1.21)	0.08 (0.24)	0.756
(mg/dL)	400 mg Fe	17.8 (0.86)	17.3 (0.73)	-0.42 (0.42)	0.320
Creatinine	200 mg Fe	1.1 (0.05)	1.1 (0.05)	0.01 (0.011)	0.313
(ng/dL)	400 mg Fe	1.2 (0.11)	1.1 (0.08)	-0.06 (0.048)	0.213
Calcium	200 mg Fe	9.3 (0.05)	9.3 (0.05)	-0.04 (0.04)	0.289
(mg/dL)	*400 mg Fe*	*9.4 (0.05)*	*9.3 (0.06)*	*-0.12 (0.05)*	*0.011*
Potassium	*200 mg Fe*	*4.4 (0.04)*	*4.3 (0.04)*	*-0.08 (0.03)*	*0.015*
(mg/dL)	400 mg Fe	4.3 (0.04)	4.3 (0.04)	-0.1 (0.05)	0.215
Sodium	200 mg Fe	140.1 (0.33)	139.8 (0.34)	-0.32 (0.22)	0.150
(mEq/L)	400 mg Fe	140.2 (0.27)	140.0 (0.33)	-0.25 (0.23)	0.273
Chloride	200 mg Fe	100.6 (0.34)	100.5 (0.38)	-0.14 (0.26)	0.583
(mEq/L)	400 mg Fe	100.0 (0.32)	100.3 (0.34)	0.28 (0.28)	0.245

* Comparison of the change from pre- to post-OMR using paired t-test;

The incidence of pre-to post-OMR value changes in blood chemistry parameters is presented in the Table below. Although 12 patients (#111A, #213A, #402A, #415A, #605A, #623A, #205B, #402B, #403B, #628B, #630B, #717B) showed >40% change from pre- to post-OMR values for liver function parameters, this was not related to OMR ingestion. Among 3 of these patients (#605A, #402B, #717B) who had multiple abnormalities in liver function parameters both pre- and post-OMR, indicated value changes due primarily to the patient's underlying disease. There were 10 patients (#119A, #205A, #254A, #404A, #405A, #201B, #403B, #508B, #630B, and #720B) who had concurrent clinically significant post-OMR increases of SGOT (>120 IU/L) and SGPT (>120 IU/L), and 13 patients (#119A, #404A, #405A, #407A, #410A, #413A, #425A, #102B, #203B, #205B, #403B, #628B, and #630B) who had concurrent clinically significant post-OMR increases of alkaline phosphatase (>150 IU/L) & bilirubin (>2.4 mg/dL). All of these 10 patients also had similar abnormal values in pre-OMR tests. Again, this abnormal baseline was related to the patient's underlying disease.

Percentage Change in Blood Chemistry Parameters
(pre- to post-contrast): Pooled Phase II/III Studies

Parameter	# Pts	No Change (±20%)	Increase >20%	>40%	>60%	Decrease >20%	>40%	>60%
200 mg Fe (6 g FerriSeltz)								
AST (SGOT)	133	105	8	5	0	20	4	0
ALT (SGPT)	132	104	11	2	1	17	2	1
GGT	132	110	10	2	1	12	2	0
Alk Phos	133	130	2	0	0	1	0	0
Bilirubin	132	73	28	12	3	31	2	1
BUN	132	103	18	5	4	11	1	0
Creatinine	133	122	10	1	1	1	0	0
Calcium	133	133	0	0	0	0	0	0
Potassium	133	129	2	0	0	2	0	0
Sodium	133	133	0	0	0	0	0	0
Chloride	132	132	0	0	0	0	0	0
400 mg Fe (12 g FerriSeltz)								
AST (SGOT)	130	100	8	1	1	22	2	0
ALT (SGPT)	130	99	15	4	2	16	2	1
GGT	129	109	10	4	3	10	5	3
Alk Phos	130	126	2	0	0	2	0	0
Bilirubin	129	81	28	14	7	20	4	1
BUN	130	104	14	3	2	12	2	1
Creatinine	130	123	4	1	0	3	2	1
Calcium	130	128	0	0	0	2	0	0
Potassium	130	122	4	1	1	4	1	0
Sodium	130	130	0	0	0	0	0	0
Chloride	130	130	0	0	0	0	0	0

Hematology parameters including RBC, and WBC with differentials, were measured prior to and 24 hours after OMR ingestion. Following ingestion of OMR there appears to be significant decreases in mean values of RBC, WBC, hemoglobin and hematocrit in both dose groups. Decreases were small but the mean values remained within limits of normal for each parameters. There were significant shifts from within normal reference range to outside threashold limits for hemoglobin, hematocrit and reticulocyte count in the high dose group. Fourteen patients had abnormal pre-OMR values and remained abnormal (or in a few became normalized) after ingestion of OMR. It is interesting to note that 7 patients had clinically significant increases in their reticulocyte counts but no good explanation was given. Three patients (#201B, #501B, #516) with treatment-emergent abnormalities in RBC, hemoglobin, hematocrit also had abnormalities in other parameters both pre- and post-OMR. These abnormalities are primarily due to patient's underlying diseases.

Dose Group Absolute Differences in
Mean Hematology Parameters: Pooled Phase II/III Studies

(statistically significant differences italicized)

		Means (± S.E.)			Within
				Change	Group
Parameter**	**Dose Group**	**Pre-**	**24±4 hr Post-**	**(post - pre)**	**p-value***
RBC	*200 mg Fe*	*4.30 (0.056)*	*4.26 (0.055)*	*-0.049 (0.019)*	*0.010*
($x10^6/mm^3$)	*400 mg Fe*	*4.27 (0.060)*	*4.20 (0.060)*	*-0.068 (0.020)*	*<0.001*
Hemoglobin	*200 mg Fe*	*13.1 (0.18)*	*13.0 (0.18)*	*-0.12 (0.058)*	*0.043*
(g/dL)	*400 mg Fe*	*13.0 (0.19)*	*12.8 (0.19)*	*-0.19 (0.060)*	*0.002*
Hematocrit	*200 mg Fe*	*39.4 (0.53)*	*39.0 (0.54)*	*-0.42 (0.191)*	*0.031*
%	*400 mg Fe*	*39.0 (0.56)*	*38.3 (0.56)*	*-0.65 (0.182)*	*<0.001*
Reticulocyte	**200 mg Fe**	**1.1 (0.06)**	**1.0 (0.05)**	**-0.04 (0.041)**	**0.372**
count (%)	**400 mg Fe**	**1.2 (0.09)**	**1.2 (0.09)**	**-0.02 (0.041)**	**0.705**
WBC	*200 mg Fe*	*6.7 (0.21)*	*6.4 (0.20)*	*-0.29 (0.123)*	*0.021*
($x10^3/mm^3$)	*400 mg Fe*	*7.5 (0.30)*	*7.3 (0.31)*	*-0.27 (0.122)*	*0.028*
Platelets	**200 mg Fe**	**262.4 (9.20)**	**261.5 (9.11)**	**-0.74 (2.15)**	**0.731**
($x10^3/mm^3$)	**400 mg Fe**	**269.0 (11.94)**	**268.6 (12.44)**	**-2.1 (2.79)**	**0.457**

*** Comparison of the change from pre- to post-OMR using paired t-test;**

Reticulocytes **Platelets**

Shifts in Hematology Parameters
Within and Outside Normal Range from Pre- to Post-Contrast ("OMR"):

Pooled Phase II/III Studies

(statistically significant changes italicized)

			Post-OMR	
			Low Normal High	Low Normal High
Hemoglobin		Low		
(g/dL)	Pre-OMR	Normal	86	67
		High		
			p-value =0.497	*p-value=0.043*
			Low Normal High	Low Normal High
Hematocrit		Low		
(%)	Pre-OMR	Normal	78	68
		High		
			p-value =0.403	*p-value=0.011*
			Low Normal High	Low Normal High
Reticulocyte		Low		
Count	Pre-OMR	Normal	82	88
(%)		High		
			p-value =0.248	*p-value=0.009*
			Low Normal High	Low Normal High
WBC		Low		
($x10^3/mm^3$)	Pre-OMR	Normal	105	94
		High		
			p-value =0.549	p-value=0.430

p-values based on Stuart-Maxwell test to evaluate shift from pre- to post-OMR;

*** NS = Undefined test (zero denominator); too few patients shifting categories**

There were 48 patients that had abnormal low post-OMR values for both hemoglobin (<11g/dL) and hematocrit (<34%), in all but one patient (#516B), the abnormalities were present prior to ingestion of OMR, which means unrelated to the drug administered. Patient (#118B) had clinically significant increases in hemoglobin (>17 g/dL) and hematocrit (>53%); this patient had surgery the day after ingestion of OMR (see Table below):

Cross-Classification of Post-Contrast Values for Hematology Tests: Pooled Phase II/III Studies

		Hematocrit (%)					
		200 mg Fe (6 gm OMR) n = 132			400 mg Fe (12 gm OMR) n= 129		
		<34	34–53	>53	<34	34–53	>53
Hemoglobin	<11	23	2	0	25	3	0
(g/dL)	11-17	2	104	0	6	92	0
	>17	0	0	1	0	3	0

Urinalysis parameters, however, revealed no significant abnormal changes from pre-to post-OMR in both dose groups.

Post - Marketing Experience

Ferric Ammonium Citrate (FAC) was approved for marketing as FerriSeltz™ (OMR) in Japan. OMR has not been withdrawn for any reason.

Labeling Review

The labeling meets the requirements of the regulations with regard to style, format and content. It is acceptable, but we suggest the following changes (a draft labeling attached):

Division of Medical Imaging, Surgical and Dental Drug Products
Medical Imaging Group
Medical Officer's Review and Evaluation of New Correspondence

OCT - 7 1994

NDA 20-292 New Correspondence
FerriSeltz™ Oral MRI Contrast Agent
Oncomembrane, Inc
1201 Third Avenue
Seattle, WA 98101

M.O.: J.A. Pierro,M.D.
Document Date: 8-31-94
Date Received: 9-1-94
Date Assigned: 9-26-94
Date Completed: 9-30-94

The sponsor has submitted a plan for clinical data presentation following a meeting with this Division (August 5, 1994). The following sample presentations (as appropriate) have been proposed:

1. Mean values with mean changes from pre- to post-dosing with paired t-tests to assess within group changes.
2. Shift tables
3. Contingency tables with specific threshold levels of ±20%, ±40%, ±60%.
4. Relevant pairs of laboratory parameters such as hemoglobin vs. hematocrit, BUN vs. creatinine, AST vs. ALT, alkaline phosphatase vs. bilirubin, and serum iron vs. ferritin will be cross-classified to asses related effects which might suggest organ toxicity.
5. Scattergrams for selected parameters.

Reviewer's comments: The sponsor should consider the following:

a. The contingency tables as presented in Tables 19.1 - 19.3 would be easier to review if the table was arranged as follows
-80%, -60%, -40%, -20%, no change, +20%, +40%, +60%, +80%

b. Scattergrams would be useful for all clinical parameters.

c. An alternate way to present the cross-classification of laboratory parameters would be with a contingency table using specified threshold levels, ie. percentage change (-40%, -20%, no change, +20%, +40%) rather than actual laboratory values or ranges.

d. The following comments may assist the sponsor in preparation of the NDA:

- *appropriate presentation of the data (demographic, dosing, clinical, safety, and efficacy. etc)*
- *appropriate calculation of the value (for each described term)*
- *clear classification and enumeration of patients, including discontinuations*
- *enumeration and identification of patients with clinically significant abnormalities (clinical, laboratory,etc.). Appropriate investigator commentary should be included. A similar presentation for adverse events should be provided.*
- *appropriate subgroup displays should be provided where appropriate*
- *adverse event incidence tables*
- *enumeration and identification of serious adverse events, deaths and discontinuations include a narrative summary for each serious ADR*
- *individual patient displays for laboratory and clinical data (including efficacy)*
- *an organ system safety summary may also be provided including information derived from the preclinical and clinical data. Examples of organ systems considered relevant*

would include hematologic, hepatic, renal, cardiovascular..)
- reference laboratory values and those considered clinically significant should be provided.

e. An appropriate presentation of the efficacy data would be required as discussed with the Agency previously.

Note to the Consumer Safety Officer:

The entire section of reviewer's comments may be provided to the sponsor. Dr. Chow (primary reviewer) received and reviewed this submission prior to my assignment and may have additional items for the sponsor's review.

Joseph A Pierro M.D. (MO) September 30, 1994

Group Leader's Comments

I agree. A E Jones M.D. 10/4/94

A. E. Jones M. D. (Group Leader)

Division of Medical Imaging, Surgical and Dental Drug Products
Medical Imaging Group

NOV 16 1993

Medical Officer's Review and Evaluation of New Correspondence: "Protocol for the Evaluation and Analysis of the Clinical Studies Diagnostic Data"

NDA 20-292 New Correspondence
FerriSeltz™
An Oral MRI Contrast Agent
Oncomembrane, Inc.

M.O.: J.A. Pierro,M.D.
Document Date: 10-1-93
Date Received: 10-1-93
Date Assigned: 10-25-93
Date Completed: 10-27-93

1. Proposed Study Analysis Protocol:
   a. Objectives:
      1. In a blinded manner, determine the normality or abnormality of the stomach, duodenum and pancreas, in pre- and post contrast images.
      2. To validate the agreement of the MRI diagnosis with a gold standard clinical diagnosis.
      3. To evaluate the increase in diagnostic accuracy of post-contrast MRI versus pre-contrast MRI.
   b. Endpoints:
      1. Contrast assessment: Primary endpoint.
         a. Opacification, signal intensity, signal homogeneity of the stomach, duodenum and jejunum.
         b. Distension of the stomach. duodenum and jejunum.
         c. Delineation of the G.I. tract and the pancreas.
         d. Image quality, and presence/absence of artifacts.
      2. Diagnostic assessment:
         a. Assessment if post-contrast images provided any additional information, and if patient management changed.
         b. Blinded, comparative diagnostic assessment of pre- and post-contrast images.
   c. Methods:
      1. Randomized Blinded Review of the MRI Films: Two blinded reviewers, experts in abdominal imaging, will independently review the random MRI films. Paired films will not be included in any batch. Reviewers will limit their review to the stomach, duodenum and pancreas (the sponsor acknowledges that only two locations, ie stomach and pancreas will be diagnostically impacted by the use of the contrast agent since few patients with duodenal pathology were enrolled in the study). A five point scoring system will be used: 1= definitely normal, 2= probably normal, 3= uncertain, 4= probably abnormal and 5= definitely abnormal. Additionally, unblinded experts will draw up reading guidelines to be utilized to orientate blinded

reviewers to ensure consistency in reading film.

Reviewer's Comments: Consideration to evaluate contrast enhancement in the remainder of the bowel (eg. small bowel in the pelvis) should be given so that labelling will not be too restrictive. Blinded reviewers should asses the images paired, pre-contrast with post-contrast images and analysis of agreement or change in diagnosis or patient management should be performed. Sponsor should clarify which CRFs in the original NDA will be replaced, ie. will conspicuity, size, margins, location, degree of distension etc. still be evaluated.

Additionally reviewers are experts in abdominal imaging and should not be biased with an orientation to reading guidelines.

2. Unblinded investigator will compare the pre- and post images and assess the degree of change from the addition of the contrast agent.

Reviewer's Comments: Statistical analysis should include only the blinded reviewers readings. Comparative results from the unblinded investigator could only be supportive of the blinded reviewers.

3. Establishment of a clinical "gold standard": Prior to the MRI exam, review of available clinical data, including other diagnostic tests (CT, ultrasound, biopsy, endoscopy etc.) will be utilized to establish whether these anatomic regions are normal or abnormal. If data is not available at study entry, follow-up information will be pursued. In the event of conflicting information, three experts will evaluate the available data to try to reach a consensus. Patients will be excluded from the diagnostic analysis if a "gold standard" cannot be established (these patients will be included for contrast enhancement and image assessment). Therefore, 3 "gold standard" categories are developed:

1. Diagnoses proven by surgery and biopsy results
2. Diagnoses based on other non-invasive diagnostic modalities, other than the MRI study.
3. Clinical diagnoses made in the absence of # 1or #2, but based on available clinical data and the study MRI information.

Gold standard ground rules as defined include only mass lesions and wall thickness abnormalities of the stomach, duodenum and pancreas. The following abnormalities are specifically excluded: previous surgeries, varices, carcinoma in situ, gastric or duodenal ulceration/erosions, hiatal hernia, atrophic gastritis, small diverticuli, pancreatic calcifications, atrophy or pancreatitis.

Reviewer's Comments: The gold standard guidelines severely limit inclusion of abnormalities into the analysis and should be broadened so that diagnostic utility of the contrast agent may be demonstrated.

d. Statistical methods: see statistical review/comments.

Reviewer's comments: Only the unblinded investigator will view the film pairs (pre- and post-contrast side by side). The blinded reviewers should be allowed to evaluate the images paired and the results may be compared to the unpaired reading sessions to evaluate reader variability and consistency.

The sponsor describes primary efficacy comparisons for the stomach only, and secondary comparisons for the pancreas and duodenum. This is inconsistent with the primary contrast assessment endpoints stated above and should be clarified. Another point requiring clarification is the use of a 5 point diagnostic scale described in several places as 1-5 and in the introduction as 0-4. The sponsor proposes to define normal as scores 1 or 2, uncertain as score 3 and abnormal as scores 4 or 5 to generate a 3x3 pre- versus post-contrast contingency table. The Stuart-Maxwell test will then be computed for the blinded reviewers at $p \leq 0.05$. The sponsor states "it is difficult to show statistically significant ($p=0.05$) diagnostic accuracy improvement with each individual reviewer and will provide additional ancillary data analysis employing the five point diagnostic scale to create ROC (Receiver Operating Characteristic) curves utilizing the bootstrap methodology to generate reviewer significance levels. The ancillary analysis may only be looked upon as supportive if statistically significant p-values are attained.

Joseph A. Pierro MD 10/27/93

Joseph A Pierro M.D. (MO)

Group Leader's Comments

See my 11/1/93 comments.

APPEARS THIS WAY
ON ORIGINAL

A. E. Jones 11/16/93

A. E. Jones M. D. (Group Leader)

cc: Original NDA 20-292
HFD-160/ J. Pierro (MO), S. Chow (MO)
HFD-161/S. Kummerer (CSO)
HFD-713/M. Ponnapalli (Stat.)

DIV.

GROUP LEADER'S COMMENTS

NDA: 20-292

MEDICAL OFFICER: Dr. Lionel Lieberman
Dr. Joseph Pierro

SPONSOR: Oncomembrane Inc.

SUBMITTED: October 1, 1993

NOV - 1 1993

M.O. REVIEW: October 27, 1993

AGENT: Ferriseltz

1. I agree with Dr. Pierro's review and fully agree with his first two comments which should be sent to the sponsor. In particular, the sponsor (page 3 under "Materials and Methods" item (1) "Randomized Blinded Review of MRI Films") stated:

> "...diagnostic information will focus primarily on two locations in the GI tract...."
> G.I tract = stomach + intestines, in continuity

The "two locations are stomach and pancreas." This, first of all, is only one location in the GI tract; stomach. The minimal objective was:

> Page 1: "Introduction-Background and Rationale (A)"
>
> ..."contrast assessment" of item (5) "delineation of the upper G.I. tract and of the pancreas."

This included stomach duodenum and jejunum.

The sponsor intends the NDA to support a stomach indication only. I agree with Dr. Pierro's comment (1).

2. The following "Setting of Gold Standard Ground Rules" is not sufficient:

> The following abnormalities will not be specified as abnormalities for this exercise; both for setting clinical gold standard and for blinded reading of the MRI films.
>
> Previous surgeries
> Varices - gastric and esophageal
> Carcinoma in situ
> Gastric or duodenal ulcerations or erosions
> Incidental hiatal hernia
> Gastritis - atrophic
> Small diverticuli

Pancreatic "atrophy"
Pancreatitis
Calcifications in pancreas

These are disease states that should be evaluated to support a Ferriseltz claim.

3. On page 6 "..3 general categories of gold standard diagnoses are possible" - second paragraph; number three should not include MRI study information either pre or post contrast.

4. Randomized film evaluations may not be sufficient and paired (pre followed by post contrast) readings should be provided.

RECOMMENDATIONS:

Provide the sponsor with Dr. Pierro's recommendations and my concerns, items 2 and 3 above.

A. E. Jones M.D. 11/1/93
A. E. Jones, M.D.
Group Leader, Medical Imaging, HFD-160

cc:
Division file HFD-160
Dr. Lieberman/160
Dr. Pierro/160
NDA 20-292

Addendum:
"Consensus" readings by three experts is not acceptable. If conducted it will be ignored in the review for approval
A E Jones M.D.
11/8/93.

Also Gold standard based on MRI is not valid

APPEARS THIS WAY
ON ORIGINAL

Should not "agree" to the Gold standard - But Strap appears. The letter should indicate that the sponsor could submit the analysis; however, we doubt that it will be sufficient (even with modifications)
11/15/93

DIV.

DIVISION OF MEDICAL IMAGING, SURGICAL AND DENTAL DRUG PRODUCTS
INITIAL MEDICAL OFFICER'S REVIEW OF NDA 20-292

DATE; July 15, 1993

Sponsor: ONCOMEMBRANE, INC.
1201 Third Ave.
Suite 5100
Seattle, WA 98101

JUL 28 1993

Name of Drug: FerriSeltz (An Oral MRI Contrast Agent)

Subject: Proposed plan for re-submission of NDA 20-292

This NDA 20-292 initially was refused to file dated January 8, 1993 because of poorly organized and particularly lack of adequate diagnostic verification according to CFR 21: 201.57 (c)(1)(ii).

On June 4, 1993, the sponsor submitted a proposed plan with respect how to analyse (pre- & post-contrast administration of FerriSeltz) the diagnostic data from two adequate and well controlled studies.

No major disagreement with the sponsor's proposal but I have some reservations as follows:

1. Two independent blinded reviewers for data analysis would be acceptable.

2. On page 6, item 2. second paragraph stated that "The definition of normal, abnormal, and uncertain for the blinded review will be based on the 5 point diagnostic scale"

   Why is a 5 point scale better than a three or four? In the reviewer's Image Assessment (scheme-CRF), I prefer to omit both "probably normal" and "probably abnormal" indicated by 2 and 4.

   Since you have definitely normal (negative) and definitely abnormal (+) compared with the clinical "gold standard", it would be easier to establish false negative and/or true negative. However, both sensitivity and specificity should be established.

Example:

		Disease State	
		+	-
Test Result	+	TP	FP
	-	FN	TN

Sensitivity = TP/(TP+FN)
Specificity = TN/(TN+FP)

Prevalence:
Predictive value positive = TP/ (TP + FP)
Predictive value negative = TN/ (TN + FN)

3 ROC Analysis:

I have no objection with regard to use ROC curve methodology to evaluate efficacy of the contrast agent, if it is useful to determine the diagnostic effectiveness (please send us a sample analysis and the end point).

Silas Chow, M. D. MOR

APPEARS THIS WAY
ON ORIGINAL

c.c.
orig. NDA 20-292
HFD-160
HFD-160/MOR/SChow/7/15/93
HFD-160/CSO/SKummerer
HFD-160/GL/AEJones, M.D.

I agree but
A.E. Jones M.D. 7/26/93
do not want the sponsor to shuffle contrast pre contrast images. Each patients pre contrast should be read blinded to the same patients contrast but in either order — pre contrast to post contrast or post contrast to pre contrast. The same patients pre + post contrast films should be compared in sequence but blinded to one another.

A.E. Jones M.D. 7/26/93

Safety Update Review:

See Medical Review dated

Sept. 12, 1997.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

CHEMISTRY REVIEW(S)

DIVISION OF MEDICAL-IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS, HFD-160

Review of Chemistry, Manufacturing, and Control

NDA#: 20-292 **CHEMISTRY REVIEW #:** 2 **REVIEW DATE:** 15-SEP-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AC	11-APR-97	14-APR-97	18-APR-97

NAME/ADDRESS OF APPLICANT: Oncomembrane, Inc.
1201 Third Avenue, Suite 3010
Seattle, WA 98101
(206) 622-6626/ Toshihiko Tanaka, President

DRUG PRODUCT NAME:

Proprietary:	FerriSeltz™
Nonproprietary/USAN:	Ferric ammonium citrate, brown
Code Name/Number:	CAS# 1185-57-5
Chem. Type/Therap. Class:	**3 S**

PHARMACOL.CATEG./INDICATION: DIAGNOSTIC-Imaging
T_1-weighted MRI contrast agent

DOSAGE FORM: Granular Powder for reconstitution into an effervescent solution

STRENGTHS: 600mg FAC, brown (105mg Fe) per 3g packet

ROUTE OF ADMINISTRATION: Oral

DISPENSED: __X__Rx ____OTC

CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA, MOL.WT.:

IUPAC: Iron (III) ammonium citrate CAS: Ammonium iron (III) citrate
Average stoichiometric formula:
Elemental formula: $C_{6.6}H_{12.8}FeN_{1.6}O_{9.7}$ as a polymeric coordination complex
Structure: Undetermined M.W.: Undetermined
Iron Content:

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS: US Patent #: 5,174,987--Dec 29, 1992
CONSULTS: NONE

CONCLUSIONS/RECOMMENDATIONS: **Approval Letter of FerriSeltz (600 mg) power packets in 20-count container size with revised expiration dating of 15 months.** CMC deficiencies identified in Chemistry review #1 were resolved satisfactorily by the firm, except for the need to revise expiry dating from 36 months to 15 months. AAI is the sole manufacturing and control site of FerriSeltz. The post-approval commitment to monitor the stability of the drug product have also been included and are satisfactory.

REMARKS/COMMENTS:

After this second Chemistry review the conclusion is to recommend approval of the NDA based on the resolution of the deficiencies identified in chemistry review #1.

Specifically the applicant has provided additional information to satisfy the following areas:

* reference standard for the drug substance, FAC, brown,
* adequate production data at AAI commercial manufacturing site,
* adequate update of MV package,
* adequate explanation and data to justify some of the proposed specifications,
* stability data in support of 15 months of expiration dating for FerriSeltz instead of the 36 months proposed in original NDA,
* EA information, "Categorical Exclusion" proposed,
* adequate post-approval commitment to monitor the stability of FerriSeltz, and
* acceptable cGMPs status: 16-Jul-97 for FerriSeltz production and testing.

RECOMMENDATION:

APPROVAL WITH 15 MONTHS EXPIRATION DATING FOR FERRISELTZ, 600mg, POWDER , 20-COUNT SIZE CONTAINER.

cc:
Orig. NDA # 20-292
HFD-160/Division File
HFD-160/MSalazar
HFD-160/SChow
HFD-160/DBailey
HFD-160/ELeutzinger
HFR-PA300/Seattle District Office
HFR-MA160/Philadelphia District Laboratory
HFC-134/Division of Field Investigations
HFD-161/KColangelo
R/D Init. by: ELeutzinger
F/T by: MSalazar

APPEARS THIS WAY
ON ORIGINAL

E. Leutzinger 9/24/97

15/Sep/97

Milagros Salazar-Driver, Ph.D.
Review Chemist, HFD-160
ONDC II, HFD-820

Filename: **N20-292.002**

SUMMARY OF CHEMISTRY REVIEW# 2

NDA 20-292
Ferriseltz (Ferric Ammonium Citrate, brown) 600mg
Oncomembrane, Inc.

A. DRUG SUBSTANCE

1. DESCRIPTION & CHARACTERIZATION: Satisfactory, Review#1, p 10.
2. MANUFACTURER: Satisfactory, Review#1, p 11.
3. SYNTHESIS: Satisfactory , Review#1, p 12.
4. **SPECIFICATIONS / TEST METHODS/REF.STD.: Satisfactory, Review#2, p 4**
5. CONTAINER/CLOSURE SYSTEM: Satisfactory, Review#1, p 17.
6. STABILITY: Satisfactory, Review#1, pp 18-19.

B. DRUG PRODUCT

1. COMPONENTS/COMPOSITION: Satisfactory, Review#1, pp 20-22.
2. SPECIFICATIONS & METHODS FOR INGREDIENTS: Satisfactory, Review#1, p 21 .
3. MANUFACTURER: Satisfactory, Review#1, p 22.
4. **MANUFACTURING AND PACKAGING: Satisfactory, Review#2, pp 5-6**
5. **SPECIFICATIONS AND TEST METHODS: Satisfactory, Review# 2, pp 7-11**
6. CONTAINER/CLOSURE SYSTEM: Satisfactory, Review#1, p 32.
7. **STABILITY: Satisfactory for 15 months expiration dating, Review#2, pp12-16**

C. INVESTIGATIONAL FORMULATIONS: Satisfactory, review#1, p 42.

D. ENVIRONMENTAL ASSESSMENT: Satisfactory. Addendum to Review#2 dated 24-Sep-97, Categorical Exclusion granted.

E. METHODS VALIDATION: In-progress. Adequate MV package for FDA Labs to review, Review#2, pp 17-22. MV request memo dated 11-Sep-97.

F. LABELING: Satisfactory, Review#2, p23

G. ESTABLISHMENT INSPECTION: cGMP status as of 16-Jul-97: ACCEPTABLE , Review#2, p25

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION:

APPROVAL OF THE FerriSeltz 20-COUNT SIZE CONTAINER WITH 15 MONTHS EXPIRATION DATING.

APPEARS THIS WAY
ON ORIGINAL

OCT 18 1996

DIVISION OF MEDICAL IMAGING AND RADIOPHARMACEUTICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Control

NDA#: 20-292 **CHEMISTRY REVIEW #:** 1 **REVIEW DATE:** 23-AUG-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12-NOV-92	16-NOV-92	06-DEC-92
RESUBMISSION	15-NOV-95	16-NOV-95	28-NOV-95
NC	11-JAN-96	16-JAN-96	09-FEB-96
BZ	05-FEB-96	06-FEB-96	16-FEB-96
N (BC)	28-FEB-96	29-FEB-96	18-MAR-96
N (BC)	10-JUL-96	11-JUL-96	17-JUL-96

NAME/ADDRESS OF APPLICANT: Oncomembrane, Inc.
1201 Third Avenue, Suite 3010
Seattle, WA 98101
(206) 622-6626/ Toshihiko Tanaka, President

DRUG PRODUCT NAME:

Proprietary:	FerriSeltz™
Nonproprietary/USAN:	Ferric ammonium citrate, brown
Code Name/Number:	CAS# 1185-57-5
Chem. Type/Therap. Class:	**3 S**

PHARMACOL.CATEG./INDICATION: DIAGNOSTIC-Imaging
T_1-weighted MRI contrast agent

DOSAGE FORM: Granular Powder for reconstitution into an effervescent solution

STRENGTHS: 600mg FAC, brown (105mg Fe) per 3g packet

ROUTE OF ADMINISTRATION: Oral

DISPENSED: __X__Rx ____OTC

CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA, MOL.WT.:

IUPAC: Iron (III) ammonium citrate CAS: Ammonium iron (III) citrate
Average stoichiometric formula:
Elemental formula: $C_{6.6}H_{12.8}FeN_{1.6}O_{9.7}$ as a polymeric coordination complex
Structure: Undetermined M.W.: Undetermined
Iron Content:

SUPPORTING DOCUMENTS:

RELATED DOCUMENTS: US Patent #: 5,174,987--Dec 29, 1992
CONSULTS: NONE

CONCLUSIONS/RECOMMENDATIONS: Non Approval Letter. CMC deficiencies include lack of reference standard for the drug substance, FAC, brown. Inadequate production data and stability studies in support of the expiration dating for FerriSeltz intended for marketing, as well an inadequate justification for proposed specs, EA report and post-approval commitment to monitor the stability of the drug product.

REMARKS/COMMENTS:

Background

Ferric Ammonium citrate (FAC) has been used in about 25 OTC products (oral solutions), 4 prescription products in the past as hematinic nutrient or dietary supplement. Most of these OTC products were withdrawn during 1970 and 1971 (DESI initiative), while the prescription ones are reported with No Action status.

Geritol Liquid/oral, iron as FAC, 50 mg/15mL (Beecham Products), and Geriplex-FS Liquid/oral, iron (as FAC, green), 15mg/30mL are OTC products currently in the market containing ferric ammonium citrate.

Recommendation at the 45 DAY file meeting: to file NDA after the applicant agreed to withdraw proposed manufacturer of drug product, Applied Analytical Industries, Inc., since this site has not produced the product at this site, nor has generated stability data in support of AAI site. (Communication of 11-Jan-96 NC).

The proposed manufacturing site for FerriSeltz effervescent powder will be Pharmavite, Inc. which was the site originally proposed for the NDA and the one manufacturing all stability and production size batches presented in this NDA.

In the 5-Feb-96 BZ communication the applicant responded to preclinical, clinical, and CMC comments raised during the filing of the application.

On 28-Feb-96 N(BC) amendment the applicant informed the Agency of a decision in which was no longer to be the manufacturer of FerriSeltz and their inability to manufacture the product since part of the production equipment had been transferred to AAI. Therefore, the company proposed AAI again as the commercial production site; however, they would not be ready for inspection until mid-July.

Amendment of 10-Jul-96 N(AC), provides the information on the transfer of analytical methodology to AAI as well as stability data for 3 lots manufactured at AAI including their production batch records.

After this first comprehensive Chemistry review the conclusion is to withhold approval of the NDA based on major deficiencies which include the following areas:

* include lack of reference standard for the drug substance, FAC, brown,
* inadequate production data,
* applicant withdrawal of readiness for inspection after 45 day filing commitments,
* Inadequate explanation and data to justify some of the proposed specifications,
* inadequate stability studies in support of the expiration dating for FerriSeltz intended for marketing,
* inadequate EA report, and
* inadequate post-approval commitment to monitor the stability of FerriSeltz.

RECOMMENDATION: NON APPROVAL LETTER

cc:
Orig. NDA # 20-292
HFD-160/Division File
HFD-160/MSalazar
HFD-160/SChow
HFD-160/DBailey
HFD-160/ELeutzinger
HFR----------PA300/Seattle District Office
HFR----------MA160/Philadelphia District Laboratory
HFC-134/----------Division of Field Investigations
HFD-161/Cusack
R/D Init. by: ELeutzinger
F/T by: MSalazar

E. Leutzinger 10/15/96

23-Aug-96

Milagros Salazar-Driver, Ph.D.
Review Chemist, HFD-160
ONDC II, HFD-820

Filename: **N20-292.001**

APPEARS THIS WAY
ON ORIGINAL

Consult #597 (HFD-160)

FERRISELTZ ferric ammonium citrate, brown for oral administration

The LNC found no look alike/sound alike conflicts nor misleading aspects in the proprietary name.

The Committee believes the correct established name for the product should be effervescent ferric ammonium citrate, brown, for oral solution to be in conformance with the USP oral solution categories.

The LNC has no reason to find the proposed proprietary name unacceptable.

D L Boring 5/23/96, Chair
CDER Labeling and Nomenclature Committee

APPEARS THIS WAY
ON ORIGINAL

cc
orig NDA 20-292
DJJ file

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

* * * SENSITIVE * * *

REVIEW

OF

ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-292

FerriSeltz (Ferric ammonium citrate, brown) Effervescent Powder

Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160

CENTER FOR DRUG EVALUATION AND RESEARCH

First Review
DATE COMPLETED 7/10/96

ENVIRONMENTAL ASSESSMENT

NDA 20-292 FerriSeltz, Ferric ammonium citrate, brown (FAC, brown) Granular Powder.

This is the first review of the environmental assessment (EA) submitted under 21 CFR 25.31a(a). During a pre-NDA meeting, 21-Feb-95, the company was advised by the Agency to provide a full environmental assessment in the NDA. During the 45 day NDA file meeting, 3-Jan-96, the EA section was considered to be fileable for review.

Items 1, 2, 3:
Submission is dated July 1, 1994. Name of Applicant, Oncomembrane, Inc., and address are included. Adequate

Item 4:
a), b)
The drug is FerriSeltz (Ferric ammonium citrate, brown, FAC) Granular Powder. Each packet contains 3 g of dry powder which has
The indication is for use as diagnostic Magnetic Resonance Imaging (MRI) enhancement agent.

EA submitted using a document format arranged under 21 CFR 25.31a(a).

c), d), e)
The location of manufacture and site description for the manufacturer of the Drug substance (FAC, brown) and the drug product (FerriSeltz) are adequate.

Drug substance:

Drug Product: Applied Analytical Industries, Inc. (AAI)
1206 North 23rd St.
Wilmington, NC 28405

The drug will be used by physicians at health care facilities. Disposal is discussed later.

Item 5
Identification of the drug substance 's molecular formula, weight, structure discussion is included. A material Safety Data Sheet for FAC, brown is included in

Appendix A of the NDA/EA section. The list of reagents used in the manufacture of the FAC. Brown drug substance is not presented as part of EA. However, this information is presented in a CMC Section 2. II. 1. And in the DMF# 9603. Identification of all components of the drug product are included in Appendix B of the NDA/EA section.

Adequate

Item 6
a), b)
For Drug Substance-- manufacturer The applicant states that the emissions from the facility are in compliance with the government environmental laws according with appropriate laws and regulations.

For Drug Product-- manufactured in North Carolina. Applicant states that manufacturer complies with federal and state regulations.

Air emissions-- discussion adequate.

Water emissions/Wastewater-- discussion adequate. Waste waters discharged through sewer system.

c) Compliance
For drug substance-- Appendix C of NDA/EA section contains EA from facility from with signature of responsible official. Appendix D of NDA/EA section contains letters of compliance certified by the Prefectural government of Adequate

For drug product-- Applicant states that AAI facility with federal and state laws as per Clean air Act, and Federal Water Pollution Control Act of 1972, the clean Water Act, and the Water Quality Act of 1987. Waste discharge being in compliance as per 40 CFR 439. Solid waste-- AAI is registered as a hazardous waste generator. According to
Other compliance status include chemicals stored and handled and managed according to GMPs and OSHA standards. Adequate

d), e) Expected Introduction Concentrations
Estimated 5th year production volume information is included in Appendix F of the NDA/EA section. Calculation in item 6 states the MEEC, based on 5-yr production data, is Adequate

Deficiency: The applicant needs to described how the rejected lots and returned lots of the product will be disposed of.

Item 7:
FAC, brown is very soluble in water, but insoluble in alcohol. Therefore, the compound is to enter the aquatic compartment as the parent compound and reside as this form in that environment.
Estimated biodegradability for FAC, brown in an aerobic medium, at dark at temperature o 22 ± 3°C, and concentration of Mineralization (CO_2 production) degradation was The Microbial inoculum was activated sludge an secondary effluent from Columbia wastewater Treatment Plant. The theoretical value for FAC, brown was against a reference substance (dextrose) with a mineralization (CO_2 production) value of A report of this testing is presented with test results and summary discussion in Appendix G.

Test substance, FAC, Brown, Lot#: D1262018 provided by

Reference Substance: Dextrose, ACS grade
Appendix G--Vol 2.03, 030001 presents the results of study on Aerobic Biodegradation in water of FAC, brown. The study was performed by:

Compliance Certification by environmental officers (with names/titles and signatures) in the company is presented too.
ADEQUATE

Item 8:
Microbial Inhibition test with FAC, brown, on microbes in the environment as EC_{50} was estimated to be but was not calculated because the highest concentration tested did not cause 50% or greater inhibition. The maximum inhibition was . Microbial inoculum: activated sludge from Columbia Waste treatment Plant/Columbia, MO (this plant received domestic sewage).
Test substance : FAC, Brown, Lot# D12620/provided by

Reference Substance:

A report of this testing, with results,calculations, and a summary discussion, is presented in Appendix H.

Appendix H--Vol 2.03, 030370 presents the results of study on Activated Sludge Respiration Inhibition Test with FAC, BROWN. The study was performed by:

Compliance Certification by environmental officers (with names/titles and signatures) in the company is presented too. No potential effect on microbial environment is expected.
ADEQUATE

Item 9, 10, and 11:
Meets requirements. Adequate

REVIEWER'S NOTES:
Items 7 through 11 are not needed because the application meets requirements for abbreviated AEA, both for infrequent use and according to Tier 0 approach, i.e. < 1 ppb.

Item 12:
Preparer is stated by name as Nancy Grice McGowan.
Deficient

Deficiency: Job Title and qualifications (e.g., educational degrees) of the preparer should be presented, contract testing laboratories, and agencies consulted should be identified.

Item 13:
Certification is given by the President of the Company. Adequate.

Appendices are given for MSDS for FAC, brown (drug substance) not for FerriSeltz powder packets (drug product), Composition of FerriSeltz powder 3g packets, Compliance certification for production of drug substance, Compliance certification for production of drug product, 5-year production proforma. Adequate

Deficiencies: A dated, signed certification should be signed by the responsible official, and the following statement should be included in item 13:

1. "The undersigned official certifies that the EA summary document (pages x-x) and Appendices x-x (pagesx-x) contain non-confidential information and acknowledges that this information will be made available to the public in accordance with 40 CFR § 1506.6."

Item 14, & 15:
Adequate information.

CONCLUSION:
There is adequate information contained here for a full or Tier 0 EA abbreviated format, except for the deficiencies stated in the review. The MEEC is than 1ppb. The applicant needs to be informed of the deficiencies. All permits, including those for the foreign facility, appear to be accounted for and cited. No likely significant adverse environmental effects are determined from the review of this EA. A FONSI is recommended.
Draft comments attached.

Prepared by _____ 7/10/96
Milagros Salazar, Ph.D. Review Chemist, HFD-160 Date

cc:
HFD-160/ orig NDA
HFD-160/Div file
HFD-160/Leutzinger/Salazar
HFD-160/Cuzack
HFD-357/file NDA 20-292
HFD-357/Sager

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Date: 18 November 1996
To: File NDA 20-292 (FerriSeltz)
From: Laraine L. Meyers, PhD, RPh

Subjects: 1. Genetic toxicity studies
2. Acute i.p. study

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1. This NDA does not include genetic toxicity studies which currently are generally required for characterization of the safety profile of a marketed drug. At the time of IND and NDA submissions for FerriSeltz (orally administered), genetic toxicity studies were not requested, most likely because iron salts have been extensively utilized as OTC oral hematinics for many years and because the other NF and USP ingredients are also commonly used in OTC preparations and/or food. I agree that the lack of genotoxicity studies is not a critical deficiency in the NDA. I suggest that the labeling section on carcinogenesis/mutagenicity simply state that studies for genotoxic potential were not performed.

2. An acute intraperitoneal toxicity study in rats was performed in compliance with GLPs at . in 1991. The purpose was to investigate potential toxicity of FerriSeltz in the event of leakage into the peritoneum via a gut perforation. An intraperitoneal study is required routinely for orally administered contrast agents used for imaging the gastrointestinal tract.

The study did not reveal adverse effects during the 14-day observation period following a single dose of 120 mg/kg (1/2 the maximum recommended dosage of 12 grams based upon body weight for a 50 kg patient). It is important to note that according to the study protocol, only gross lesions were to be examined histologically. Since no lesions were noted at necropsy, no abdominal tissues were examined for microscopic lesions. This is a protocol deficiency; abdominal tissues should be evaluated for potential histopathology such as inflammatory response which may lead to adhesions regardless of whether there are macroscopic findings.

For the use of FerriSeltz in the indicated populations for the present NDA, the lack of histologic examination of abdominal tissues is considered not to be a critical deficiency. However, if patients with GI perforations/fissures or prolonged GI transit time are studied in the future, or if clinical use otherwise places patients at risk of peritoneal exposure, a more complete intraperitoneal study to include histologic examination of exposed tissues should be conducted with exaggerated doses in an appropriate animal model.

Laraine L. Meyers 18 Nov 1996
Laraine L. Meyers, PhD,RPh / Date

cc: Achiv NDA 20-292
HFD-160 Div file NDA 20-292
HFD-160//Love/Raczkowski/Jones/Chow

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
NDA 20-292 RS

Ronald L. Dundore, Ph.D.
Reviewing Pharmacologist

DOCUMENT NUMBER: NDA 20-292 RS
SUBMISSION DATE: November 15, 1995
CENTER RECEIPT DATE: November 16, 1995
REVIEWER RECEIPT DATE: March 27, 1996
DRAFT REVIEW COMPLETE: July 10, 1996

SPONSOR: Oncomembrane, Inc.
1201 Third Ave., Suite 3010
Seattle, WA 98101

DRUG: FerriSeltz™, ferric ammonium citrate, OMR

PROPOSED INDICATION: Oral contrast agent for magnetic resonance imaging of the upper abdomen.

FORMULATION: Each 3 gram packet of FerriSeltz™ contains the following:

Ingredient	Amount
Ferric ammonium citrate, brown, USP	600 mg
(as elemental iron)	105 mg
Sodium bicarbonate, USP	1250 mg
Tartaric acid, NF	1100 mg
Aspartame, NF	47 mg
Grape flavoring, Micron ZD-3870	3 mg

PROPOSED DOSING REGIMEN: FerriSeltz™ is administered orally to patients who have fasted for a minimum of 6 hr. The recommended dose of FerriSeltz™ is 2-4 packets dissolved in 600 ml of water. Therefore, the proposed human dose is 6-12 g or 120-240 mg/kg of FerriSeltz™ (assuming a 50 kg human). The human dose of FerriSeltz™ also represents 210-420 mg Fe or 4-8 mg Fe/kg.

RELATED NDA/IND:

BACKGROUND INFORMATION: The original NDA was submitted on 11/12/92 but was not filed (refusal to file letter dated 1/8/93); no pharmacology/toxicology issues were included in the refusal to file letter. The NDA was resubmitted on 11/16/95. The active ingredient in FerriSeltz™, ferric ammonium citrate (FAC), is the active ingredient in a number of OTC products including Geritol® Liquid. FAC has been granted Generally Recognized as Safe (GRAS) status as a nutrient supplement with no limitations other than good manufacturing practice (53 FR 16862). A number of the studies included in the application were submitted

previously to support and, as such, were reviewed by Dr. A. Weir . A portion of this review was excerpted from the previous review

ABSORPTION, DISTRIBUTION, METABOLISM AND EXCRETION

No nonclinical ADME studies were included in the application.

ACUTE TOXICITY

1. Acute oral toxicity study of ferric ammonium citrate in rats. Study no. 005852, conducted by Otsuka Pharmaceutical Co., Ltd., Tokushima, Japan, in-life phase 9/12/89-11/22/89, report dated 2/13/90, in compliance with Japanese Good Laboratory Practice standards.

Methods: Sprague-Dawley rats, 5/sex/group, received an oral dose of distilled water or 2000 mg/kg FAC (amount of Fe not provided). The dose volume for both groups was 10 ml/kg. The rats were maintained for 14 days after dosing. Toxicity was assessed by clinical observations (1, 2, 4, 6, and 8 hr after dosing and daily thereafter), body weight (pretest and on days 1, 3, 7, 10 and 14), food consumption (weekly) and necropsy.

Results: Diarrhea and perianal staining were observed on the day of treatment. On days 1 and 2, black feces were observed. No other effects were noted.

2. An acute oral toxicity study of OMR formulation in the rat. Study no. 5859-90, conducted by in-life phase 6/21/90-7/5/90, report dated 1/3/91, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Sprague-Dawley rats, 5/sex/group, received an oral dose of distilled water or 120, 1200 or 2000 mg/kg of FerriSeltz™ (4, 40 or 67 mg Fe/kg). The dose volume for all groups was 10 ml/kg. The rats were maintained for 14 days after dosing. Toxicity was assessed by clinical observations (daily checks for clinical signs and twice daily checks for mortality), body weight (pretest and on days 3, 7, 10 and 14), food consumption (weekly), gross pathology, organ weight (absolute and relative) and histopathology of all relevant tissues.

Results: Soft stools and/or fecal staining in several mid and high dose (1200 and 2000 mg/kg) animals at 2 and/or 4 hr after dosing were the only treatment-related findings in this study.

Reviewer comments: Due to the relatively insignificant nature of the treatment-related effects, 2000 mg/kg is considered the no observed effect level (NOEL) for this study. The

softened stool and fecal staining were not observed in the repeat dose study in which rats received 40, 120, 360 or 1200 mg/kg/day of FerriSeltz™ for 14 days. This difference may be due to the rats in the repeat dose study not being fasted prior to treatment.

3. An acute intraperitoneal toxicity study of OMR formulation in the rat. Study no. 5858-90, conducted by in-life phase 6/20/90-7/10/90, report dated 1/7/91, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Sprague-Dawley rats, 5/sex/group, received a 10 ml/kg i.p. injection of saline or a 120 mg/kg i.p. injection of FerriSeltz™. The animals were maintained for 14 days after treatment. Toxicity was assessed by clinical observations (daily monitoring for clinical signs and twice daily mortality checks), body weight (pretest and on days 3, 7, 10 and 14), food consumption (twice weekly), clinical pathology (hematology, coagulation studies, clinical chemistry and urinalysis), gross pathology and histopathology of gross lesions.

Results: No adverse effects were reported.

4. An acute oral toxicity study of OMR formulation in the dog. Study no. 90-3577, conducted by in-life phase 7/6/90-7/22/90, report dated 1/7/91, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Beagle dogs, 3/sex/group, received an oral dose of distilled water of 120, 1200 or 2000 mg/kg of FerriSeltz™ (4, 40 and 67 mg Fe/kg). The dose volume for all groups was 10 ml/kg. The dogs were maintained for 14-16 days after dosing. Toxicity was assessed by observations for mortality and clinical signs (1, 2, and 4 hr after dosing and daily thereafter), body weight (pretest, days 3, 4, 7, 11 and 14 and prior to necropsy), food consumption (weekly), gross pathology, organ weight (absolute and relative) and histopathology of all relevant tissues (control and high dose dogs only except for the testes and epididymides in which case all groups were examined).

Clinical observations: Emesis shortly after dosing in all high dose males and watery stools for 1 or 2 days after dosing in all mid and high dose dogs were associated with treatment.

Body weight and food consumption: Body weight gain for females in the 2000 mg/kg dose group was significantly decreased relative to controls at 3, 4 and 7 days after treatment. Although food consumption was decreased during week 1 for these animals, the difference was not statistically significant.

Gross pathology: No effects were observed.

Organ weight: In dogs receiving 1200 and 2000 mg/kg, mean testes weight (absolute and relative to body and brain weights) were decreased approximately 40% relative to the control value. The testes/body weight ratio was significantly decreased in both treatment groups. This effect may be related to variations in the stage of sexual maturity.

Histopathology: No effects were observed. The reproductive organs were characteristic of young sexually immature dogs.

Reviewer comment: Since neither the weight loss nor the testicular effect observed in this study were observed in the repeat dose dog study described below, these effects are not considered treatment-related. The NOEL is considered to be 2000 mg FerriSeltz™/kg.

REPEAT DOSE TOXICITY

1. A 14-day subacute oral toxicity study of OMR formulation in the rat. Study no. 90-3604, conducted by in-life phase 9/17/90-10/8/90, report dated 1/7/91, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Sprague-Dawley rats received an oral dose of distilled water or 40, 120, 360 or 1200 mg/kg/day of FerriSeltz™ (5 times the maximum human dose) for 14 days. The groups receiving 40, 120 and 360 mg/kg/day contained 10 rats/sex/group; the control and 1200 mg/kg/day groups contained 15 rats/sex/group. All dose volumes were 10 ml/kg. One or two days after the last dose was given, 10 rats/sex/group were sacrificed. The remaining 5 rats/sex/group in the control and 1200 mg/kg groups were sacrificed after a 7 day recovery period. Toxicity was assessed by observations for mortality and clinical signs (twice daily), physical examination (pretest and daily), ophthalmoscopic examination, body weight (pretest and twice weekly thereafter), food consumption (pretest and twice weekly thereafter), clinical pathology (clinical chemistry, hematology and urinalysis), necropsy, organ weight (absolute and relative) and histopathology of relevant tissues (for the control and high dose groups only).

Results: No effects clearly attributable to FerriSeltz™ were evident.

Reviewer comment: The NOEL for this study is considered to be 1200 mg FerriSeltz™/kg/day.

2. Dosage-range repeated administration toxicity study of OMR formulation administered orally via stomach tube to nonpregnant New Zealand white rabbits. Study no. 215-003, conducted by in-life phase 9/9/91-9/23/91, report dated 1/3/92, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Female rabbits (n=5/group) were given distilled water (10 ml/kg) or 120, 360, 1200 or 2000 mg/kg/day of FerriSeltz™ orally by gavage daily for 14 days. The animals were observed daily for clinical signs of toxicity, body weight and food consumption. After the 14 day observation period, the animals were sacrificed and subjected to necropsy.

Results: One animal given 120 mg/kg/day of the test agent died as a result of a intubation accident. No other deaths were observed. The daily administration of FerriSeltz™ at doses as high as 2000 mg/kg/day did not produce biologically relevant changes in body weight, body weight gain or food consumption. The gross pathological examinations were unremarkable.

3. A 14-day subacute oral toxicity study of OMR formulation in the dog. Study no. 90-3578, conducted by in-life phase 9/21/90-10/9/90, report dated 1/7/91, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Beagle dogs, 3/sex/group, received an oral dose of distilled water or 40, 120, 360 or 1200 mg/kg (5 times the maximum human dose) of FerriSeltz™ per day for at least 2 weeks. All dose volumes were 10 ml/kg. The dogs were sacrificed 1 day after receiving the final dose. Toxicity was assessed by observation for mortality and clinical signs (twice daily), testes measurements (prior to dose and on days 1 and 7 and prior to sacrifice), ophthalmoscopic examination, body weight (pretest and twice weekly thereafter), food consumption (pretest and twice weekly thereafter), clinical pathology (clinical chemistry, hematology and urinalysis), necropsy, organ weight (absolute and relative) and histopathology of relevant tissues (for the control and high dose groups only).

Results: Abnormalities attributed to FerriSeltz™ were limited to a marked increase in the incidence of watery stools in dogs receiving 360 and 1200 mg/kg/day. No other effects clearly attributable to FerriSeltz™ were evident.

Reviewer comment: Based on the increased incidence of watery stools, the NOEL was considered to be 120 mg/kg/day.

REPRODUCTIVE TOXICITY

1. Dosage-range developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of OMR formulation administered orally via gavage to Crl:CDBR VAF/Plus presumed pregnant rats (including skeletal and soft tissue evaluation of two dosage groups). Study no. 215-003P, conducted by in-life phase 9/3/91-9/26/91, report dated 1/23/92, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Eight presumed pregnant rats were randomly assigned to each of 4 treatment groups and received distilled water (10 ml) or 120, 360 or 1200 mg/kg/day of FerriSeltz™ orally by gavage on days 6 through 15 of gestation. The rats were observed daily for signs of toxicity, abortion, premature deliveries, body weight and food consumption. Rats were sacrificed on day 20 of presumed gestation. A gross necropsy of the thoracic and abdominal viscera was performed. The uterus of each rat was excised and examined for pregnancy, number and distribution of implantations, live and dead fetuses and early and late resorptions. The number of corpora lutea in each ovary was recorded. Each fetus was weighed and examined for gross external alterations. Approximately one-half of the fetuses in the control and high dose groups were examined for soft tissue alterations. The remaining fetuses in each litter were examined for skeletal alterations.

Maternal observations: No deaths, abortion or premature deliveries were caused by treatment. The average maternal body weight gain was significantly decreased by 20% during days 6 to 20 of gestation in the 1200 mg/kg/day dose group when compared to controls. Food consumption was also decreased in these animals. No other signs of toxicity were observed.

Fetal observations: The administration of the test agent had no effects on the numbers of corpora lutea, resorptions or live and dead fetuses. The fetal sex ratio and body weights were not affected by treatment. Two fetuses from the 1200 mg/kg/day dose group exhibited depressed eye bulges; one of the fetuses exhibited microphthalmia of the right eye and one exhibited small eye sockets and a bifid centrum of the 9th thoracic vertebra. Although these alterations are occasionally noted in control animals in this laboratory, a relationship to treatment could not be ruled out since the alterations were observed in the high dose group only in this study.

Reviewer comment: Since the decreases in maternal body weight gain and the fetal abnormalities observed in this pilot study were not observed in the definitive study described below, a relationship to treatment seems unlikely.

2. Developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of OMR formulation administered orally via gavage to Crl:CDBR VAF/Plus presumed pregnant rats. Study no. 215-003, conducted by in-life phase 11/5/91-11/27/91, report dated 3/20/92, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Twenty-five presumed pregnant rats were randomly assigned to receive distilled water (10 ml/kg) or 120, 360 or 1200 mg/kg of FerriSeltz™ orally be gavage on days 6 through 15 of gestation. The rats were examined daily during the dosage and postdosage periods for clinical observations, abortion, premature deliveries and mortality. Body weights and food consumption were determined on day 0 and days 6 through 20 of gestation. On day 20 of gestation, all rats were sacrificed and subjected to necropsy. The

numbers and distribution of implantations, early and late resorptions, live and dead fetuses and corpora lutea were determined. Each fetus was weighed and examined for sex and gross external alterations. Approximately one-half of the fetuses were examined for soft tissue alterations. The remaining fetuses were examined for skeletal alterations.

Maternal observations: The administration of FerriSeltz™ produced no obvious signs of maternal toxicity. Maternal body weight gain and food consumption were not affected by treatment.

Fetal observations: The numbers of corpora lutea, implantations, resorptions and live and dead fetuses were not affected by treatment with FerriSeltz™. The fetal sex ratio and body weights were also unaffected by treatment. The visceral and skeletal abnormalities observed in the litters of treated dams occurred at incidences not statistically different from those of the control group.

3. Dosage-range developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of OMR formulation administered orally via stomach tube to New Zealand white rabbits (including soft tissue and skeletal evaluation of two dosage groups). Study no. 215-002P, conducted by in-life phase 10/30/91-11/28/91, report dated 4/13/92, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Inseminated rabbits (5/group) received distilled water (10 ml/kg) or 360, 1200 or 2000 mg/kg/day of FerriSeltz™ orally on days 6 through 18 of gestation. The rabbits were examined daily for signs of toxicity. Body weights were recorded twice before dosing and on days 0 and 6 through 29 of gestation. Food consumption was measured on days 0 through 29 of gestation. On day 29 of gestation, rabbits were sacrificed and subjected to gross necropsy of the thoracic and abdominal viscera. The uterus from each rabbit was excised and examined for pregnancy, number and distributions of implantations, live and dead fetuses and early and late resorptions. The number of corpora lutea in each ovary was recorded. Each fetus was examined for sex and gross external alterations. The fetuses from the control and high dose groups were examined for visceral and skeletal alterations.

Maternal observations: No rabbits died, aborted or delivered prematurely. No signs of toxicity were noted. Body weight and food consumption were not affected by treatment.

Fetal observations: The numbers of corpora lutea, implantations and live fetuses were not different among the treatment groups. The percentage of resorbed conceptuses per litter tended to increase in a dose-related manner. However, the percentages of resorbed conceptuses were not statistically different among the treatment groups and were within the historical laboratory control limits. Fetal weight was unaffected by treatment. The examination of the fetuses from the control and high dose groups revealed no visceral or

skeletal alterations due to treatment.

4. Developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of OMR formulation administered orally via stomach tube to New Zealand white rabbits. Study no. 215-002, conducted by in-life phase 2/10/92-3/13/92, report dated 7/17/92, in compliance with US Good Laboratory Practice regulations (21 CFR 58).

Methods: Inseminated rabbits (20/group) were given distilled water (10 ml/kg) or 360, 1200 or 2000 mg/kg/day of FerriSeltz™ orally on days 6 through 18 of gestation. The rabbits were examined daily for signs of toxicity, abortions and premature deliveries. Body weights were measured on days 0 and 6 through 29 of gestation. Food consumption was measured daily on days 0 through 29 of gestation. On day 29 of gestation, the rabbits were sacrificed and subjected to gross necropsy of the thoracic and abdominal viscera. The uterus was excised and examined for the number and distribution of implantations, early and late resorptions and live and dead fetuses. The number of corpora lutea in each ovary was recorded. Each fetus was weighed and examined for sex and visceral alterations. The fetuses were eviscerated and examined for skeletal alterations.

Maternal observations: No deaths occurred during the conduct of the study. Two animals (one in the control group and one in the mid dose group) aborted spontaneously. Four of the animals in the high dose group exhibited abnormal feces (soft or liquid feces, dried feces or no feces). No other clinical observations related to treatment were noted. The treatment with FerriSeltz™ had no obvious effect on body weight, body weight gain or food consumption.

Fetal observations: The numbers of corpora lutea, implantations, live fetuses and early and late resorptions were similar among the groups. Treatment with the test agent had no effect on fetal body weight. Treatment with FerriSeltz™ had no statistically significant, dose-related effects on the incidence of visceral or skeletal alterations in the fetuses.

GENETIC TOXICITY

At the time the sponsor submitted the IND for FerriSeltz™ genetic toxicity studies were not given the critical status currently given to these studies. Due to the GRAS status of FAC and its use in OTC products and as a food additive, genetic toxicity studies were not requested when the IND and the original NDA for FerriSeltz™ were submitted.

SUMMARY AND EVALUATION

FerriSeltz™ is a preparation of ferric ammonium citrate (FAC) which is intended for use as an oral contrast agent in magnetic resonance imaging of the upper abdomen. FAC, the active ingredient in FerriSeltz™, is the active ingredient in a number of OTC products including Geritol® Liquid and has been granted Generally Recognized as Safe (GRAS) status as a nutrient supplement with no limitations other than good manufacturing practice (53 FR 16862). The proposed human dose of FerriSeltz™ is 6-12 g or 120-240 mg/kg (assuming a 50 kg human). This dose of FerriSeltz™ also represents 210-420 mg Fe or 4-8 mg Fe/kg.

The acute administration of FerriSeltz™ to rats and dogs at oral doses up to 2000 mg/kg (approximately 8 times the maximum human dose on a mg/kg basis) produced no obvious signs of toxicity other than a change in stools (soft or watery stools). No obvious toxic effects were noted after the acute intraperitoneal administration of 120 mg/kg of FerriSeltz™ (approximately one-half of the maximum human oral dose) in rats. The lack of overt toxicity after the intraperitoneal administration of the test agent suggests that the toxicological consequences of leakage into the peritoneum from a perforation in the GI tract after oral administration are minimal. The draft labeling states, however, that FerriSeltz™ is contraindicated in patients with known or suspected complete bowel obstruction or perforation of the bowel.

The repeated (14-day) oral administration of FerriSeltz™ to rats and rabbits at doses up to 1200 mg/kg (5 times the maximum human dose) and 2000 mg/kg (8 times the maximum human dose), respectively, produced no obvious toxicity. Watery stools appeared to be the only negative effect produced by the repeated (14-day) administration of FerriSeltz™ to dogs at doses up to 1200 mg/kg. When administered repeatedly to pregnant rats and rabbits at doses of 1200 mg/kg and 2000 mg/kg, respectively, during the period of organogenesis (days 6 through 15 or 18 of gestation), FerriSeltz™ produced no obvious signs of maternal toxicity, embryo-fetal toxicity or teratogenic potential.

The sponsor did not provide rationale for the maximum doses of FerriSeltz™ used in the toxicity studies. The maximum doses used in the toxicity studies represented approximately 5-8 times the maximum human clinical dose on a mg/kg basis. FerriSeltz™ is intended for use as an acutely administered (single dose) diagnostic agent. FAC, the active ingredient in FerriSeltz™, has been granted GRAS status and is used in OTC products and as a food additive. Because no significant toxicity was observed after the repeated administration of FerriSeltz™, a preparation of the GRAS substance FAC, at doses representing 5-8 times the human clinical dose, the toxicity studies included in the application appear to support the safe use of FerriSeltz™ for the proposed indication.

Genetic toxicity studies were not requested from the sponsor during the development of FerriSeltz™ and, consequently, were not included in the application. Given the intended use

for FerriSeltz™ (acute administration as a diagnostic agent) and the GRAS status of FAC, the lack of genetic toxicity studies does not pose a significant safety concern.

LABELING

No changes in the draft labeling are suggested.

RECOMMENDATION

Approval of FerriSeltz™ as an oral contrast agent for magnetic resonance imaging of the upper abdomen is recommended.

Ronald L. Dundore, Ph.D.
Reviewing Pharmacologist

7/18/96
Date

I concur with conclusions and recommendation.
Lauren A. Meyers 7-18-96

cc: Orig NDA
HFD-160/Div File
HFD-160/MO/Chow
HFD-160/PharmTL/Meyers
HFD-160/Chem/Salazar
HFD-160/CSO/Cusack
HFD-345
HFD-427/Biopharm/Udo
HFD-713/Stat/Davi

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ON ORIGINAL

MEMORANDUM

CHEMISTRY REVIEW

To: NDA 20-292, FerriSeltz (ferric ammonium citrate, brown) 600mg

From: Milagros Salazar-Driver, Ph.D., HFD-160 MSD.

9/25/97

Subject: ADDENDUM TO REVIEW #2--
Environmental Assessment (EA): Categorical Exclusion Request

Date: September 24, 1997

The applicant's submission dated 19 September 1997 requests a Categorical Exclusion under 21 CFR 25.31(b) for the EA of this application according to the new EA regulations of July 1997.

The basis for the request is that the expected concentration entering into the aquatic environment has been calculated to be that 1 ppb using the FDA guidance for Industry for the submissions of EA in human drug applications and supplements (Nov. 1995).

The submission describes that assuming all drug substance produced and evenly distributed though the U.S. per day, and no metabolism, the environmental introduction concentration (EIC) is calculated to be as follows:

EIC-Aquatic (ppm) = AxBxCxD =

where: A = kg/year production =
B = l/liters per day entering POTWs =
C = year/365days
D =

Comments: This application would qualify for Categorical Exclusion according to the new regulation criteria under the following type of action for the following:

1. NDA does not result in increase use of an active moiety since it consists of a different formulation and dosage form of some already in the environment; and

2. The calculated EIC is 1ppb.

Categorical exclusion is granted under 21CFR 25.31(b).
ADEQUATE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

STATISTICAL REVIEW(S)

OCT 3 1996

STATISTICAL REVIEW AND EVALUATION

NDA#:	20-292
SPONSOR:	Oncomembrane, Inc.
DRUG:	FerriSeltz (ferric ammonium citrate, brown)
INDICATION:	Upper abdominal imaging agent (T1 images only)
DOCUMENTS REVIEWED:	Volumes 2.01, 2.29 to 2.39, and 2.45 to 2.48 of the sponsor's NDA resubmission dated 11/15/95

DATE: Date received by Medical Division (Stamp Date): 11/16/95
Date received by Division of Biometrics: 11/22/95

MEDICAL REVIEWER:	S. Chow, M.D.
STATISTICAL REVIEWER:	R. Davi, M.S.

MAJOR REVIEW ISSUES:

- Although many of the primary efficacy parameters showed a highly statistically significant improvement for the post-dose images compared to the pre-dose images, other secondary parameters showed that the post-dose images were statistically inferior to the pre-dose images.
- In some cases, the pre-dose study image was used to develop the "gold standard diagnosis". This may have caused the pre-dose image diagnosis to agree with the "gold standard diagnosis" more often than was appropriate.
- The site investigators' evaluation of the images were unblinded with respect to dose and were based on viewing pre-contrast and post-contrast images side by side. The evaluations were also based on a scale which did not allow for the possibility of the post-dose image being worse than the pre-dose image.

I. Introduction

The sponsor has resubmitted the results of two open label, multi center, baseline-controlled phase 3 clinical trials designed to show that FerriSeltz is safe and efficacious as an oral contrast agent for marking the upper gastrointestinal tract in patients undergoing T1 weighted magnetic resonance imaging (MRI) of the upper abdomen (filing meeting 1/4/93, no major statistical issues were cited as reasons for refusal to file). Studies A and B involved six centers each (no center participated in both studies). Two doses, 200 mg Fe/600 mL (6 g FerriSeltz) and 400 mg Fe/600 mL (12 g FerriSeltz), were evaluated in these trials. This submission also includes the results of a retrospective assessment of the images from these trials. The objective in re-evaluating these images was to gain an assessment of the clinical utility of FerriSeltz as was requested by FDA.

II. Study Design

Two hundred seventy five patients who were scheduled to undergo abdominal MRI

studies due to suspected or known diseases were enrolled in these trials (160 in Study A and 115 in Study B). Subjects were required to be able and willing to tolerate a six hour fast and to give their written informed consent. Patients who met any of the following exclusion criteria were not enrolled in the trial: less than 18 years of age; pregnant or nursing a child; "MRI exclusions" (e.g. pacemakers, surgical clips, or metallic implants, or claustrophobia); history of allergy or sensitivity to iron; history of hyperferremia, memochromatosis, or hemosiderosis; high grade intestinal tract obstruction; phenylketonuria; medical condition, presentation (vital signs), or medical history which may prevent safe participation in this study; received treatment with an investigational drug within the past 30 days; treatment with enteric agent or contrast agent within 24 hours prior to FerriSeltz; and treatment with glucagon, scopolamine, or other anti-peristaltic agent within 24 hours prior to FerriSeltz and concomitant with study MRI.

Subjects were randomized to receive a single dose of either 200 mg Fe/600 mL (6 g FerriSeltz) or 400 mg Fe/600 mL (12 g FerriSeltz). T1-weighted spin-echo MRI of the upper abdomen was performed before and 15 minutes after ingestion of FerriSeltz. All MRI variables were consistent for the pre- and post-contrast imaging series. At the discretion of the investigator, T1- and T2-weighted fast scanning sequences were also acquired. However, since the sponsor is not seeking approval of this agent for these image sequences and because of the potential biases associated with the manner in which these images were collected, this review will not address the evaluation of the T1- and T2-weighted fast scanning images. Instead emphasis will be placed on the evaluation of the T1-weighted spin-echo MR images since they are pertinent to the indication desired by the sponsor.

Baseline history and physical examinations were performed within 72 hours before the subjects ingested FerriSeltz. Blood and urine samples were collected for analysis within 24 hours before ingestion of FerriSeltz. Vital signs were monitored immediately before and 30-60 minutes after ingestion of FerriSeltz. Subjects returned 24 hours after FerriSeltz ingestion for measurement of vital signs, collection of blood and urine samples, and questioning about any adverse experiences following dosing. According to the sponsor, subjects with abnormal findings were followed until their measurements returned to baseline.

As part of the original study protocol, the subjects' images were to be evaluated by the site investigators as well as by a blinded reader (a different blinded reader was used for each study).

The site investigators (unblinded to dose) evaluated the pre- and post-dose images side-by-side and rated the degree of improvement in signal intensity, opacification, signal homogeneity, distention, and delineation of gastrointestinal tract in three regions, the stomach, duodenum, and jejunum. The degree of improvement in the

delineation of the gastrointestinal tract was also rated for the stomach wall, bowel wall, head of pancreas, tail of pancreas, and body of pancreas. Possible ratings for the improvement in these parameters were 'none', 'minimal', 'moderate', or 'significant'. Note that this rating scale does not allow for the possibility that the quality of these variables was worse on the post-dose images than on the pre-dose images. This may have introduced bias in the summary statistics (e.g. mean, proportion, etc.) in favor of the contrast enhanced images.

The blinded readers (blinded to clinical history, site, and dose level) rated the same parameters as the site investigators. However, unlike the site investigators, the blinded readers evaluated the images in an unpaired fashion using various scales[1]. The order in which the blinded readers evaluated the images was randomized with respect to pre- and post-dose images, dose level, and investigational site. The differences in the ratings from pre- to post-dose were analyzed. It should be noted that not all of the subjects who were enrolled and imaged in this trial were evaluated by the blinded readers. The sponsor wished to limit the duration of the blinded readers' review so the sponsor amended the original protocol to set a cutoff date for a subject's eligibility to be part of the blinded review. Thirty-eight subjects in Study A and eight subjects in Study B enrolled in the trial after the cutoff date and therefore were not evaluated by the blinded reviewers. In August of 1994, FDA statisticians suggested to the sponsor that the 46 images which were omitted from the blinded review should be blindly read and included in the analysis.

In response to an FDA request for information concerning the clinical utility of FerriSeltz, the sponsor re-evaluated images from these two trials. Pre- and post-dose scans were assessed independently by two blinded readers (not the same readers who participated as the blinded readers for the original protocol). The images were presented to the readers randomized with respect to pre- and post-dose images, dose level, and investigational site. The blinded reviewers assessed the stomach, duodenum, and pancreas in each image for the presence or absence of pathology using a five point scale (1 = definitely normal, 2 = probably normal, 3 = uncertain, 4 = probably abnormal, 5 = definitely abnormal). These image diagnoses were compared to "gold standard" diagnoses which were developed by a Clinical Trials Consultant using all available confirmatory diagnostic data contained in hospital records (including discharge summaries and copies of laboratory tests)

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[1] The rating scales used by the blinded readers to evaluate each efficacy parameter follow:
Signal Intensity: 0 = dark/air, 1 = soft tissue, 2 = intermediate, 3 = body fat, 4 = bright
Opacification: 0 = unmarked, 1 = faintly marked, 2 = moderately, 3 = clearly marked
Signal Homogeneity: 0 = N/A or low intensity, 1 = patchy/compromises interpretation, 2 = slightly patchy/acceptable, 3 = uniform in regions of high intensity
Distention: 1 = collapsed, 2 = partially filled, 3 = distended
Delineation: 0 = indistinct, 1 = minimal, 2 = moderate, 3 = clear distinction

and readings of diagnostic procedures (from CT, ultrasound, endoscopy, biopsy tests, and in some cases the pre-dose MRI image). Since in some cases, the pre-dose MR image was used to develop the "gold standard" diagnosis, the "gold standard" diagnosis may have agreed with the pre-dose image diagnosis more often than was appropriate. As long as the data from the aforementioned sources were not conflicting, the diagnosis was made by the consultant. When any of the above information was conflicting, a consensus diagnosis from three expert radiologists (other than the consultant) was used. The sponsor did not indicate how many subjects had conflicting information and were therefore diagnosed by the panel of experts.

III. Subject Enrollment and Resulting "Analysis Groups"

Two hundred seventy five subjects were enrolled in these trials (160 in Study A and 115 in Study B). As illustrated in Figures 1 and 2 below, 153 subjects in Study A and 114 subjects in Study B had images which were evaluated by the site investigators. The images from 115 subjects from Study A and 103 subjects from Study B were evaluated by the blinded readers. The most frequently reported reason for not including a subject in the blinded readers' evaluation was that the subject enrolled after the cutoff date listed in a protocol amendment to limit the duration of the blinded readers' evaluations.

Figure 1: Number of Subjects in Study A who were Included in the Site Investigators' Evaluation Group and in the Blinded Reader's Evaluation Group

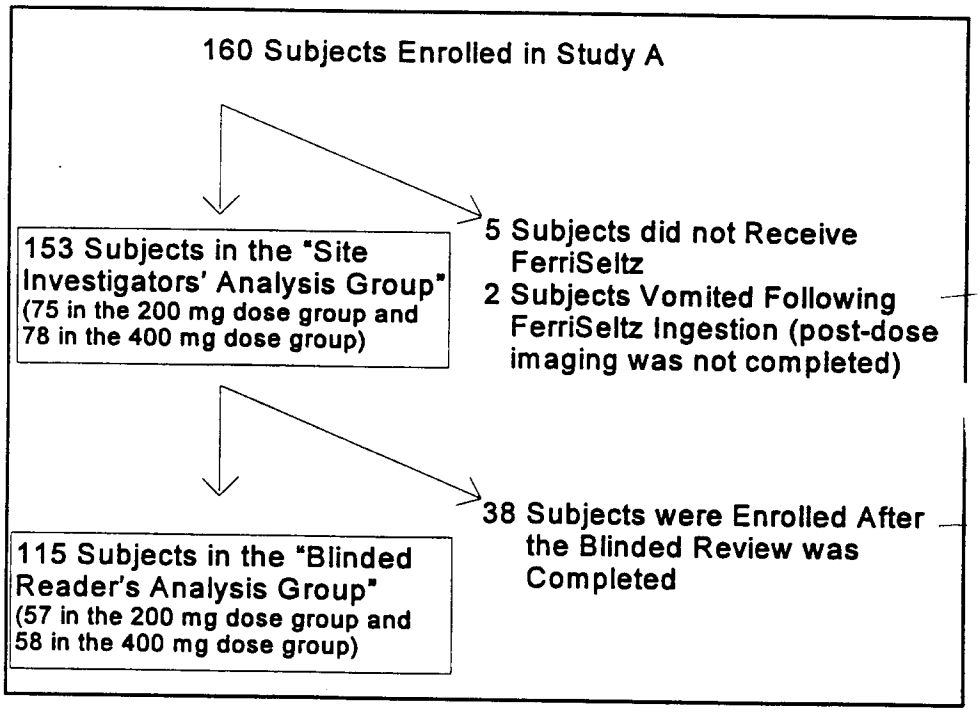
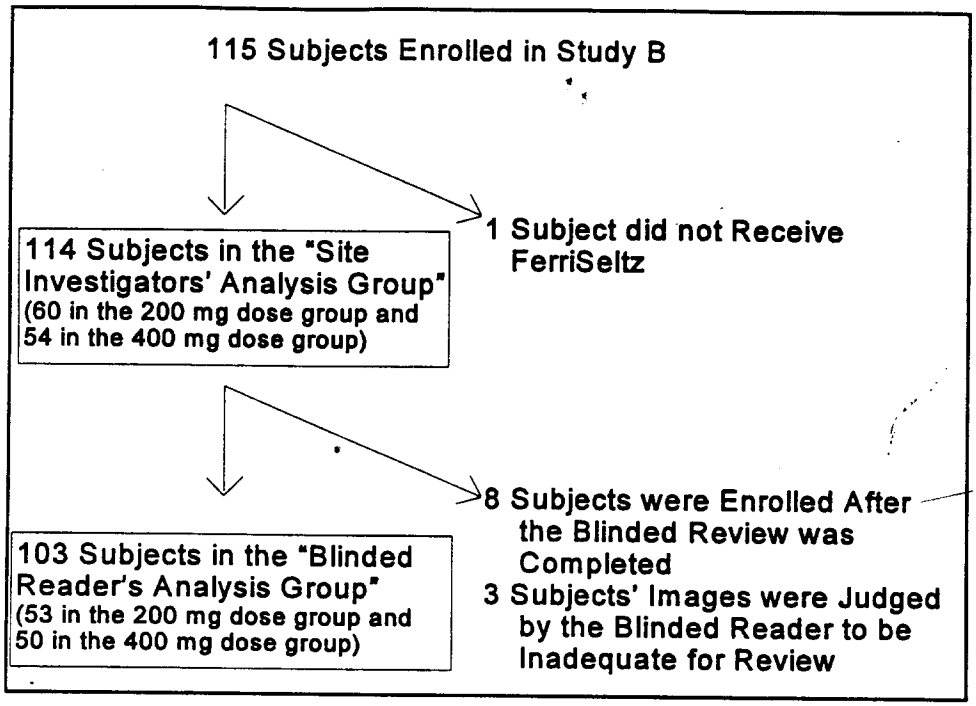


Figure 2: Number of Subjects in Study B who were Included in the Site Investigator's Evaluation Group and in the Blinded Reader's Evaluation Group



All subjects from both trials were included in the retrospective re-evaluation of the images as long as a "gold standard" diagnosis could be established. "Gold standard" diagnoses were established for 151 of the 160 subjects enrolled in Study A and for 113 of the 115 subjects enrolled in Study B. Although the subjects in Studies A and B were originally randomized to one of the two doses, the two dose groups were combined for this analysis. The sponsor justified this on the basis that bowel marking and organ delineation studies showed similar effectiveness of the agent in both dose groups.

IV. Efficacy Results

Site Investigators' Analysis

Because of the fact that the site investigators' evaluations of the images were unblinded paired evaluations and utilized a rating scale which only measure pre to post *improvement*, the data from the site investigators' evaluations of the images is most likely the least reliable of the three data sets submitted by the sponsor. Therefore, discussion of this data set will be included only as an appendix to this review.

Blinded Readers' Analysis

The blinded readers rated the signal intensity, opacification, signal homogeneity,

distention, and delineation of the pre- and post-dose image series. In addition, the blinded readers rated delineation in the stomach wall and bowel wall and in the head, tail, and body of the pancreas for the pre- and post-dose image series. In this review, the pre-dose image series is referred to as the pre-dose image. Similarly, the post-dose imaging slices are collectively referred to as the post-dose image. Note that the ratings assigned by the blinded readers are assessments of the qualities of an image series as a whole rather than ratings of an individual slice. Unlike the site investigators, the blinded readers evaluated the images in an unpaired fashion. The differences in the ratings from pre- to post-dose were analyzed. Thirty-eight subjects in Study A and eight subjects in Study B were not evaluated by the blinded readers because they enrolled in the trials after the cut-off date set to limit the duration of the blinded review.

The differences in the ratings from pre- to post-dose were analyzed using the Wilcoxon signed-rank test. Technically due to the number of comparisons being made, an adjustment for multiple comparisons is necessary. However, since these endpoints are highly correlated and the associated p-values are very low, this adjustment would make little difference in the overall result. **The post-dose image ratings were found to be statistically significantly better than the pre-dose images for signal intensity, opacification, signal homogeneity, and distention in all three anatomical sites, stomach, duodenum, and jejunum in both studies and both dose groups ($p \leq 0.001$ for all 48 comparisons).**

The delineation of the post-dose images was found to be statistically significantly better than the pre-dose images for some region-dose-study combinations. In Study A, all 16 region and dose group combinations showed statistically significant improvement in delineation ($p \leq 0.001$ for all 16 comparisons except for the 6 g FerriSeltz dose group and bowel wall region where $p = 0.008$). In Study B, in the 6 g FerriSeltz dose group, delineation was significantly improved for 5 of the 8 comparisons i.e., for the duodenum ($p < 0.001$), jejunum ($p = 0.005$), bowel wall ($p = 0.004$), head of the pancreas ($p = 0.018$), and tail of the pancreas ($p = 0.012$). For the 12 g FerriSeltz dose group in Study B, delineation was improved for 4 of the 8 comparisons i.e., the stomach ($p = 0.005$), stomach wall ($p < 0.001$), jejunum ($p < 0.001$), and bowel wall ($p = 0.001$).

The sponsor conducted an intent-to-treat (ITT) analysis by assigning images which were not evaluated by the blinded readers a score of zero for all efficacy parameters in all regions (38 images in Study A, 8 in Study B). However, since the same score was assigned to the pre-dose image and the post-dose image, the difference from pre- to post-dose was zero. Therefore the results of the sponsor's ITT analysis did not differ from the per-protocol (PP) analysis.

An more appropriate ITT analysis was completed by this reviewer for Study A.

(Due to the small number of missing evaluations for Study B, the results of an ITT analysis in this instance would be essentially unchanged from that of the PP analysis.) Missing image evaluations were accounted for by assigning scores to the pre- and post-dose images such that the efficacy variable rating decreased by one category for the post-dose image compared to the pre-dose image. A summary of the results of this analysis follows in Table 1.

Table 1: ITT Analysis of Blinded Reader's Image Evaluations[1] for Study A

Region	Efficacy Parameter	Dose Level	
		6g FerriSeltz	12g FerriSeltz
Stomach	Signal Intensity	$p<0.0001$	$p<0.0001$
	Opacification	$p<0.0001$	$p<0.0001$
	Signal Homogeneity	$p<0.0001$	$p<0.0001$
	Distention	$p<0.0001$	$p<0.0001$
	Delineation	$p<0.0001$	$p<0.0001$
Duodenum	Signal Intensity	$p<0.0001$	$p<0.0001$
	Opacification	$p<0.0001$	$p<0.0001$
	Signal Homogeneity	$p<0.0001$	$p<0.0001$
	Distention	$p=0.0009$	$p<0.0001$
	Delineation	$p=0.0003$	$p<0.0001$
Jejunum	Signal Intensity	$p<0.0001$	$p<0.0001$
	Opacification	$p<0.0001$	$p<0.0001$
	Signal Homogeneity	$p=0.0024$	$p=0.0005$
	Distention	$p=0.4600$	$p=0.2200$
	Delineation	$p=0.1400$	$p=0.0370$
Bowel Wall	Delineation	$p=0.5500$	$p=0.1700$
Stomach Wall	Delineation	$p<0.0001$	$p<0.0001$
Pancreas Head	Delineation	$p=0.0062$	$p=0.0001$
Pancreas Body	Delineation	$p=0.0017$	$p=0.0580$
Pancreas Tail	Delineation	$p=0.0660$	$p=0.2100$

1. ITT analysis was completed by this reviewer by assigning the images with missing evaluations scores which decreased by 1 category from pre- to post-dose.

Comparisons between dose groups were made using the Wilcoxon rank-sum test. Overall, 20 comparisons were made as part of this analysis therefore, standards require that a multiple comparison adjustment in the significance level of the tests be made. However, since these endpoints are highly correlated and the associated

p-values are very small, accounting for multiple comparisons would make little difference in the overall result. **The higher dose is significantly better than the lower dose for signal intensity, opacification, and signal homogeneity of the duodenum in Study A ($p=0.002$, $p<0.001$, and $p=0.004$ respectively). None of the dose comparisons in Study B were statistically significant even without an adjustment for multiple comparisons.**

The blinded readers also rated the image quality (inadequate, poor, good, excellent) and artifacts (severe, moderate, minimal, none). Tables 2 and 3 below contain these ratings and the p-values comparing the pre- and post-dose images.

Table 2: Pre- and Post-Dose Image Quality by Dose Level [1]

	Study A				Study B			
	6 g FerriSeltz		12 g FerriSeltz		6 g FerriSeltz		12 g FerriSeltz	
	Pre N=57	Post N=57	Pre N=58	Post N=58	Pre N=53	Post N=53	Pre N=50	Post N=50
Quality of Images for iologic Interpretation								
4 = Excellent	30	26	31	26	12	8	17	6
3 = Good	21	24	23	27	28	23	24	35
2 = Poor	6	7	4	5	13	21	8	8
1 = Inadequate	0	0	0	0	0	1	0	0
Missing [2]	0	0	0	0	0	0	1	1
p-value [3]	0.329		0.208		0.013		0.034	

1. This table was created based on data in the sponsor's submission.
2. The quality of this image was not evaluated by the blinded reader. A reason for this omission was not provided in the sponsor's submission.
3. Changes from pre- to post-dose were evaluated using Wilcoxon signed-rank test.

No significant differences were found between doses in the quality of the images for radiologic interpretation. However, as indicated in Table 2, a statistically significant decrease from pre- to post-dose in the quality of the images was found in Study B ($p=0.013$ for the low dose group, $p=0.034$ for the high dose group). These relationships were verified by this reviewer using an exact test. Though not statistically significant in Study A the pre to post difference trended in the same direction. **These results imply that the blinded readers felt the quality of the pre-dose image for radiologic interpretation was better than that of the post-dose image.**

Table 3: Artifact/Effect on Interpretation of Pre- and Post-Images by Dose Level [1]

	Study A				Study B			
	6 g FerriSeltz		12 g FerriSeltz		6 g FerriSeltz		12 g FerriSeltz	
	Pre N=57	Post N=57	Pre N=58	Post N=58	Pre N=53	Post N=53	Pre N=50	Post N=50
Artifact/Effect on Interpretation								
1 = None or no effect	38	24	41	28	12	11	15	7
2 = Minimal	13	20	10	20	27	18	28	26
3 = Moderate	6	9	5	9	10	12	6	14
4 = Severe	0	3	1	1	4	10	0	3
Missing [2]	0	1	1	0	0	2	1	0
p-value [3]	0.001		0.021		0.029		<0.001	

1. This table was created based on data in the sponsor's submission.
2. The extent of artifact/effect on interpretation was not evaluated by the blinded reader for these images. Reasons for these omissions were not provided in the sponsor's submission.
3. Changes from pre- to post-dose were evaluated using Wilcoxon signed-rank test.

No significant differences were found between doses in the artifact/effect on interpretation. However, as indicated in Table 3, a statistically significant increase from pre- to post-dose in the artifact/effect on interpretation was found in both Study A ($p=0.001$ for the low dose group, $p=0.021$ for the high dose group) and Study B ($p=0.029$ for the low dose group, $p<0.001$ for the high dose group). These relationships were verified by this reviewer using an exact test. **These results indicate that the blinded readers felt the artifact/effect on interpretation seen for the pre-dose image was less than that of the post-dose image.**

Pre- and Post-Dose Image Diagnoses Compared to "Gold Standard Diagnoses"

The clinical utility of FerriSeltz was assessed based on a re-evaluation of the image sets from these two trials. The 6 g and 12 g FerriSeltz dose groups were combined for this analysis. The pre- and post-dose image sets were assessed randomly (randomized with respect to pre- and post-dose, dose level, and investigational site) and independently by two blinded readers who rated the stomach, duodenum, and pancreas for each image set using a five point scale (1 = definitely normal, 2 = probably normal, 3 = uncertain, 4 = probably abnormal, 5 = definitely abnormal). The five point scale listed above was reduced to a three point scale as per protocol, by defining a score of 1 or 2 on the previous scale as "normal", 4 or 5 was listed as "abnormal", and 3 remained "uncertain". These image diagnoses were compared to "gold standard" diagnoses which were developed by a Clinical Trials Consultant using all available confirmatory diagnostic data. In some cases the pre-

dose MRI image was used to develop the "gold standard" diagnosis. This could cause the "gold standard" diagnosis to agree with the pre-dose image diagnosis more often than is appropriate. When any of the confirmatory diagnostic data was conflicting, the consensus of three expert radiologists (the "Clinical Trials Consultant" was not included) was used as the "gold standard" diagnosis. The sponsor did not provide the number of cases which involved conflicting information and were referred to the expert panel for diagnosis.

Tables 3, 4, and 5 contain the comparison of the pre- and post-dose image diagnoses to the gold standard diagnoses for each anatomical region (stomach, duodenum, and pancreas, respectively) by each blinded reader. The data for Studies A and B have been combined for this analysis.

Calculating sensitivity and specificity estimates from this data is not appropriate due to the large number of "uncertain" diagnoses. Therefore, the comments following Tables 3, 4, and 5 address the relationships between actual cell frequencies rather than sensitivity and specificity measurements. Specifically it is noted how many "uncertain" pre-image diagnoses fell into correct diagnoses using the post-image and if this proportion is statistically significant.

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Table 3: Comparison of Pre- and Post-Dose Image Diagnoses to the "Gold Standard Diagnoses" for the Stomach Region [1]

Blinded Reader #1			Gold Standard Diagnosis	
	Pre-Dose Image Diagnosis		Normal	Abnormal
		Normal	84	1
		Uncertain	159	11
		Abnormal	2	4

			Gold Standard Diagnosis	
	Post-Dose Image Diagnosis		Normal	Abnormal
		Normal	220	5
		Uncertain	16	5
		Abnormal	9	6

Blinded Reader #2			Gold Standard Diagnosis	
	Pre-Dose Image Diagnosis		Normal	Abnormal
		Normal	20	0
		Uncertain	220	15
		Abnormal	5	1

			Gold Standard Diagnosis	
	Post-Dose Image Diagnosis		Normal	Abnormal
		Normal	188	3
		Uncertain	47	4
		Abnormal	10	9

1. Table was created by the statistical reviewer.

The following conclusions **regarding the stomach region** were noted using the data in Table 3:

(1.) There were 159 (BR#1) and 220 (BR#2) uncertain pre-image diagnoses which according to the gold standard were truly normal. Of the post-dose images, 140/159 = 88.05% CI: (81.97%, 92.65%) (BR#1) and 170/220 = 77.27% CI: (71.16%, 82.64%) (BR#2) were correctly diagnosed with respect to the gold standard diagnosis. This shift away from the uncertain category, pre- to post-dose, is statistically significant in the stomach region for subjects with normal gold standard diagnoses ($p < 0.0001$ for BR#1 and BR#2). Conclusion: The use of FerriSeltz aids in the recognition of normal images where without the drug the images may have been inconclusive.

(2.) The number of images for which the gold standard was abnormal and the pre-image diagnosis was uncertain was, 11 (BR#1) and 15 (BR#2). Of the post-dose images, 4/11 = 36.36% CI: (10.93%, 69.21%) (BR#1) and 8/15 = 53.33% CI: (26.59%, 78.73%) (BR#2) were correctly diagnosed with respect to the gold standard diagnosis. This shift away from the uncertain category, pre- to post-dose, for subjects with abnormal gold standard diagnoses is not statistically significant for BR#1 ($p = 0.097$) but is significant for BR#2 ($p = 0.004$). Conclusion: Although the number of subjects with abnormal gold standard diagnoses is small, it appears (at least according to BR#2) that FerriSeltz is advantageous in the identification of abnormal images where without the drug the images may have been inconclusive.

Table 4: Comparison of Pre- and Post-Dose Image Diagnoses to the "Gold Standard Diagnoses" for the Duodenum Region [1]

Blinded Reader #1			Gold Standard Diagnosis	
	Pre-Dose Image Diagnosis		Normal	Abnormal
		Normal	165	2
		Uncertain	91	2
		Abnormal	0	1

			Gold Standard Diagnosis	
	Post-Dose Image Diagnosis		Normal	Abnormal
		Normal	223	4
		Uncertain	32	0
		Abnormal	1	1

Blinded Reader #2			Gold Standard Diagnosis	
	Pre-Dose Image Diagnosis		Normal	Abnormal
		Normal	66	1
		Uncertain	187	3
		Abnormal	3	1

			Gold Standard Diagnosis	
	Post-Dose Image Diagnosis		Normal	Abnormal
		Normal	144	2
		Uncertain	100	0
		Abnormal	12	3

1. Table was created by the statistical reviewer. Some results are partially based on imputed data.

The following conclusions **regarding the duodenum region** were noted using the data in Table 3:

(1.) There were 91 (BR#1) and 187 (BR#2) uncertain pre-image diagnoses which according to the gold standard were truly normal. Of the post-dose images, 68/91 = 74.73% CI: (64.53%, 83.25%) (BR#1) and 108/187 = 57.75% CI: (50.33%, 64.93%) (BR#2) were correctly diagnosed with respect to the gold standard diagnosis. This shift away from the uncertain category, pre- to post-dose, is statistically significant in the duodenum region for subjects with normal gold standard diagnoses ($p < 0.0001$ for BR#1 and $p = 0.0403$ BR#2). Conclusion: The use of FerriSeltz aids in the recognition of normal images where without the drug the images may have been inconclusive.

(2.) The number of images for which the gold standard was abnormal and the pre-image diagnosis was uncertain was 2 (BR#1) and 3 (BR#2). Of the post-dose images, 0/2 = 0.00% CI: (0.00%, 84.19%) (BR#1) and 2/3 = 66.67% CI: (9.43%, 99.16%) (BR#2) were correctly diagnosed with respect to the gold standard diagnosis. These results were was not statistically significant ($p = 0.50$ for BR#1 and $p = 1.0$ for BR#2). Conclusion: Since the number of subjects with abnormal gold standard diagnoses is small, the data is not sufficient to demonstrate whether FerriSeltz is advantageous in the identification of abnormal images for those subjects who had uncertain pre-dose image diagnoses.

Table 5: Comparison of Pre- and Post-Dose Image Diagnoses to the "Gold Standard Diagnoses" for the Pancreatic Region [1]

Blinded Reader #1		Gold Standard Diagnosis	
Pre-Dose Image Diagnosis		Normal	Abnormal
	Normal	153	12
	Uncertain	60	10
	Abnormal	6	22

		Gold Standard Diagnosis	
Post-Dose Image Diagnosis		Normal	Abnormal
	Normal	179	14
	Uncertain	27	7
	Abnormal	13	23

Blinded Reader #2		Gold Standard Diagnosis	
Pre-Dose Image Diagnosis		Normal	Abnormal
	Normal	148	9
	Uncertain	60	14
	Abnormal	11	21

		Gold Standard Diagnosis	
Post-Dose Image Diagnosis		Normal	Abnormal
	Normal	157	10
	Uncertain	47	11
	Abnormal	15	23

1. Table was created by the statistical reviewer. Some results partially based on imputed data.

The following conclusions **regarding the pancreatic region** were noted using the data in Table 3:

(1.) There were 60 (BR#1) and 60 (BR#2) uncertain pre-image diagnoses which according to the gold standard were truly normal. Of the post-dose images, 39/60 = 65.00% CI: (51.60%, 76.87%) (BR#1) and 38/60 = 63.33% CI: (49.90%, 75.41%) (BR#2) were correctly diagnosed with respect to the gold standard diagnosis. This shift away from the uncertain category, pre- to post-dose, is statistically significant in the pancreatic region for subjects with normal gold standard diagnoses for BR#1 ($p = 0.0273$) but not for BR#2 ($p = 0.0519$). Conclusion: The use of FerriSeltz (at least according to BR#1) aids in the recognition of normal images where without the drug the images may have been inconclusive.

(2.) The number of images for which the gold standard was abnormal and the pre-image diagnosis was uncertain was, 10 (BR#1) and 14 (BR#2). Of the post-dose images, 3/10 = 30.00% CI: (6.67%, 65.25%) (BR#1) and 6/14 = 42.86% CI: (17.66%, 71.14%) (BR#2) were correctly diagnosed with respect to the gold standard diagnosis. These results were not statistically significant ($p = 0.3438$ for BR#1, $p = 0.7905$ for BR#2). Conclusion: Since the number of subjects with abnormal gold standard diagnoses is small, the data is not sufficient to demonstrate whether FerriSeltz is advantageous in the identification of abnormal images for those subjects who had uncertain pre-dose image diagnoses.

V. Safety Results

The number of adverse events experienced in each dose group and study are presented in Table 6. Thirty-five percent (54/155) of patients in Study A reported a total of 85 adverse events. In Study B, 25% (29.114) of patients reported a total of 43 adverse events. In both studies, the highest proportion of adverse events was reported for the digestive system (32% in Study A, 21% in Study B). In Study A, there was a statistically significantly higher proportion of digestive system adverse events in the 12 g FerriSeltz dose group when compared to that of the 6 g FerriSeltz dose group.

Table 6: Incidence of Adverse Events by Body System and Study [1]

Body System / Adverse Event	Study A Total Adverse Events 6 g FerriSeltz	Study A Total Adverse Events 12 g FerriSeltz	Study B Total Adverse Events 6 g FerriSeltz	Study B Total Adverse Events 12 g FerriSeltz
Number of Patients Assessed	76	79	60	54
Number of Patients Experiencing Adverse Events	21 (28%)	33 (42%)	13 (22%)	16(30%)
Body as a Whole	4 (5%)	8 (10%)	4 (7%)	1 (2%)
fever	0 (0%)	1 (1%)	0 (0%)	0 (0%)
headache	3 (4%)	4 (5%)	2 (3%)	1 (2%)
pain	1 (1%)	3 (4%)	2 (3%)	0 (0%)
diovascular	2 (3%)	1 (1%)	0 (0%)	1 (2%)
hypotension	1 (1%)	0 (0%)	0 (0%)	0 (0%)
sickle crisis	0 (0%)	0 (0%)	0 (0%)	1 (2%)
tachycardia	2 (3%)	1 (1%)	0 (0%)	0 (0%)
Digestive	17 (22%) [2]	32 (41%) [2]	10 (17%)	14 (26%)
constipation	1 (1%)	0 (0%)	2 (3%)	0 (0%)
diarrhea	9 (12%)	23 (29%)	5 (8%)	13 (24%)
dyspepsia	1 (1%)	0 (0%)	0 (0%)	0 (0%)
flatulence	1 (1%)	1 (1%)	0 (0%)	0 (0%)
nausea	5 (7%)	6 (8%)	1 (2%)	3 (6%)
pain, abdominal	3 (4%)	8 (10%)	1 (2%)	2 (4%)
pain, rectal	0 (0%)	0 (0%)	0 (0%)	1 (2%)
vomiting	1 (1%)	3 (4%)	2 (3%)	0 (0%)
Nervous System	1 (1%)	0 (0%)	2 (3%)	0 (0%)
anxiety	0 (0%)	0 (0%)	1 (2%)	0 (0%)
convulsions	0 (0%)	0 (0%)	1 (2%)	0 (0%)
insomnia	1 (1%)	0 (0%)	1 (2%)	0 (0%)
Respiratory System	0 (0%)	2 (3%)	1 (2%)	0 (0%)
coughing	0 (0%)	1 (1%)	0 (0%)	0 (0%)
epistaxis	0 (0%)	0 (0%)	1 (2%)	0 (0%)
rhinitis	0 (0%)	1 (1%)	0 (0%)	0 (0%)
enital System	1 (1%)	0 (0%)	0 (0%)	1 (2%)
dysmenorrhea	1 (1%)	0 (0%)	0 (0%)	0 (0%)
infection (UTI)	0 (0%)	0 (0%)	0 (0%)	1 (2%)

1. This table with minor modifications in format was submitted by the sponsor.
2. The incidence of digestive system adverse events was statistically significantly higher in the 12 g FerriSeltz group th[illegible] the 6 g FerriSeltz group (p=0.017)

VI. Conclusions

From a statistical perspective, conclusions regarding the primary and secondary endpoints favor the use of FerriSeltz as an adjunctive imaging agent. However, other comparisons indicated that the post-contrast agent images were inferior to the pre-contrast images with regard to image quality and artifacts.

The following conclusions are based on the blinded readers' evaluations of the pre- and post-dose images.

- The post-dose images are statistically significantly better than the pre-dose images for *signal intensity, opacification, signal homogeneity, and distention in all three anatomical sites, stomach, duodenum, and jejunum* in both studies and both dose groups ($p \leq 0.001$ for all 48 comparisons). The *delineation* of the post-dose images are statistically significantly better than the pre-dose images for 25 of the 32 region-dose-study combinations (the p-value varies across the region, dose, and study combinations).

- The results of Study A indicate that the *higher dose of FerriSeltz is statistically significantly better than the lower dose for signal intensity and opacification of the duodenum* ($p = 0.002$ and $p < 0.001$, respectively). This relationship is not confirmed by the results of Study B.

- The results of Study B reveal a *statistically significant decrease from pre- to post-dose in the quality of the images* ($p = 0.013$ for the low dose group, $p = 0.034$ for the high dose group). Such a relationship is not confirmed by Study A. These results seem to imply that the quality of the pre-dose images for radiologic interpretation is better than that of the post-dose images.

- The results of both Study A and B reveal a *statistically significant increase from pre- to post-dose in the artifact/effect on interpretation* ($p = 0.001$ for the low dose group in Study A, $p = 0.021$ for the high dose group in Study A, $p = 0.029$ for the low dose group in Study B, $p < 0.001$ for the high dose group in Study B). These results indicate that the artifact/effect on interpretation seen for the pre-dose image is less than that of the post-dose image.

The following conclusions are based on the comparisons of the pre- and post-dose image diagnoses to the gold standard diagnoses:

- FerriSeltz seems to be advantageous in correctly determining that a subject is *normal* where without FerriSeltz, that patients' images may have been

- FerriSeltz seems to be advantageous in correctly determining that a subject is *normal* where without FerriSeltz, that patients' images may have been inconclusive. This relationship is statistically significant for both blinded readers in all three regions studied ($p<0.001$ in all cases) except for blinded reader 2's assessment of the pancreatic region ($p=0.269$).

- Because of the small number of subjects with true abnormalities (as judged by the gold standard), it is not possible to conclude from this data whether FerriSeltz is advantageous in correctly determining that a subject is *abnormal* when without FerriSeltz, that patients' images may have been inconclusive. This type of relationship is statistically significant in these studies in only one instance; the stomach region as assessed by blinded reader 2 ($p=0.004$). However, it is possible that in a study with a larger number of truly abnormal subjects, this relationship could become statistically significant in the other regions as well.

Ruthanna C. Davi
Statistician, HFD-720

Concur:

Michael Welch, Ph.D. 10/3/96
Acting Team Leader

Nancy Smith, Ph.D. 10/3/96
Division Director

APPEARS THIS WAY
ON ORIGINAL

cc:
Archival NDA#20-292
HFD-160/P. Love
HFD-160/V. Raczkowski
HFD-160/E. Jones
HFD-160/S. Chow
HFD-160/S. Cusack
HFD-160/File Copy
HFD-344/A. Lisook
HFD-720/Chron. Copy
HFD-720/N. Smith
HFD-720/M. Welch
HFD-720/R. Davi
HFD-720/File Copy
R. Davi/827-3122/WordPerfect/08/19/96
This review contains 21 pages of text, tables, and figures.

Appendix A

Discussion of the Site Investigators' Evaluation of the Images

Site Investigators' Image Evaluation

The unblinded site investigators evaluated the pre- and post-dose images side-by-side and rated the degree of improvement in signal intensity, opacification, signal homogeneity, distention, and delineation of gastrointestinal tract in three regions, the stomach, duodenum, and jejunum. Delineation was also rated for the stomach wall and bowel wall. The site investigators had the following categories as options to assign to each pair of images to describe the 'improvement' from pre- to post-dose: none, minimal, moderate, and significant. Figures 1 through 5 below illustrate the ratings assigned by the site investigators for Study A. Figures 6 through 10 illustrate these scores for Study B. Note that because the rating scale for this analysis did not allow the investigators the option to rate the post-dose images as being worse than the pre-dose images, the data portrayed in Figures 1 through 10 may be artificially inflated.

Because of the fact that the site investigators' evaluations of the images were unblinded paired evaluations and utilized a rating scale which was not properly designed, the data set portrayed in Figures 1 through 10 is most likely the least reliable of the data sets (site investigators' image evaluations, blinded readers' image evaluations, and the gold standard comparisons) submitted by the sponsor. However, it may still be worth noting the following trends which seem to be appearing in this data.

(1.) When comparing the dose groups for each parameter across each anatomical region (a total of 17 comparisons in each study) using the Wilcoxon rank-sum test, the scores for the 12 g FerriSeltz group are statistically significantly better than for the 6 g FerriSeltz group for the following parameters and anatomical regions:

For Study A:

Signal Intensity ($p = 0.019$), Opacification ($p = 0.015$), Homogeneity ($p = 0.033$), and Delineation ($p = 0.013$) in the stomach region.

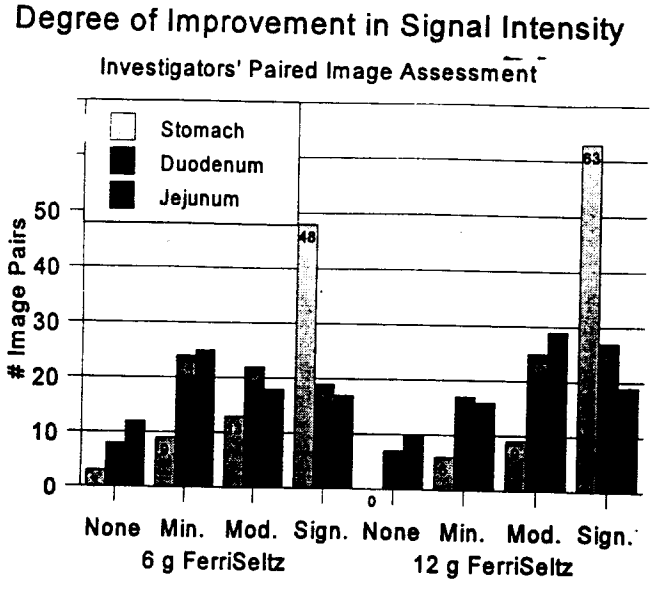
For Study B:

Signal Intensity ($p = 0.044$), Opacification ($p = 0.019$), Homogeneity ($p = 0.038$), and Delineation ($p = 0.043$) in the jejunum region as well as Homogeneity ($p = 0.033$) in the duodenum region.

It is not unusual however, that four or five statistically significant results would be found when this number of multiple comparisons are being made, even if there is no true difference in the dose groups. In fact, if the significance levels of the tests were adjusted to account for multiple comparisons, the p-values which are greater than 0.003 would no longer be considered statistically significant.

(2.) From visual observation of the graphs in Figures 1 through 10, it appears that FerriSeltz is adding some degree of improvement for most parameters in the stomach region and for delineation of the stomach wall as illustrated by the 'moderate' and 'significant' columns in the histograms being taller than the 'mild' or 'none' columns for both dose groups for these regions. It is not visually apparent that there is improvement being added in other regions (duodenum and jejunum) as the 'moderate' and 'significant' columns in the histograms are not markedly taller than the 'mild' or 'none' columns for these regions.

Figure 2 (Study A)



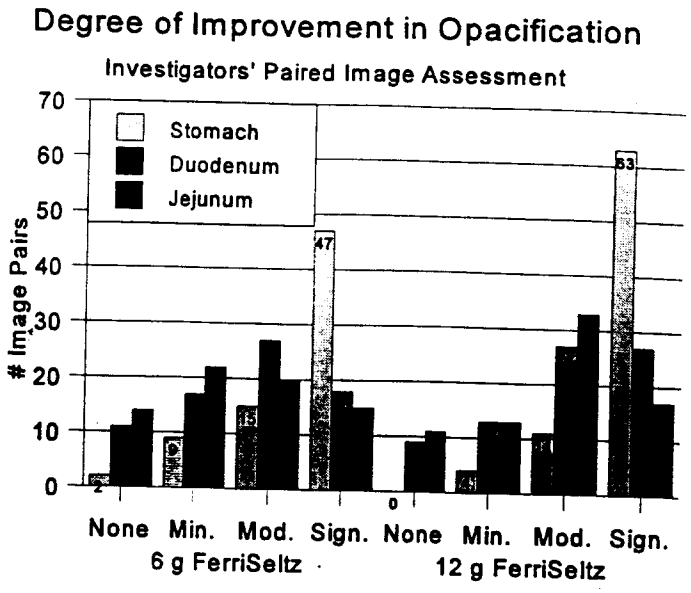
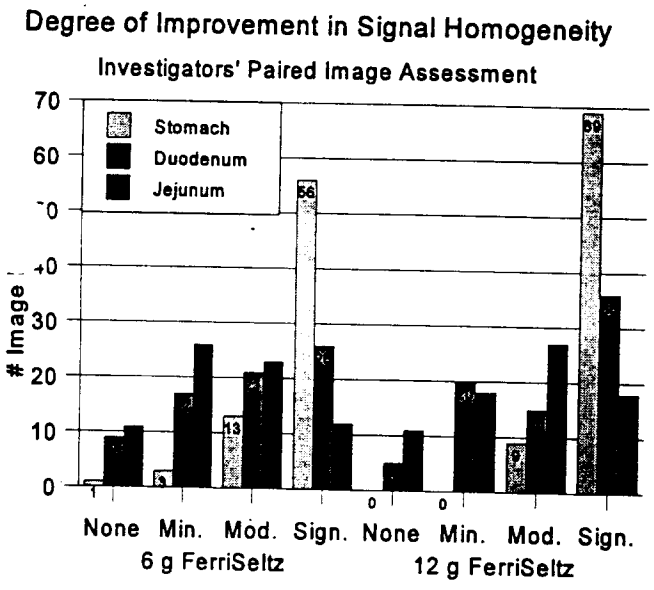


Figure 3 (Study A)

Figure 4 (Study A)



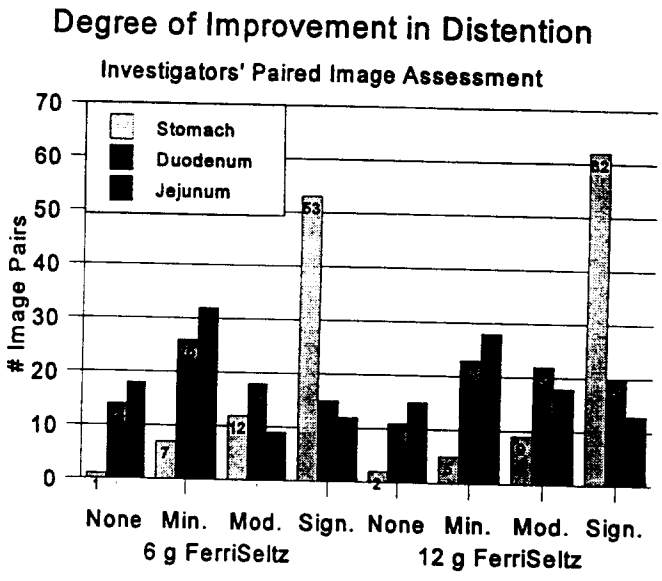


Figure 5 (Study A)

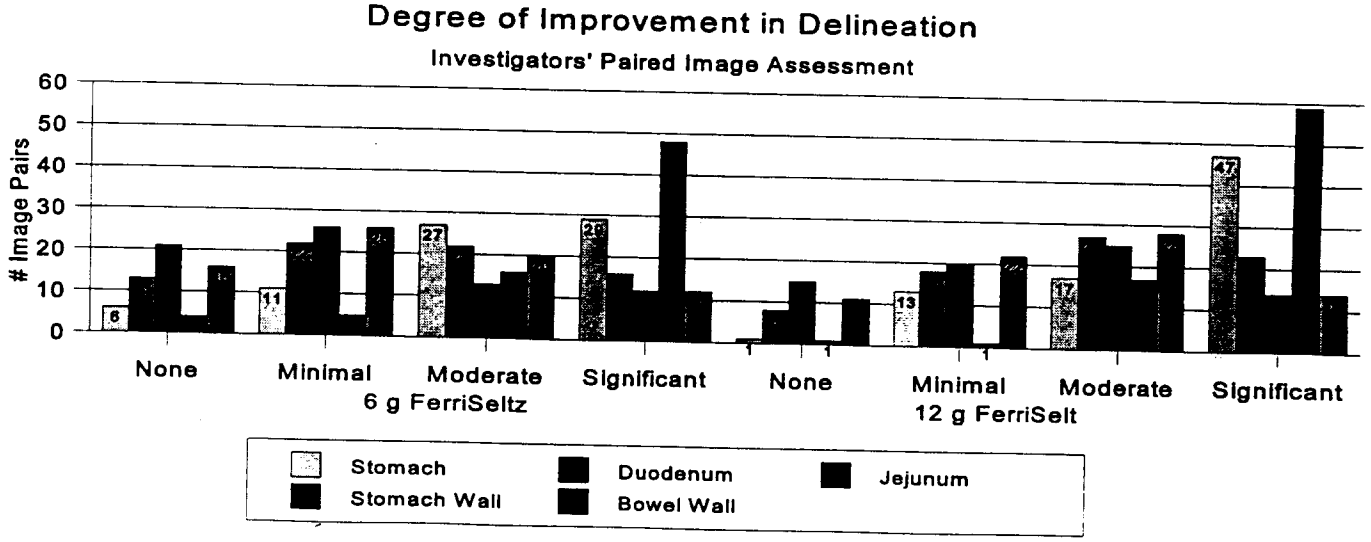
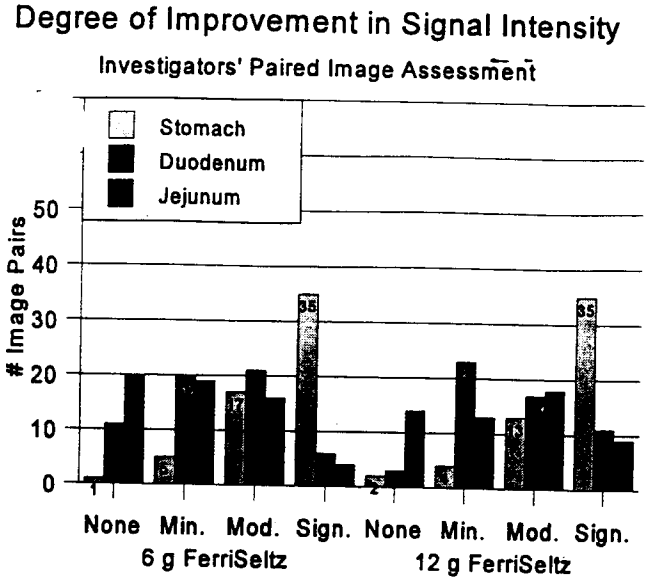


Figure 7 (Study B)



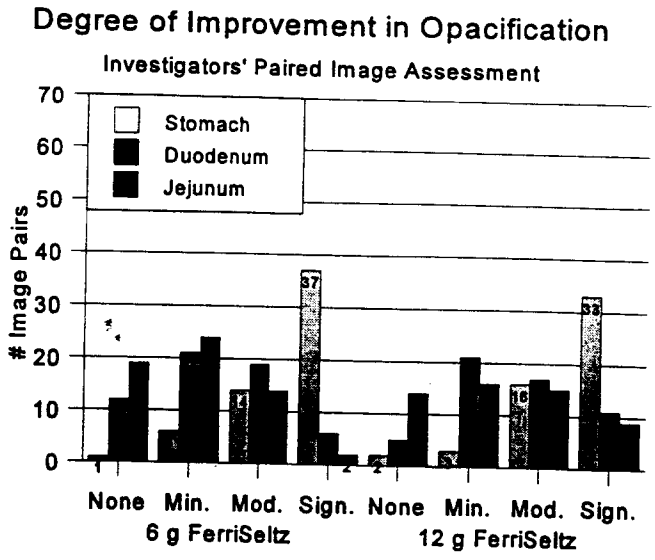
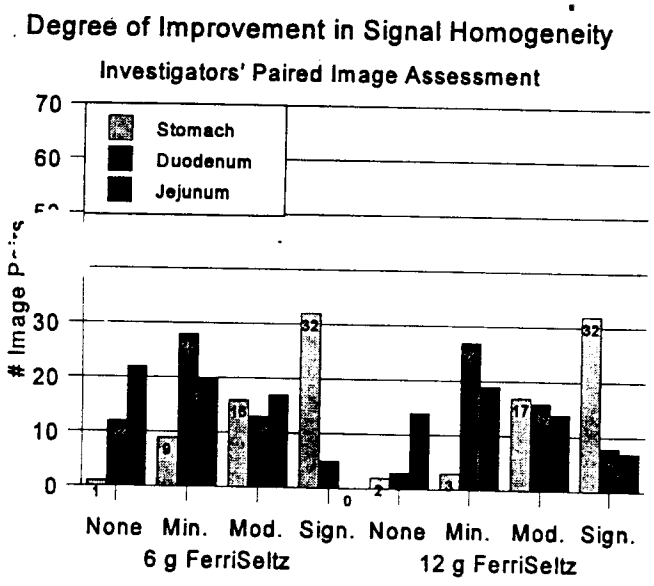


Figure 8 (Study B)

Figure 9 (Study B)



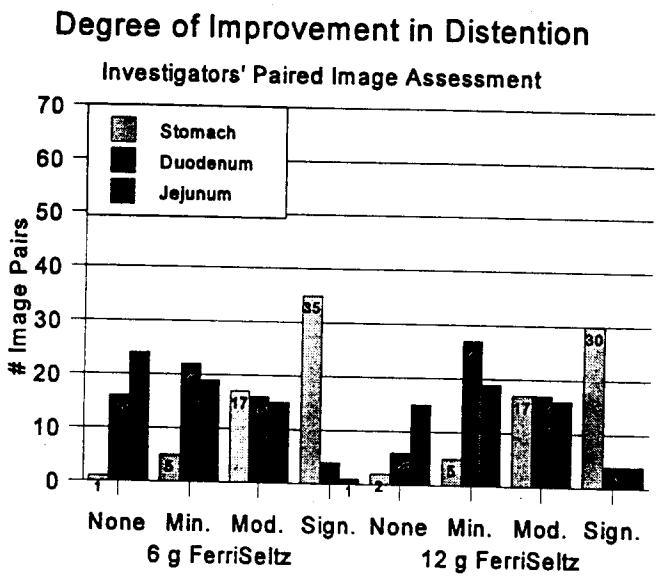
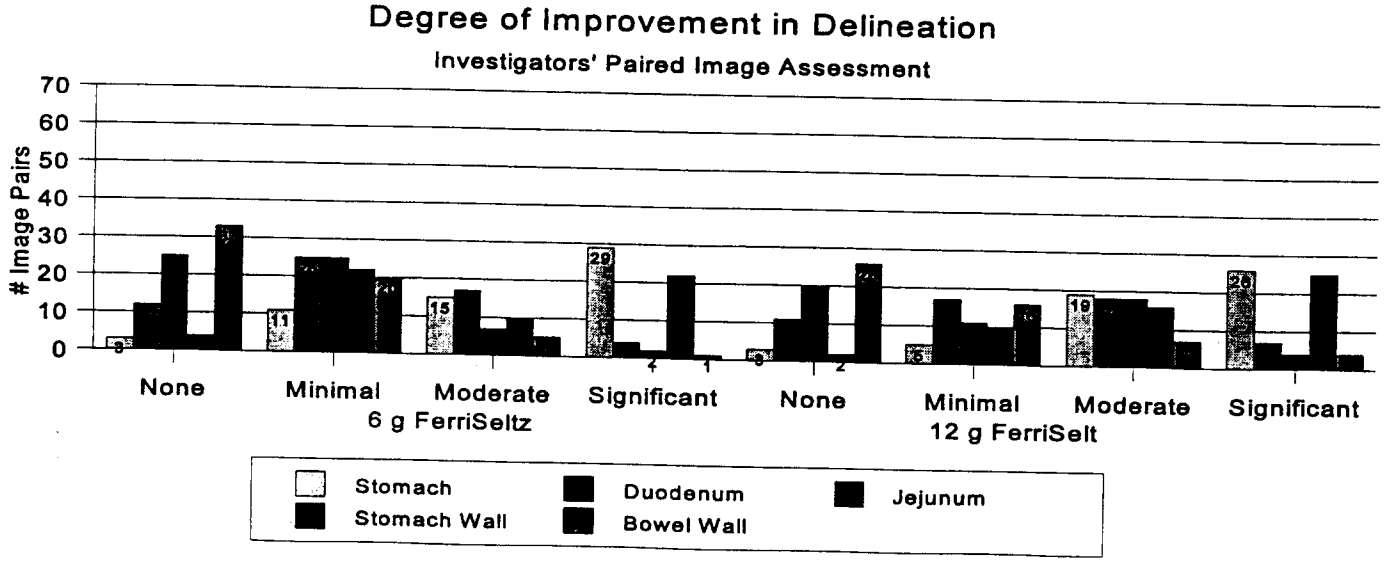


Figure 10 (Study B)



The delineation of the head, tail, and body of the pancreas was also scored by the site investigators. The scores for the 'improvement' in delineation of the pancreas for the pre- and post-dose image pairs follow in Figures 11 and 12. Hypothesis tests comparing dose groups and testing the degree of 'improvement' in pre- and post-dose image pairs yielded no statistically significant results for either Study A or B in the pancreatic region.

Figure 11 (Study A)

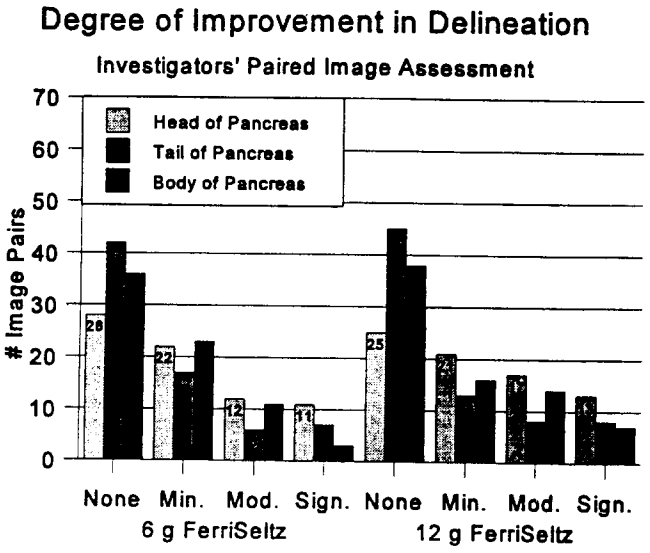
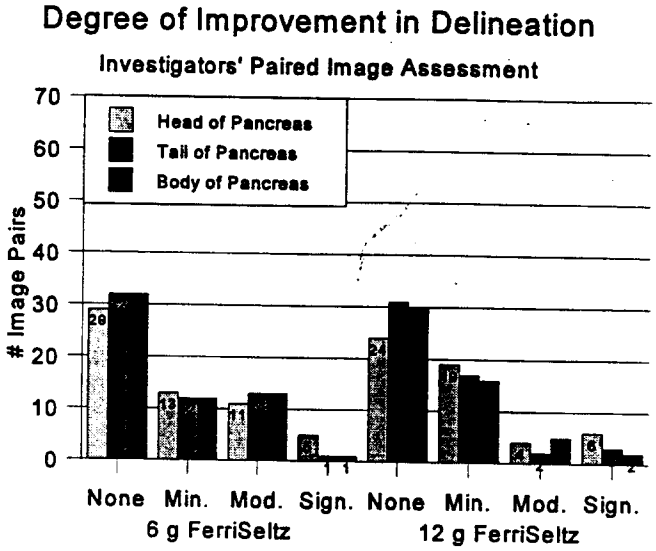


Figure 12 (Study B)



APPEARS THIS WAY
ON ORIGINAL

NOV 2 2 1993

NDA Statistical Consult

NDA#: 20,292

Applicant: Oncomembrane, Inc.

Name of Drug: Ferriseltz

Documents Reviewed: Sponsor's submission dated October 1, 1993

Indication: MR Imaging

Medical Input: HFD-160

The sponsor submitted an NDA for the above indication which was 'refused to file' on January 8, 1993. The sponsor submitted a plan for resubmission on June 4, 1993 inviting comments from the FDA. The present submission is a revised plan taking into account the comments and suggestions from HFD-160 and me.

The primary efficacy comparisons, as described on page 7 of the sponsor's submission, seem to me to be statistically sound. The first test, based on the number of correct diagnoses with the pre-and post- scans, tests for diagnostic capability and the second test, based on a comparison of pre- and post- scans, tests for contrast enhancement. I suggest that the Stuart-Maxwell test for ordered categories given by (8.20), page 123 of the reference at the end be used for contrast enhancement.

The secondary efficacy comparisons are based on the pre- and post-ROC curves as described on page 8 and in the appendix of their submission. The sponsor seems to suggest the following: Let = probability that the bootstrap simulated D exceeds the observed D where D= area under the post-ROC curve- area under the pre-ROC curve summed over the readers. An estimate of D is the ratio of the number of bootstrap simulated D's exceeding the observed D to the number of bootstrap simulations. If $\alpha < .05$, we conclude that the post-scans are better than the pre-scans; otherwise, we conclude that the post-scans are no better than the pre-scans. If the simulations are done thousands of times, the procedure seems sound to me; but the conclusion should only be used as a confirmation of the Stuart-Maxwell test. The main reason is that this test is a conditional test and nothing is known about its power. Consequently, we do not know how good the test is.

The sponsor accepts suggestions (1) to (5) and questions suggestions (6) and (7) of my memorandum of consultation dated July 15, 1993. With respect to (6), I am prepared to go along with the sponsor's suggestion if my clarification in the second paragraph is right. As regards (7), if the diagnoses can be given only in terms of probabilities, there is no choice except

to rely on ROC curves. In such a case, definite values for sensitivity and specificity cannot be arrived at to examine whether they are close to 1 as I suggested. For ready reference, I am enclosing a copy of my memorandum dated July 15, 1993.

REFERENCE

Joseph L. Fleiss(1981). Statistical Methods for Ratios and Proportions, Second Edition. John Wiley and Sons.

R. Murty Ponnapalli, Ph.D.
Biomedical Statistician
Group 7

Concur: Nancy Smith, Ph.D.
11/22/93

cc:

Orig. NDA: 20,292
HFD-160
HFD-160/Dr. Blay
HFD-160/Dr. Love
HFD-160/Dr. Chow
HFD-713/Dr. Dubey [File DRU 1.3.1]
HFD-713/Dr. Smith
HFD-713/Dr. Ponnapalli
Chron.

This review contains 2 pages and an attachment.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF CONSULTATION

DATE: July 15, 1993

FROM: Biomedical Statistician (HFD-713)

THROUGH: Dr. Satya D. Dubey, Ph.D.
Chief, Statistical Evaluation and Research Branch
Division of Biometrics, CDER (HFD-713)

SUBJECT: Proposed plan for resubmission of NDA# 20-292

TO: File (NDA 20-292, Ferriselz)

The Division of Medical Imaging, Surgical and Dental Drug Products (HFD-160) refused to file the above NDA on January 8, 1993. In their letter dated June 4, 1993, the sponsors outlined a plan for resubmission of the NDA after reevaluation of the films taken before and after the administration of the contrast agent. Through this memorandum, I offer the following comments on the statistical aspects of the proposed protocol:

(1) For the primary objective of contrast assessment or image enhancement, one should <u>not</u> exclude patients for whom a gold standard assessment cannot be made.

(2) As suggested to me by the medical officer, I am in favor of <u>two</u> blinded radiologists reading the films instead of <u>three</u>. Not only does the assignment of batches to radiologists in a random fashion become simpler, but this also has implications on what the sponsors call summary level of significance as my subsequent comments will indicate.

(3) The primary efficacy comparisons on page 6 of their letter should also cover the films for pancreas.

(4) If, for both the studies, both reviewers' findings show evidence of positive effect of the contrast agent, each at level of significance .05, this will be sufficient evidence to claim enhancement of the film.

(5) I cannot see any use of the summary significance level obtained by the bootstrap method. The problem here is the following converse: In order that the summary significance level be .05, what significance levels should be chosen for each of the two radiologists? I do not think that the FDA will accept any solution to this problem obtained by the bootstrap method since it is at best only an estimate. Instead, I suggest that .05 be chosen as the level significance for each of the radiologists. It can then be easily seen that the summary level of significance is controlled at .05.

(6) The above comments of mine about bootstrap methodology also apply to the comparison of areas under ROC curves determined by the pre and post scans.

(7) To justify diagnostic claims for the agent, it appears to me that it is not enough if the proportion of "correct" diagnoses after the administration of the agent is statistically significantly better than before the administration. In my opinion, the sensitivity and the specificity after the administration of the agent should both be high (say >.8) to substantiate the diagnostic claim.

R. Murty Ponnapalli

R. Murty Ponnapalli, Ph.D.
Biomedical Statistician
Group 7

cc:
Orig. NDA 20-292
HFD-160
HFD-160/Dr. Chow
HFD-160/Ms. Kummerer
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Dr.Harkins
HFD-713/Dr. Ponnapalli
Chron.

This memorandum contains 2 pages.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

MICROBIOLOGY REVIEW(S)

APR 1 1996

REVIEW for DIVISION of MEDICAL IMAGING and RADIOPHARMACEUTICAL DRUG PRODUCTS
OFFICE OF NEW DRUG CHEMISTRY, MICROBIOLOGY STAFF, HFD-805
MICROBIOLOGIST'S REVIEW NO. 1
April 1, 1996

MICROBIOLOGY REVIEWER: Carol K. Vincent

A. 1. NDA No.: 20-292

DRUG PRODUCT NAME: FerriSeltz (ferric ammonium citrate, brown)

APPLICANT: Oncomembrane, Inc.
201 3rd Avenue, Suite 3010
Seattle, WA 98101

2. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Dry powder to mix with water at point of use for oral ingestion.

3. METHOD(s) OF STERILIZATION:

4. PHARMACOLOGICAL CATEGORY AND/OR PRINCIPAL INDICATION:

Oral contrast agent for marking the upper gastrointestinal tract in patients undergoing T_1-weighted magnetic resonance imaging (MRI) of the upper abdomen.

5. DRUG PRIORITY CLASSIFICATION: 1 S

B. 1. DOCUMENT DATE: 11-15-95
2. AMENDMENT: 12-22-95
5. ASSIGNED: 03-08-96
4. RECEIVED FOR REVIEW: 03-11-96

C. REMARKS: The FDA asked the applicant to provide microbiological 'limits' information concerning the drug product. The December 22, 1995 amendment contains methods for and results from microbial limits testing on five lots of ferric ammonium citrate, brown [FAC] used in manufacturing the FerriSeltz drug product.

D. CONCLUSION: We recommend approval on the basis of microbiological quality. The information provided for microbial limits in the December 22, 1995 amendment is adequate; no further microbiological information is necessary for this product.

cc:
Orig. NDA 20-292
HFD-160/Consult/Chow/Salazar/Weir/Cusack
HFD-160/CKVincent [HFD-805]
Drafted by: CKVincent/03-11-96/30-29-96
R/D Init by: PHCooney/04-1-96
Filename: NDA20292

Carol K. Vincent 4/1/96
Carol K. Vincent
Review Microbiologist [HFD-805]

4/1/96

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-292 SUBMISSION DATE: 11/15/95

FERRIC AMMONIUM CITRATE, BROWN
FERRISELTZ®
2 OR 4 PACKETS (200 OR 400 MG ELEMENTAL IRON)

ONCOMEMBRANE, INC.
1201 THIRD AVE, SUITE 3010
SEATTLE, WASHINGTON 98101 REVIEWER: David G. Udo, Ph.D.

TYPE OF SUBMISSION: RE-SUBMITTED ORIGINAL NDA CODE: 3S

CONTENT PAGE

I. SYNOPSIS/BACKGROUND

NDA 20-292 for ferric ammonium citrate, brown (FerriSeltz®) was submitted by the sponsor on November 15, 1995. FerriSeltz®, a brownish-yellow powder is an oral iron formulation which is proposed as a contrast agent for marking the upper gastrointestinal tract in adult patients undergoing T_1-weighted magnetic resonance imaging (MRI) of the upper abdomen. The sponsor proposes that following oral administration, ferric ammonium citrate, brown mixes with bowel contents and lowers the spin lattice (T_1) relaxation times thereby increasing intraluminal signal intensity on T^1-weighted magnetic resonance images. The package insert recommended doses of FerriSeltz® (2 or 4 packets) are 200 or 400 mg of elemental iron. It is also stated in the package insert that FerriSeltz® is to be administered following reconstitution with 600 mL of tap water and that patients should fast for at least 6 hours before receiving the drug.

For the treatment of iron deficiency anemia, the average daily oral dose of iron is about 200 mg (65 mg t.i.d.). The lethal dose of iron for humans is, on the average, 200-250 mg/kg. However, iron doses as low as 40 mg/kg have been known to be lethal in children. The maximum package insert iron dose (400 mg) in FerriSeltz® is equivalent to 8 mg Fe^{2+}/kg in a 50 kg person. In the CFR, ferric ammonium citrate is listed as one of the "substances added directly to human food affirmed as generally recognized as safe" (GRAS) and are "used in food as nutrient supplements with no limitation other than current good manufacturing practice" (21 CFR Part 184.1(b)(1) and Part 184.1296(b)-(d). "Nutrient supplements" are further defined as "substances which are necessary for the body's nutritional and metabolic processes" (21 CFR Part 170.3(o)(20).

NDA 20-292 was initially submitted on November 12, 1992 and was refused filling on January 4, 1993 primarily due to a number of chemistry, environmental and clinical issues (see Appendix I (pages 8-9). Regarding biopharmaceutic issues, the sponsor's request for a waiver of the Agency's bioavailability requirements was denied (see Appendix I [page 9]). In the "Refuse to File Letter" to the sponsor dated January 8, 1993 (see Appendix I [pages 10-12), the sponsor was informed that meeting the bioavailability requirements with a bioavailability study would be a condition for final NDA approval (see Appendix I [page 12]). Ultimately, it was learned that the sponsor had blood levels of iron and related iron metabolism parameters that would be re-analyzed and submitted to the Agency (see Appendix I [page 20]).

In the re-submitted NDA, the sponsor provided only pooled pre-dose values and 24 ± 4 h mean ($\pm$SE) postdose values for serum iron, total iron binding capacity (TIBC), ferritin and percentage saturation of transferrin obtained in Phase II/III clinical studies which utilized two dose levels of FerriSeltz® containing 200 mg Fe^{3+} (n=136) and 400 mg Fe^{3+} (n=133) (see page 3). The adverse events observed in the Phase II/III studies were also provided (see page 5). Submitted along with these data were 55 literature articles on iron absorption, metabolism and toxicity.

In the literature, it is stated that following oral doses of iron formulations, the time of peak iron absorption is usually 2-4 h postdose. Thus, the pooled Phase II/III 24 ± 4 h postdose values of serum iron and the associated iron metabolism parameters submitted by the sponsor were considered inadequate for accurately assessing the possible absorption of iron from the

FerriSeltz® doses administered in the Phase II/III studies. From a biopharmaceutic perspective, it was considered that the new information provided by the sponsor was not sufficient to permit a substantive review of the NDA. Accordingly, the NDA was considered not filable (see Appendix I [page 23]).

It was felt that in order for NDA 20-292 to be acceptable for filing, the sponsor needed to conduct a study/studies ($n \geq 10$ for each study) using the to-be-marketed FerriSeltz® formulation to assess the potential absorption, systemic exposure, metabolism and elimination of the active moiety/iron. It was recommended that the blood sampling scheme for the requested study/studies allow for an accurate assessment of these parameters and that the blood sampling times should include 0, 1, 2, 3, 4, 6, and 12 h postdose. In this regard, HFD-160 stated (i) that the sponsor had not been explicitly informed that the type of study that is being requested would be needed and (ii) that the NDA would be filed and then the sponsor would be required to conduct the requested study/studies prior to NDA approval (see Appendix I [page 23]).

In the proposed package insert, it is recommended that imaging be performed 5-20 min following FerriSeltz® administration. It is also stated that the FerriSeltz® doses of 200 and 400 g Fe^{3+} are equivalent in contrast enhancement except that the 400 mg Fe^{3+} dose provides better contrast in the "**delineation of the stomach wall and jejunum**". Based on the data provided by the sponsor, overall, the FerriSeltz® doses containing 200 mg Fe^{+3} and 400 mg Fe^{3+} were similar in incidence of adverse events. However, the incidence of gastrointestinal tract related adverse events was 70% higher for the 400 mg iron dose.

The submitted pooled pre-dose and 24 ± 4 h mean ($\pm$SE) postdose values for serum iron, total iron binding capacity (TIBC), ferritin and percentage saturation of transferrin from the Phase II/III clinical studies that utilized the two FerriSeltz® doses containing 200 and 400 mg of iron are considered less than adequate for accurately assessing the possible absorption and disposition of iron. Ideally, the sponsor should have collected more postdose blood samples in the studies to further assess FerriSeltz® absorption and disposition in these clinical studies. However, at both the 200 mg Fe^{3+} and 400 mg Fe^{3+} dose levels, the pooled 24 ± 4 h mean ($\pm$SE) postdose values for serum iron, total iron binding capacity (TIBC), ferritin and percentage saturation of transferrin from the Phase II/III clinical studies were not significantly higher than the corresponding pre-dose values (page 3). These data suggest that at both FerriSeltz® dose levels, any increase in serum iron and the associated iron metabolism parameters that might have occurred in the time interval between FerriSeltz® administration and 24 ± 4 h postdose might have been rather transient. Given these findings, the single dose indication of FerriSeltz® and the limited systemic availability of orally administered ferric iron reported in the literature (see Appendix 1 [pages 24-25]), it seems reasonable not to ask for studies to further assess the potential absorption, systemic exposure, metabolism and elimination of iron for the proposed package insert doses of FerriSeltz®.

II. SUMMARY OF INFORMATION ON BIOAVAILABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, METABOLISM, DRUG-DRUG INTERACTIONS, ETC.

1. BIOAVAILABILITY: No study was conducted to accurately evaluate the bioavailability of FerriSeltz®. The sponsor provided only pooled pre-dose and 24±4 h mean (±SE), values for serum iron, total iron binding capacity (TIBC), ferritin and percentage saturation of transferrin from Phase II/III clinical studies which utilized FerriSeltz® doses containing 200 mg Fe^{3+} (n=136) or 400 mg Fe^{3+} (n=133) (Table 1).

Table 1. Dose Group Absolute Differences in Mean Iron Metabolism Parameters: Pooled Phase II/III Studies (statistically significant differences italicized)

Parameter**	FerriSeltz Dose	Means (± S.E.) Pre-	24±4 hr Post-	Change (post - pre)	Within Group p-value*
Serum iron (mcg/dL)	200 mg Fe	76.5 (3.97)	78.8 (4.11)	1.17 (2.69)	0.663
	400 mg Fe	78.4 (4.13)	78.8 (4.58)	0.71 (3.46)	0.839
TIBC (mcg/dL)	*200 mg Fe*	*327.3 (6.35)*	*320.3 (5.84)*	*-6.58 (3.25)*	*0.045*
	400 mg Fe	*317.2 (6.46)*	*306.1 (6.94)*	*-9.72 (3.73)*	*0.010*
Ferritin (ng/mL)	200 mg Fe	276.1 (37.83)	270.9 (36.62)	-1.28 (7.91)	0.866
	400 mg Fe	452.7 (84.36)	428.0 (68.32)	-32.06 (24.48)	0.193
% Saturation	200 mg Fe	24.3 (1.41)	25.6 (1.48)	0.87 (0.87)	0.319
	400 mg Fe	25.7 (1.54)	26.2 (1.61)	1.04 (1.21)	0.390
Transferrin (mg/dL)	*200 mg Fe*	*238.5 (5.75)*	*282.3 (5.56)*	*-5.64 (2.06)*	*0.007*
	400 mg Fe	*277.9 (6.07)*	*268.3 (6.14)*	*-7.96 (2.34)*	*<0.001*

* Comparison of the change from pre- to post-contrast using paired t-test

** Normal ranges for SmithKline Beecham Labs:

serum iron	50 - 200 mcg/dL (M): 35 - 200 mcg/dL (F)
TIBC	250 - 425 mcg/dL
ferritin	15 - 445 ng/mL (M): 6 - 270 ng/mL (F)
% saturation	20 - 55%
transferrin	214 - 370 mg/dL

Based on literature information, peak absorption of iron from oral iron formulations usually occurs 2-4 h postdose. Therefore, the pooled Phase II/III 24±4 h postdose values of serum iron and the associated iron metabolism parameters were considered less than accurate for assessing the possible absorption and disposition of iron from the FerriSeltz® doses administered in the Phase II/III studies. However, at both dose levels, the pooled 24±4 h mean (±SE) postdose values of serum iron, total iron binding capacity (TIBC), ferritin and percentage saturation of transferrin from the Phase II/III clinical studies were not significantly higher than the corresponding pre-dose values. For some of the iron metabolism parameters, the 24±4 h postdose values were even significantly lower than pre-dose values. These data suggest that at both FerriSeltz® dose levels, any increase in serum iron and the associated iron metabolism parameters that might have occurred in the time interval between FerriSeltz® administration and 24±4 h postdose might have been rather transient.

2. DISTRIBUTION AND METABOLISM: No study was conducted to evaluate the distribution and metabolism of FerrisSeltz®. However, based on literature information, it appears that iron, if absorbed from Ferriseltz®, would undergo the same distribution and metabolic processes as the iron from other oral iron formulations or dietary sources. On this premise, it is reasonable to assume that some of it would enter the hematopoietic pathway and would be incorporated into the hemoglobin of the red blood cells.

The remaining portion would be incorporated into ferritin for storage.

3. ELIMINATION: It appears that unabsorbed iron in FerriSeltz® is eliminated in feces. The amount of iron absorbed from an oral iron formulation depends largely on the iron need of the body. Therefore, once absorbed into the blood, iron is highly conserved. Only about 10% of the body's iron store is lost per year (1 mg per day) in normal adult males. Iron is excreted from the gastrointestinal tract in extravasated red cells. It is also eliminated in bile and in exfoliated mucosal cells. Small amounts of iron are lost in the urine and in desquamated skin. Additional iron loss occurs in menstruating females.

4. PLASMA PROTEIN BINDING: No study was conducted to evaluate the plasma protein binding of FerriSeltz®.

5. FOOD EFFECT: In the package insert, it is stated that FerriSeltz® should be administered under fasted conditions. The effect of food on the disposition of FerriSeltz® has not been studied.

6. SPECIAL POPULATIONS: (a) **Patients with Impaired Bowel**: Studies have not been conducted to assess the disposition of FerriSeltz® in patients with impaired bowel. In the proposed package insert, it is stated that FerriSeltz® "is contraindicated in patients with known or suspected complete bowel obstruction or perforation of the bowel".

(b) **Patients with Iron Overload**: Studies have not been conducted to assess the disposition of FerriSeltz® in patients with iron overload. In the propose package insert, there is no statement of caution or contraindication related to this patient population.

(c) **Pediatric Patients**: Studies have not been conducted to assess the disposition of FerriSeltz® in pediatric patients. In the proposed package insert, it is stated that "safety and effectiveness of FerriSeltz® in children under 18 years of age have not been established".

7. DRUG-DRUG INTERACTIONS: Drug-drug interaction studies with FerriSeltz® have not been conducted. However, based on literature information, iron absorption from the gastrointestinal tract may be enhanced by organic acids such as ascorbic acid, citric acid, and tartaric acid and may be inhibited by complexing agents such as oxalates, phosphates, carbonates, polyphenols, tannins and some antacids that contain carbonate. This information is provided in the proposed package insert under the sub-heading of Drug-Drug Interactions.

8. PHARMACOKINETIC/PHARMACODYNAMIC (PK/PD) RELATIONS: FerriSeltz® is administered for local effect in the gastrointestinal tract. In the proposed package insert, it is recommended that imaging be performed 5-20 min postdose. No information was provided as to whether or not there are differences in the quality of contrast for the images obtained at different times within the specified time window. However, it appears that the imaging time window is the time that optimal gastrointestinal tract distension is attained following FerriSeltz® administration. In the proposed package insert, the sponsor also states the following: "**The improvement in delineation of the stomach wall and jejunum was significantly greater with the higher dose compared to the lower dose; otherwise, the two doses showed equivalent improvement**". However, there is no statement that the higher dose (400 mg Fe^{3+}) is proposed only for MRI procedures involving the stomach wall and the jejunum. Based on the data provided by the sponsor (Table 2), overall, the FerriSeltz® doses containing 200 mg Fe^{+3} and 400 mg Fe^{3+} were similar in incidence of adverse events. However, the incidence of gastrointestinal tract related adverse events were 70% higher for the 400 mg iron dose.

Table 2. Incidence of Adverse Events by Body System:
Pooled Phase II/III Studies
(number of patients with event**, excluding laboratory parameters)

	Total Adverse Events			Moderate or Severe Events***		
Event Severity	200mg Fe (6g OMR)	400mg Fe (12g OMR)	Between Group p-value*	200mg Fe (6g OMR)	400mg Fe (12g OMR)	Between Group p-value*
Patients Assessed	136	133		136	133	
Patients with AE	35 (26%)	49 (37%)	0.065	13 (10%)	15 (11%)	0.693
Adverse Events by Body System:						
Body as Whole:	8 (6%)	9 (7%)	0.807	3 (2%)	2 (2%)	1.000
— fever	-0-	1 (1%)		-0-	1 (1%)	
— headache	5 (4%)	5 (4%)		1 (1%)	1 (1%)	
— pain	3 (2%)	3 (2%)		2 (1%)	-0-	
Cardiovascular:	2 (1%)	2 (2%)	1.000	-0-	1 (1%)	0.494
— hypotension	1 (1%)	-0-		-0-	-0-	
— sickle crisis	-0-	1 (1%)		-0-	1 (1%)	
— tachycardia	2 (1%)	1 (1%)		-0-	-0-	
Digestive:	27 (20%)	46 (35%)	0.089	9 (7%)	11 (8%)	0.648
— constipation	3 (2%)	-0-		1 (1%)	-0-	
— diarrhea	14 (10%)	36 (27%)		4 (3%)	7 (5%)	
— dyspepsia	1 (1%)	-0-		-0-	-0-	
— flatulence	1 (1%)	1 (1%)		-0-	-0-	
— nausea	6 (4%)	9 (7%)		2 (1%)	3 (2%)	
— pain, abdominal	4 (3%)	10 (8%)		2 (1%)	3 (2%)	
— pain, rectal	-0-	1 (1%)		-0-	1 (1%)	
— vomiting	3 (2%)	3 (2%)		1 (1%)	2 (2%)	
Nervous system:	3 (2%)	-0-	0.247	3 (2%)	-0-	0.247
— anxiety	1 (1%)	-0-		1 (1%)	-0-	
— convulsion s	1 (1%)	-0-		1 (1%)	-0-	
— insomnia	2 (1%)	-0-		2 (1%)	-0-	
Respiratory system:	1 (1%)	2 (2%)	0.619	-0-	1 (1%)	0.494
— coughing	-0-	1 (1%)		-0-	1 (1%)	
— epistaxis	1 (1%)	-0-		-0-	-0-	
— rhinitis	-0-	1 (1%)		-0-	-0-	
Skin:	-0-	1 (1%)	0.494	-0-	-0-	
— pruritis	-0-	1(1%)		-0-	-0-	
Urogenital system:	1 (1%)	1 (1%)	1.000	-0-	-0-	
— dysmenorrhea	1 (1%)	-0-		-0-	-0-	
— infection (UTI)	-0-	1 (1%)		-0-	-0-	

* Based on Fisher's Exact test (two-tailed)
** A patient may appear more than once within a body system
***Toxicity grade 2, 3, or 4

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9. FORMULATION: The composition of FerriSeltz® is presented below.

COMPOSITION AND DOSAGE FORM

FerriSeltz™ is formulated as a powder that readily dissolves in water to create a grape-flavored effervescent drink. The composition is as follows:

Ingredient	mg/packet
Ferric ammonium citrate, brown	600
Sodium bicarbonate, USP	1250
Tartaric acid, NF	1100
Aspartame, NF	47
Flavor- Grape Micron ZD-3870	3
Total	3000 mg

III LABELING COMMENTS

1. In the proposed package insert, it is stated that "**safety and effectiveness of FerriSeltz® in children under 18 years of age have not been established**". Therefore, for the **Indication and Usage** section of the proposed package insert, the following might be considered:

> FerriSeltz™ is an oral contrast agent for marking the upper gastrointestinal tract in **adult** patients undergoing T_1-weighted magnetic resonance imaging (MRI) of the upper abdomen.

2. Will FerriSeltz® be used in patients with iron overload (i.e., patients with hemochromatosis and hemosiderosis)? If so, a statement related to the possible risks needs to be included in the package insert. If not, an explicit statement of contraindication should be included in the package insert.

3. In the proposed package insert, the following is stated: "**The improvement in delineation of the stomach wall and jejunum was significantly greater with the higher dose compared to the lower dose; otherwise, the two doses showed equivalent improvement**". Why is the higher dose (400 mg Fe^{3+}) not recommended only for MRI procedures involving these two organs (i.e., stomach wall and jejunum)?

IV. RECOMMENDATION

NDA 20-292, which was re-submitted by the sponsor for ferric ammonium citrate, brown (FerriSeltz®) on November 15, 1996, has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics. Based on the information that is provided, from a clinical pharmacology/pharmacokinetic perspective, the NDA is considered approvable. The General Comment (page 6) should be brought to the attention of the reviewing medical officer. Labeling Comments 1, 2 and 3 (page 6) should also be brought to the attention of reviewing medical officer in order to assess if they have merit for inclusion in the package insert.

Please convey this Recommendation, as appropriate, to the sponsor. Labeling Comments 1, 2 and 3 (page 6) should also be conveyed to the sponsor, as appropriate, if the medical officer concurs.

Appendix I is retained in the Office of Clinical Pharmacology and Biopharmaceutics and may be obtained upon request.

APPEARS THIS WAY
ON ORIGINAL

10/25/96
David G. Udo, Ph.D.
Division of Pharmaceutical Evaluation II

RD Initialed by John Hunt 10/17/96

FT Initialed by John Hunt 10/25/96

Clinpharm/Biopharm Briefing: 25/10/96 at 9.00 a.m in PKLN Room 11-61 (Attendees: Malinowzki (HFD-860), Lazor (HFD-880), Hunt (HFD-860), Jones (HFD-160), Raczkowski (HFD-160), Chow (HFD-160) and Arnstein (HFD-160).

cc: NDA 20-292, HFD-160, HFD-870 (M. Chen, Hunt, and Udo), HFD-870 (Drug, Chron, Reviewer [Clarence Bott, PKLN Rm. 13B-31]), HFD-340 (Viswanathan).

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

ADMINISTRATIVE DOCUMENTS

The United States of America

The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person or persons having title to this patent the right to exclude others from making, using or selling the invention throughout the United States of America for the term of seventeen years from the date of this patent, subject to the payment of maintenance fees as provided by law.

Acting Commissioner of Patents and Trademarks

Attest

010001

US005174987A

United States Patent [19]

Takaichi et al.

[11] Patent Number: 5,174,987

[45] Date of Patent: Dec. 29, 1992

[54] METHOD OF USING IRON CONTAINING PREPARATION FOR NMR IMAGING

[75] Inventors: Akihisa Takaichi; Toshihiko Okamoto; Toshiaki Matsumoto, all of Tokushima; Junji Nakamura, Nara; Toshio Nakamura, Tokushima, all of Japan

[73] Assignee: Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan

[21] Appl. No.: 476,438

[22] PCT Filed: Oct. 3, 1989

[86] PCT No.: PCT/JP89/01009

§ 371 Date: Jun. 4, 1990

§ 102(e) Date: Jun. 4, 1990

[87] PCT Pub. No.: WO90/03800

PCT Pub. Date: Apr. 19, 1990

[30] Foreign Application Priority Data

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Sep. 27, 1989 [JP] Japan 1-252895

[51] Int. Cl.[5] G01N 24/00; G01N 31/00; A61L 9/04; A61K 33/00

[52] U.S. Cl. 424/9; 424/44; 424/647; 424/648; 424/700; 424/715; 424/717; 436/173; 128/653.4

[58] Field of Search ..... 424/9, 646, 647, 648, 424/44, 715, 717, 700; 436/173; 128/653 AF, 654

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Primary Examiner—Richard L. Raymond
Assistant Examiner—Gary E. Hollinden
Attorney, Agent, or Firm—Sughrue Mion Zinn Macpeak & Seas

[57] ABSTRACT

There is described an iron containing preparation for NMR imaging comprising, as necessary ingredients, the prescribed amounts of an iron containing compound, sodium carbonate or sodium hydrogencarbonate and a neutralizing agent. This preparation is safe, easy to drink, and when taking, provides clear and accurate contrast imaging of inner organs. Further, addition of potassium carbonate to this preparation gives excellent preservation stability.

24 Claims, 5 Drawing Sheets

FIG. 1

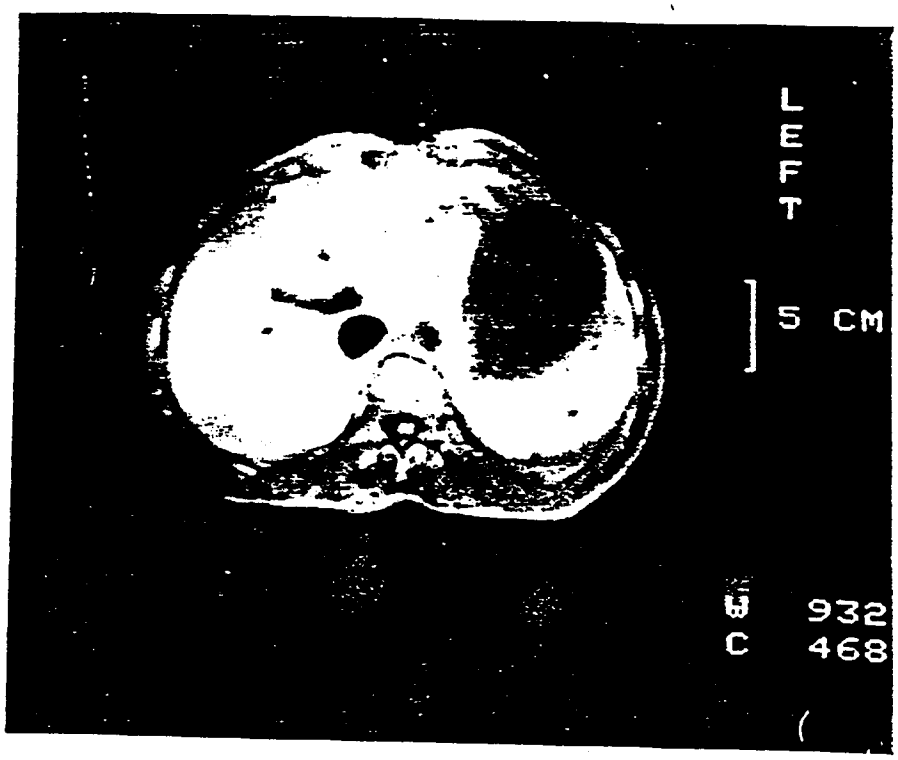


FIG. 2

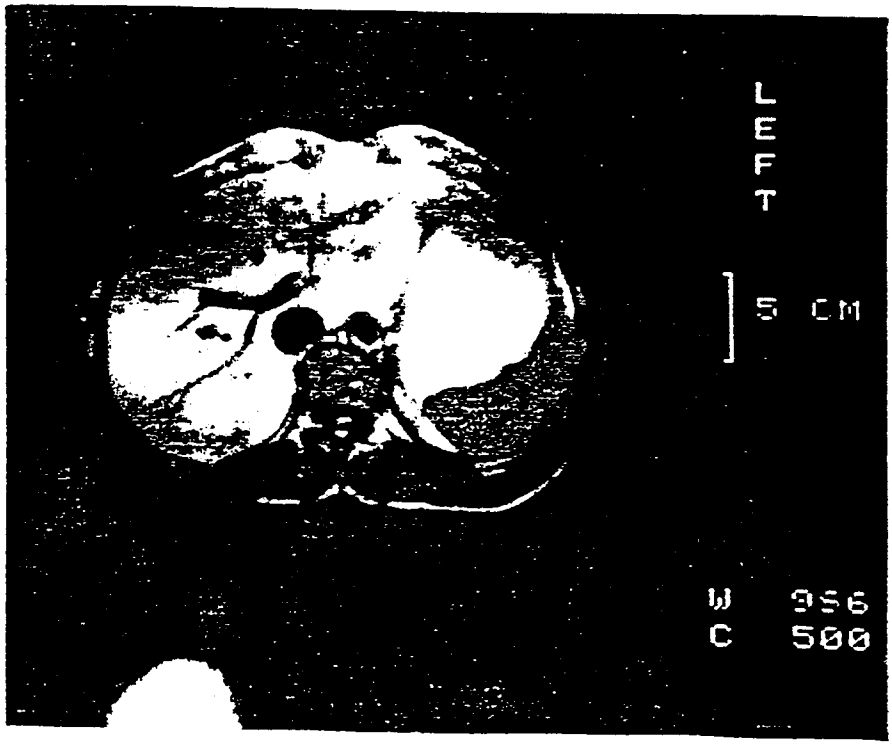


FIG. 3

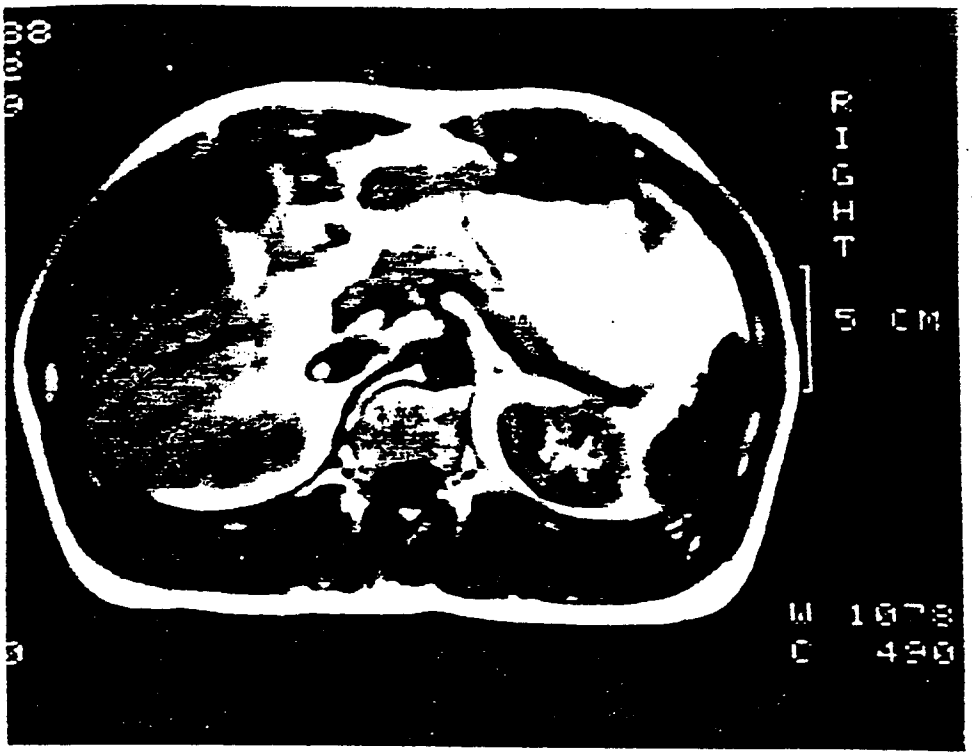


FIG. 4

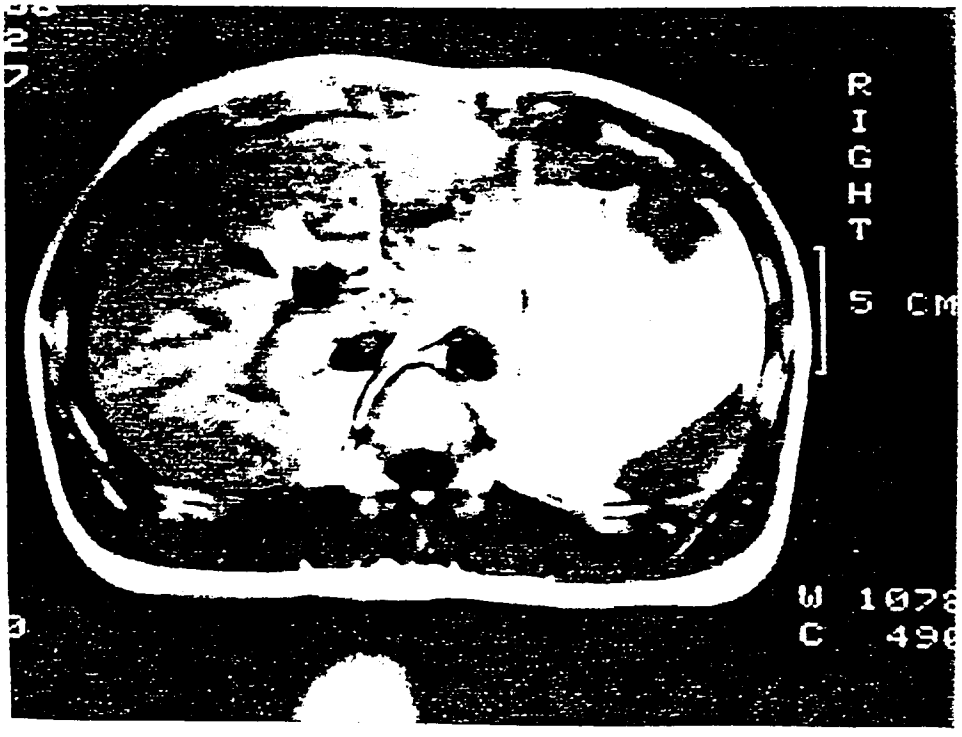


FIG. 5

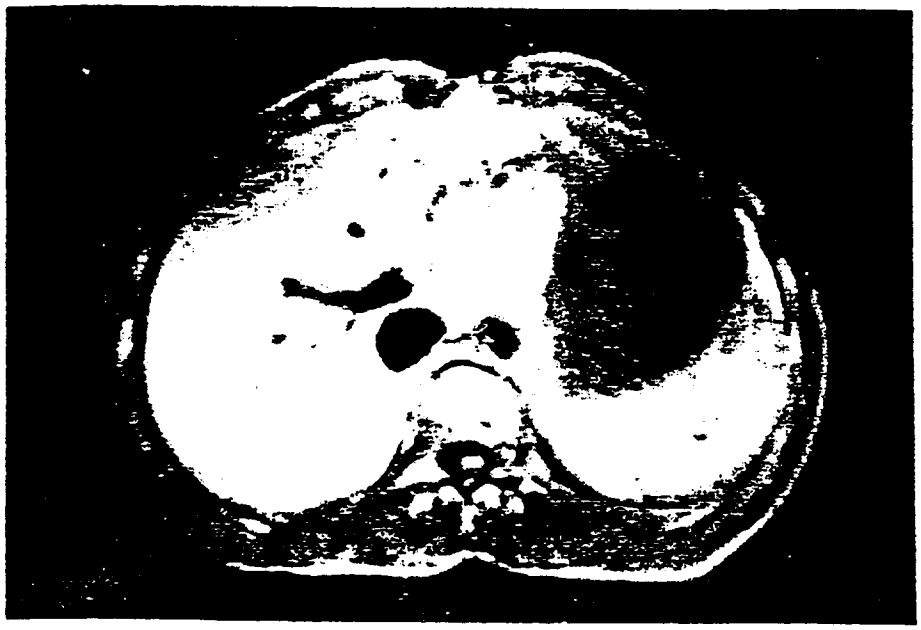


FIG. 6

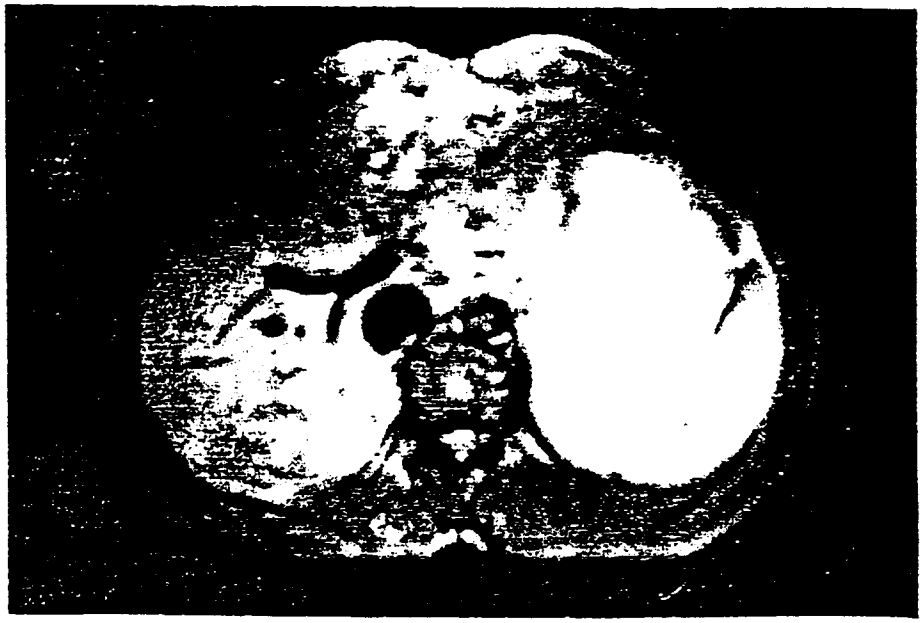


FIG. 7

FIG. 8

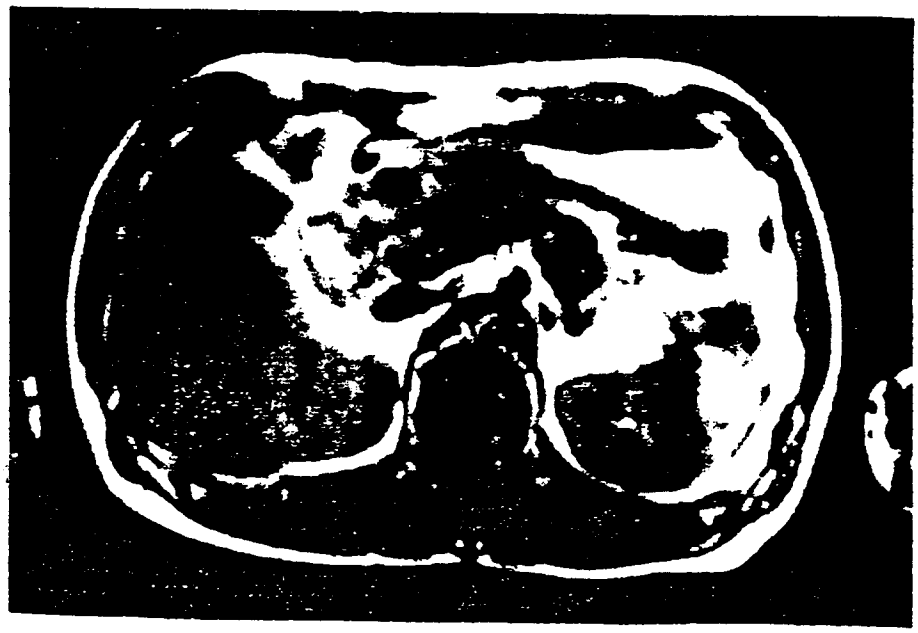
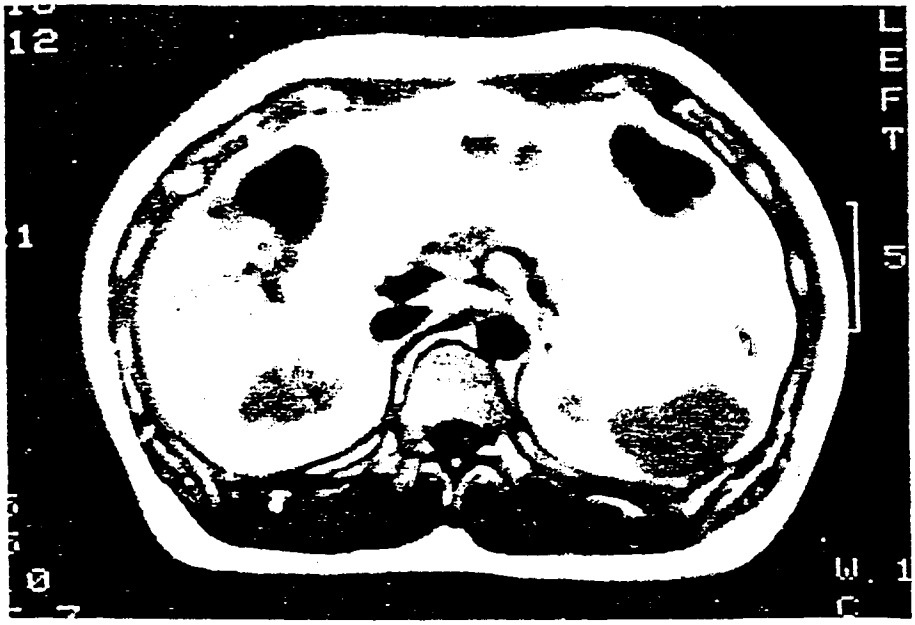


FIG. 9



METHOD OF USING IRON CONTAINING PREPARATION FOR NMR IMAGING

TECHNICAL FIELD

This invention relates to a iron containing preparation for NMR imaging and to an NMR imaging method using the same, which preparation has a form such as a foaming tablet, powder or the like.

BACKGROUND OF THE INVENTION

Since the beginning of 1970, NMR (Nuclear Magnetic Resonance) is widely utilized as a medical diagnostic apparatus, especially as an imaging means capable of providing soft organization imagings having high resolution and contrast without using detrimental x-ray.

That is to say, many atoms have a certain property called as spin to which small magnetic moment is attached.

When the outer magnetic field does not exist, configuration of a magnetic moment is irregular, but in the presence of static magnetic field, nuclear magnetic moment takes precession to approximately the magnetic field direction, so that net alignment is generated in the magnetic field. NMR imaging method is achieved by using this priciple. According to NMR imgaging method, when a short radio frequency pulse is oscillated from a coil surrounding a patient which is set in a static magnetic field, a configuration based on the new magnetic field and precession in phase are generated by this pulse. On the other hand, when oscillation of the pulse is stopped, the above moment returns to the distribution of alignment and the irregular distribution of precession phase on the basis of the former static magnetic field. In such a case, detectable nuclear magnetic resonance is generated at the receiving coil, and by measuring such NMR signals, a proton density map of the objective tissue can be represented. Also, the NMR signal is largely depended with parameters of spin-lattice relaxation time (T_1, i.e. the time specific to return of nuclear magnetic moment to balance alignment in static magnetic field) and spin-spin relaxation time (T_2, i.e. the time specific to return the nuclear magnetic moment to the irregular precession phase distribution). Therefore, these mesurements can be applied to the diagnosis of pathogenic tissue states of a patient.

In NMR imaging method, it is known that physical parameters such as temperature, viscosity and hydration or the like of the tissue is effective to increase NMR signal strength or to change the contrast an NMR image. However, these methods are apparently not suitable for clinical applications. A method for enhancing the contrast of NMR images which is known in the present stage using a paramagnetic compound, as a contrast agent, which decreases spin-lattice relaxation time (T_1) at low concentration thereof, and decreases spin-spin relaxation time (T_2) at high concentration thereof. Contrast agents have been researched, and a typical example of such contrast agents are inorganic paramagnetic salts such as iron, manganese, chromium; or a organic chelate complex which consists of the paramagnetic metal ion mentioned above and one of various complex forming agents which are usually are aminopolycarbxylic acid such as ethylenediaminetetraacetic acid or diethy lenetriaminepentaacetic acid. The contrast agent is taken orally or otherwise in the form of a solution or a colloidal dispention liquid.

However, all of the known contrast agents which are suggested are found to be insufficient practically for use in NMR imaging methods, e.g., due to the difficulty in preparing such agents in a pharmaceutically acceptable form, a lack stability of the pharmaceutical form, difficulties in oral administration, poor taste, toxicity, or the like and, and ineffective viewing for using as a contrast agent, e.g. due to accuracy, clearness.

SUMMARY OF THE INVENTION

A object of the invention is to provide an iron containing preparation for NMR imaging, which is easily prepared in pharmaceutically acceptable form, and which has excellent solubility or dispersion in water so as to rapidly and easily dissolve or disperse in water, thereby being suitable for oral administration.

Another object of the present invention of the invention is to provide an iron containing preparation for NMR imaging, which has excellent storage stability.

Another object of the present invention of the invention is to provide an iron containing preparation for NMR imaging which is capable of accurately and clearly imaging abdominal organs by use as a contrast agent, and NMR imaging method using such a preparation.

According to this invention, there is provided an iron containing preparation for NMR imaging comprising, as essential ingredients, 0.1 to 10% by weight, as elemental iron, of an iron containing compound, 8 to 60% by weight of one or both selected from sodium carbonate and sodium hydrogen carbonate and 10 to 70% by weight of neutralizing agents.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

A preparation of this invention can be used in the form of tablet, granule, powder or capsule.

A preparation of this invention, especially in the form of powder or tablets, as excellent dissolution or dispersion properties in water. Therefore, an iron containing compound contained is easily dissolved or dispersed in water by merely putting the preparation into water, which generate carbonic acid gas (carbon dioxide) due to neutralization. Accordingly, a preparation is easily taken orally. Also, carbonic acid gas generated in the body of the patient makes the alimentary canal expand and extend, so that the form of alimentary canal, the state of lumen thereof and the relation between alimentary canal and other surrounding internal organs can be easily accomplished.

Furthermore, by taking a preparation of this invention, an extremely significant effect occurs such that signal strength of lumen of alimentary canal is enhanced so that imaging of the alimentary canal wall with enhanced contrast against adjacent abdominal organs such as pancreas and the like is achieved.

In addition, each ingredient in preparations of this invention is a safe material having low toxicity.

According to this invention, in order to improve preservation stability, there is provided iron containing preparations for NMR imaging comprising the above iron containing compound, and at least one of sodium carbonate and sodium hydrogen carbonate, the neutralizing agent and potassium carbonate as a preservation stabilizing agent.

Addition of potassium carbonate overcomes a disadvantage found in conventional foam preparations, i.e. foam or degeneration of product during preservation

due to the existence of residual water resulting from the manufacturing process or hydration.

Examples of the iron containing compounds preferably employed in this invention are ammonium iron(II) citrate, ammonium iron(III) citrate, sodium iron(II) citrate, sodium iron(III) citrate, iron(II) citrate, iron-(III) citrate, iron(II) gluconate, iron(II) pyrophosphate, iron(III) pyrophosphate, iron lactate, iron(II) sulfate, iron(III) chloride, iron sesquioxide, sodium iron chlorophyn, iron(II) fumarate, iron threonine, iron(II) orotinate, saccharated iron oxide, iron(III) gluconate or the like. These iron containing compounds are excellent in soluble and dispersive properties in water. These iron containing compounds are also used as an active component of a therapeutic agents for iron deficiency anemia, deficiency anemia, hematinic iron agent or the like in pharmaceutical field, and have high safety. In the iron containing compounds mentioned above, it is preferred to use trivalent iron salt, and especially it is most preferred to use trivalent citrate type, in view of safety and enhanced imaging (on contrast) effects, good taste and ease of drinking.

The iron containing compound is added in the form of a powder, the diameter of particles of which is ordinally not more than 200 μm. Each iron containing compound may be used alone or as a mixture of 2 or more kinds thereof. The amount of iron containing compound to be added is 0.1 to 10% by weight, preferably 0.5 to 5% by weight as elemental iron. Within this amount, the preparation of this invention achieves accurate and clear contrast effects in NMR imaging. This amount corresponds with about 10 to 300 mg, preferably about 25 to 100 mg per one preparation of the foam preparation of this invention.

At least one of sodium carbonate and sodium hydrogen carbon and a neutralizing agent are added as a foaming component, together with the above iron containing compound. The term neutralizing agent 11 means an acid compound capable of neutralizing sodium hydrogen carbonate and sodium bicarbonate to generate carbonic acid gas. Such a foam has the function of expanding and extending the alimentary canal, and therefore is very advantageous to know the form of alimentary canal and the state of its lumen from an NMR picture. Examples of such neutralizing agents are organic acids such as L-tartaric acid, citric acid, fumaric acid, lactic acid, malic acid or ascorbic acid, and it is especially preferred to use L-tartaric acid and/or citric acid.

The amount of the above foam component to be blended is provided such that the solution obtained by dissolving in water that is acidic, especially at a pH of about 3 to 5.5 of pH, preferably about 3.5 to 4.6 of pH, whereby the iron containing compound is rapidly dissolved in water. In particular, for example, the blending amount of each ingredient, sodium carbonate and/or sodium hydrogencarbonate is 8 to 60% by weight, and the neutralizing agent is 10 to 70% by weight. In the case where the preparation of this invention is used in the form of powder or the like, when the amount of sodium carbonate and/or sodium hydrogencarbonate is 20 to 60% by weight, excellent imaging effect is obtained, and when the amount of sodium carbonate and/or sodium hydrogen carbonate is 8 to 45% by weight, taste is improved so as to be agreeable to drink. Practically, it is therefore desirable for providing good taste and to facilitate admistration together with high imaging effect, that sodium carbonate is added at 9 to 50% by weight, preferably 22 to 26% by weight, and that sodium hydrogen carbonate is 8 to 50% by weight, preferably 20 to 45% by weight.

It is suitable that the neutralizing agent is added in the range of 20 to 50% by weight, preferably 30 to 40% by weight, and especially it is preferable to use at the same amount as or more than the equivalent amounts of sodium hydrogen carbonate.

According to this invention, in addition to sodium carbonate and/or sodium hydrogencarbonate and a neutralizing agent added as a foam component, it is preferred that potassium carbonate is added as a preservation stabilizing agent. That is to say, since sodium carbonate or sodium hydrogen carbonate are neutralized in the presence of water by a agent such as organic acid to generate carbonic acid gas and to promote the degradation and dissolution of the preparation, the preparation should be kept in a dry condition as much as possible so as to prevent foaming. There, however, a possibility of foaming during storage due to the presence of water remaining in preparing process or as hydration, even if it is preserved in a sealed container together with drying agent. If carbonic acid gas is generated during preservation, inner pressure of the sealed container is increased, and results in deformation or damage of the container, or can inhibit foaming when the product is used. Foaming during preservation is accelerated under a high temperature condition, and further the generated reaction water and carbonic acid gas accelerate the reaction.

It is now found that potassium carbonate is very effective to prevent foaming during preservation as mentioned above, and even if drying agent is not used during storage, foaming can be prevented. In view of securing a high stability of the preparation and easily taking it without lowering taste, it is suitable that potassium carbonate is added at the amount of 0.2 to 13% by weight, preferably 0.3 to 3% by weight, more preferably 0.4 to 1% by weight per one preparation.

Potassium carbonate used in this invention is not particular limited, and it is especially preferred to use one having no hydration, such as potassium carbonate anhydride.

To a preparation of this invention, if necessary, various additives ordinally known, such as a vehicle, binding agent, disintegrator, lubricant, thickener, surface active agent, osmotic pressure adjusting agent, electrolyte, sweetening agent, perfume, coloring matter, pH adjusting agent or the like, can be added, in addition to the above iron containing compound and foam components. Examples of vehicles are starches such as wheat starch, potato starch, corn starch, dextrin; saccharides such as sucrose, glucose, fructose, maltose, xylulose, lactose or the like; sugar alcohols such as sorbitol, mannitol, maltitol, xylitol or the like; saccharide-transglycoside such as coupling sugar, palathinose or the like; calcium phosphate; calcium sulfate; or the like. Examples of the binding agents or thickeners are starch, saccharides, gelatin, gum arabic, dextrin, methyl cellulose, CMC-Na, polyvinyl pyrrolidone, polyvinyl alcohol, hydroxypropyl cellulose, xanthan gum, pectin, tragacanth gum, casein, alginic acid, or the like. Examples of lubricants are leucine, isoleucine, L-valine, sugar-ester, hardened oil, stearic acid, magnesium stearate, talc, macrogol or the like. Examples of disintegrators are avicel, CMC, CMC-Ca or the like. Example of surface active agents are polysorbate, lecithin or the like. Examples of sweetening agents are saccharides; sugar alco-

hols: dipeptides such as aspartame, alitame; stevia; saccharin; or the like.

The suitable amounts of these additives can be determined in view of the relationship between the additives and the essential ingredients, properties of preparation, process for preparing it or the like.

Furthermore, the suitable amount of various vitamines, especially cyanocobalamin, ascorbic acid (vitamine C) or the like, may be added to the preparation. Therefore, it also is possible to supply vitamin to the body. The amount of the vitamin to be added is not limited, and vitamine C may be added at an amount of not exceeding 30% by weight, preferably about 5 to 25% by weight in view of taste.

A preparation of this invention can be not only in the form of a tablet, but also may be in other solid forms such as granule, powder, capsule or the like.

In preparing a preparation of this invention, methods similar to conventional methods employed in respective preparation form may be employed. For example, a tablet form can be prepared by a method for directly pressurizing powders or by a method for dry or wet pressurizing granules, after weighing and mixing the prescribed amount of each ingredient. Also, powder can be prepared by weighing and mixing the prescribed amount of each ingredient followed by folding. Granules can be prepared by drying to form particles followed by folding, after weighing and mixing the prescribed amount of each ingredient.

A preparation of this invention which is in the form of foam tablet or powder is put into water to dissolve or disperse, and then is orally taken. Conversely, the preparation of this invention may be orally taken in its unchanged form followed by drinking water.

Dosage of a preparation of this invention should be calculatec by known methods based on which internal organ or organization of the living body is to be imaged, and in general, may be taken by dissolving 1.5 to 6 g of the preparation in 100 to 300 ml of water. In the case of contrast imaging of pancreas, 1 or 2 tablets which are prepared at about 1.5 to 6 g per one tablet are taken by dissolving in 100 to 300 ml of water.

A preparation of this invention can be utilized in NMR diagnosis of the alimentary canal, i.e. walls of alimentary canal such as stomach, duodenum, small intestine, large intestine or the like; or pancreas, liver, peritoneum, mesentery or a like. In this case, the preparation of this invention is suitable to contrast imaging representation between alimentary canal and parenchymal internal organs, whereby T_1 value is shortened.

BRIEF EXPLANATION OF THE DRAWINGS

FIG. 1 is a NMR imaging photograph of abdominal part before taking the preparation of Example 1;

FIG. 2 is a NMR imaging photograph of abdominal part after taking the preparation of Example 1;

FIGS. 3 and 4 are NMR imaging photographs of abdominal part of the other subject after taking the preparation of Example 1;

FIG. 5 is a NMR imaging photograph of abdominal part before taking the preparation of Example 20;

FIG. 6 is a NMR imaging photograph of abdominal part of the other subject after taking the preparation of Example 20;

FIGS. 7 to 9 are NMR imaging photographs of abdominal part of the other subject after taking the preparation of Example 20.

INDUSTRIAL APPLICABILITY

As mentioned above, a preparation of this invention makes it possible to take it orally with ease, and to expand and extend alimentary canal by foaming of the foaming ingredients. As a result, form of alimentary canal, the state of its lumen and the relationship between alimentary canal and the surrounding organs can be easily known. Furthermore, a preparation of this invention has an excellent imaging effect enhancing signal strength in the alimentary canal. Thus, it is expected to improve the accuracy of diagnosis of various diseases.

Also, by adding potassium carbonate to the foam preparation, foaming and altertion during preservation can be prevented, and as a result, the preparation of this invention is superior in preservation stability.

EXAMPLES

Examples of this invention are explained below in detail. In each example, "parts" and "%" mean "parts by weight" and "% by weight", respectively, except as otherwise indicated.

EXAMPLE 1

After mixing each ingredient at the ratio shown below, foam tablets (4.3 g per one tablet) were pharmaceutically prepared from the mixture by a method for directly pressurizing powder.

(Ingredients)	(%)
Granulated sugar	37
L-Ascorbic acid	12
L-Tartaric acid	22
Apartame	0.8
Sodium hydrogencarbonate	23
Ammonium iron citrate (25 mg/4.3 g as elemental iron)	3.4
Cyanocobalamin	trace amount
perfume and coloring	proper amount
Total	100

EXAMPLES 2 to 8

Foam tablets having compositions shown in Table 1 was prepared by the same method as Example 1.

TABLE 1

Ingredients		Example No. 2	3	4	5	6	7	8
Glanulated sugar	(parts)	34	30	26	14	17	39	28
L-Ascorbic acid	(parts)	12	12	12	16	16	12	12
L-Tartaric acid	(parts)	22	22	22	30	30	23	27
Aspartame	(parts)	0.8	0.8	0.8	1.0	1.0	0.8	0.8
$NaHCO_3$	(parts)	23	23	23	31	31	20	25
Ammonium iron citrate	(parts)	6.8	10.2	14	6.8	3.4	3.4	6.8
Cyanocobalamin	(parts)	*	*	*	*	*	*	*
Perfume and coloring	(parts)	**	**	**	**	**	**	**
Preparation weight (g/one tablet)		4.3	4.3	4.3	4.3	4.3	4.3	4.3

TABLE 1-continued

Ingredients	Example No. 2	3	4	5	6	7	8
Iron content/one tablet (mg)	50	75	100	50	25	25	50

*indicates "a trace amount of cyanocobalamin"
**indicates "a suitable amount of perfume and coloring matter"

EXAMPLES 9 TO 20

The prescribed amount of each ingredient shown in Table 2 was weighed and mixed, and further sweetening agent and perfume are added at suitable amounts. Then, by folding the mixture, foam powders having a weight (mg/one package) shown in the same table were prepared.

TABLE 2

Ingredients	Example No. 9	10	11	12	13	14	15	16	17	18	19	20
L-Tartaric acid (mg)	893	893	893	893	893	447	1786	893	893	447	1786	1100
$NaHCO_3$ (mg)	1000	1000	1000	1000	1000	500	2000	500	2000	1000	1000	1250
Ammonium iron citrate (mg)	60	150	300	600	1200	600	600	600	600	600	600	600
Total (mg/one package)	1953	2043	2193	2493	3093	1547	4386	1993	3493	2047	3386	2950
Iron content/ one package (mg)	10	25	50	100	200	100	100	100	100	100	100	100

It was also recognized that foam tablets obtained in Examples 2 to 11 show the same enhancement as that of each subject number at the same dose of iron as the above test. Accordingly, a foam tablet obtained in each Example can be suitably applied to abdominal diagnosis using NMR.

These test results were confirmed by administering to subjects the foam tablet obtained in each Example and taking photographs of abdominal image. That is, as shown in FIG. 1 which is T_1 enhancement image of an abdominal part of subject No. 4 before taking, since the inner part of stomach is filled by water and signal is weak, the inner part of stomach is represented by gray or black color, and it is hard to distinguish alimentary canal from other adjacent organs. On the other hand, as shown in FIG. 2 which is T_1 enhancement image after taking, time T_1 in stomach is shortened, signal strength is increased, and therefore distinction between alimentary canal and other adjacent organs is clear.

Also, as shown in FIGS. 3 and 4, according to T_1 enhancement images after taking, distinction between the alimentary canal and other adjacent organs is clear. Especially, as shown in FIG. 3, the border between pancreas and other internal organs can be clearly confirmed; the head of pancreas which is otherwise difficult to detect anatomically is apparently recognized; other organs such as lung, tail of pancreas, body of pancreas, liver, ren, blood vessel or the like were also recognized clearly; and further stomach wall was clearly identified.

NMR Imaging Test (I)

1, 1.5, 2 and 2.5 foam tablets (including 25 mg, 37.5 mg, 50 mg and 62.5 mg of iron, respectively) prepared in Example 1 were taken to four healthy and ordinary subjects (Nos. 1 to 4) by dissolving in 140 ml of water respectively. NMR imaging is carried out before and after taking foam tablets. In such a case, photographs of T_1 enhancement image (SE 500 to 600/17 m sec.) and T_2 enhancement image (SE 2000/23.90 m sec.) were taken. T_1 and T_2 values were measured from images of SE 500/23 and 2000/23.90 by double point method. Also, as a mesurment equipment, 1.5T MRI (Magnetom) manufactured by Siemens, W. Germany, and 8 to 10 mm of slice thickness and 4 to 5 mm of slice interval were set.

T_1 and T_2 values in stomach which were obtained by the above test are shown in Table 3.

TABLE 3

Subject No.	Dose (mg of iron)	Before taking (Stomach) T_1/T_2	After taking (Stomach) T_1/T_2
1	25.0	3111/122	2213/149
2	37.5	3635/193	744/179
3	50.0	2379/178	573/272
4	62.5	3305/202	565/307

The following matter becomes apparent from Table 3. Enhancement of liquid contained in stomach is recognized at all of four doses. Especially, when dose is 25 mg and 62.5 mg of iron, enhancement of liquid contained in stomach is remarkable, and images of stomach wall and pancreas, especially head of pancreas become clear. As to the degree of enhancement, when dose is 50 mg of iron, signal strength of the above liquid contained in stomach is slightly less than that of fatty tissue in abdominal cavity, and therefore the above liquid can be distinguished from the above fat.

NMR Imaging Test (II)

One package of the foam powder (including 100 mg of iron) prepared in Example 20 was taken by a healthy and ordinary subject by dissolving in 140 ml of water, and further 150 ml of water was given to the subject. FIGS. 5 and 6 are photographs for imaging abdominal part of the subject before and after taking the foam powder. FIG. 5 is T_1 enhancement image of stomach part in the condition that water was given to expand alimentary canal. As shown in FIG. 5, signal of water is weak, whereby the inner part of stomach is represented by gray or black color, and distinction between wall and lumen of alimentary canal is unclear. Furthermore, it is difficult to recognize distinction between alimentary canal and the adjacent organs such as pancreas, liver, lung, peritoneum or the like.

On the other hand, signal strength in stomach after taking is increased as shown in T_1 enhancement image of FIG. 6, the inner part of stomach is drawn out by white color, and is contrasted to the surrounding organs. Also, as described herein, the stomach wall and the duodenum wall are well recognized, and the tail and head of pancreas are clearly distinguished from the surrounding organs and alimentary canal.

FIG. 7 is T_1 enhancement image after taking one package of foam powder obtained by Example 20 with 300 ml of water. In general, it is difficult to take an image of head of pancreas, since its T_1 signal approximates to that of duodenum. However, by taking the foam powder of this Example, since the duodenum is expanded and extended by generating carbonic acid gas, and signal strength is increased, head of pancreas can be very clearly drawn out. Similarly, the stomach is fully expanded and extended by water and carbonic acid gas, the border between stomach and body of pancreas is distinct, and contrast is enhanced.

It is understood from FIG. 8 that distinction between the wall of duodenum and inner wall is clear, since the duodenum is expanded and extended by generating carbonic acid gas. It is also understood from FIG. 9 that duodenum is expanded and extended from the same reason as FIG. 8.

Accordingly, from the results shown in FIGS. 5 to 9, the form of abdominal organ and relationship between the same and other organs can be accurately and clearly known by taking the foam powder of this Example, whereby it is expected to improve the accuracy of diagnosis against various diseases.

EXAMPLE 21 (including potassium carbonate)

Foam tablet having the composition shown below was prepared by the same manner as Example 1.

(Ingredients)	(%)
Granulated sugar	40
L-Tartaric acid	29
Aspartame	0.8
Sodium hydrogencarbonate	21
Ammonium iron citrate	3.6
Potassium carbonate	0.5
Cyanocobalamin	trace amount
Sweetening agent	proper amount
Perfume and coloring	proper amount
Total	100 (4.0 g)

Stability Test

The foam tablet obtained in Example 21 was stored in a constant temperature room kept at 37° C., together with the comparative foam tablet which was prepared by the same manner as that of Example 21 except for not adding potassium carbonate, and a swelling test (by wrapping sheet) discoloration test of tablets, solubility in water and change of taste were examined with time. As a result, the foam tablet of Example 21, with added potassium carbonate had low swell, little discoloration, shorter dissolving time and less change of taste in comparison with the comparative foam tablet, and therefore is superior to the compartive foam tablet in preservation stability.

What is claimed is:

1. A nuclear magnetic resonance imaging method comprising administering a diagnostically effective amount of a contrast medium to a subject and performing nuclear magnetic resonance tomography on said subject, said contrast medium comprising:

0.1 to 10% by weight, as elemental iron, of at least one iron containing compound selected from the group consisting of an iron (II) salt and an iron (III) salt;

8 to 60% by weight of at least one of sodium carbonate and sodium hydrogen carbonate; and

10 to 70% by weight of a neutralizing agent, wherein said neutralizing agent reacts with said at least one of sodium carbonate and sodium hydrogen carbonate to produce carbon dioxide in the alimentary canal of said subject, when orally administered to the subject with water, and wherein the produced carbon dioxide expands and extends the alimentary canal.

2. A method according to claim 1, wherein said iron containing compound is at least one selected from the group consisting of ammonium iron(II) citrate, ammonium iron(III) citrate, sodium iron(II) citrate, sodium iron(III) citrate, iron(II) citrate, iron(III) citrate, iron(II) gluconate, iron(II) pyrophosphate, iron(II) pyrophosphate, iron lactate, iron(II) sulfate, iron(III) chloride, iron sesquioxide, sodium iron chlorophyn, iron(II) fumarate, iron threonine, iron(II) orotinate, saccharated iron oxide, and iron(III) gluconate.

3. A method according to claim 2, wherein said iron containing compound is a trivalent iron salt.

4. A method according to claim 3, wherein said iron containing compound is a trivalent iron citrate salt.

5. A method according to claim 1, wherein said iron containing compound is present in an amount of 0.5 to 5% by weight as elemental iron.

6. A method according to claim 1, wherein said neutralizing agent is selected from the group consisting of L-tartaric acid, citric acid, fumaric acid, lactic acid, malic acid and ascorbic acid.

7. A method according to claim 6, wherein said neutralizing agent is at least one of tartaric acid and citric acid.

8. A method according to claim 1, wherein said preparation, when dissolved in water, has a pH of 3 to 5.5.

9. A method according to claim 8, wherein the pH is 3.5 to 4.6.

10. A method according to claim 1, wherein said preparation comprises 20 to 60% by weight of said at least one of sodium carbonate and sodium hydrogencarbonate.

11. A method according to claim 10, wherein said preparation comprises 8 to 45% by weight of said at least one of sodium carbonate and sodium hydrogen carbonate.

12. A method according to claim 1, wherein said sodium carbonate is present in an amount of 9 to 50% by weight.

13. A method according to claim 12, wherein said sodium carbonate is present in an amount of 22 to 26% by weight.

14. A method according to claim 1, wherein said sodium hydrogen carbonate is present in an amount of 8 to 50% by weight.

15. A method according to claim 14, wherein said sodium hydrogen carbonate is present in an amount of 20 to 45% by weight.

16. A method according to claim 1, wherein said neutralizing agent is present in an amount of 20 to 50% by weight.

17. A method according to claim 16, wherein said neutralizing agent is present in an amount of 30 to 40% by weight.

18. A method according to claim 1, wherein said preparation is in a form capable of being dissolved or dispersed in water.

19. A method according to claim 18, wherein said preparation is in the form of a foaming powder.

20. A method according to claim 18, wherein said preparation is in the form of a foaming tablet.

21. A nuclear magnetic resonance imaging method comprising administering a diagnostically effective amount of a contrast medium to a subject and performing nuclear magnetic resonance tomography on said subject, said contrast medium comprising:

at least one iron containing compound selected from the group consisting of an iron (II) salt and an iron (III) salt

at least one of sodium carbonate and sodium hydrogen carbonate:

a neutralizing agent, and

potassium carbonate as a preservation stabilizing agent; wherein said neutralizing agent reacts with said sodium carbonate or sodium hydrogen carbonate to produce carbon dioxide in the alimentary canal of a subject, when administered to said subject together with water, and wherein said produced carbon dioxide expands and extends said alimentary canal of said subject.

22. A method useful according to claim 21, wherein said potassium carbonate is present in an amount of 0.2 to 13% by weight.

23. A method useful according to claim 22, wherein said potassium carbonate is present in an amount of 0.3 to 3% by weight.

24. A method useful according to claim 23, wherein said potassium carbonate is present in an amount of 0.4 to 1% by weight.

* * * * *

EXCLUSIVITY SUMMARY for NDA # 20-292 SUPPL # —

Trade Name FerriSeltz **Generic Name** ferric ammonium citrate, brown
Applicant Name Oncomembrane **HFD-**160

Approval Date _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /X/ NO /__/

   b) Is it an effectiveness supplement?

   YES /__/ NO /X/

   If yes, what type? (SE1, SE2, etc.) ____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO /__/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /X/

If yes, NDA #_____ Drug Name_____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / X / NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # see attached pages; no active NDA's with this active moiety
NDA # (all previously approved have been discontinued or
NDA # withdrawn) _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

APPEARS THIS WAY
ON ORIGINAL

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /[redacted]/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /[redacted]/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 07B

Investigation #2, Study # 04A

Investigation #3, Study # —

APPEARS THIS WAY
ON ORIGINAL

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /___/	NO /X/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /___/	NO /X/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #_____
NDA # _____ Study #_____
NDA # _____ Study #_____

APPEARS THIS WAY
ON ORIGINAL

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 07B

Investigation #2, Study # 04A

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND YES /X/ NO /___/ Explain: _____

Investigation #2

IND YES /X/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO / X /

If yes, explain: _____

_____

_____

_____

Kimi Cadangos 9-30-97
Signature Date
Title: Consumer Safety Officer

APPEARS THIS WAY
ON ORIGINAL

10/14/97
Signature of Division Director Date

cc: Original NDA 20-292
HFD-160/Division File
HFD-85/Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 20-292 Supplement # — Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-160 Trade and generic names/dosage form: [illegible] Action: (AP) AE NA

Applicant [illegible], Inc. Therapeutic Class 3S

Indication(s) previously approved —

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate x

Indication in this application [illegible] (For supplements, answer the following questions in relation to the proposed indication.)

__ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

X 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- __ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- __ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- X c. The applicant has committed to doing such studies as will be required.
  - __ (1) Studies are ongoing,
  - __ (2) Protocols were submitted and approved.
  - __ (3) Protocols were submitted and are under review.
  - X (4) If no protocol has been submitted, attach memo describing status of discussions.
- __ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__ 5. **If none of the above apply**, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

[signature], CSO 9-15-97

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # 20-292
HFD-160/Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 9/15/97)

BEST POSSIBLE COPY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020292

CORRESPONDENCE

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 15, 1997

FROM: Kim Colangelo, Consumer Safety Officer KMC 9-15-97

SUBJECT: Phase 4

TO: NDA 20-292

cc: Orig. NDA 20-292
HFD-160/Division File

APPEARS THIS WAY
ON ORIGINAL

ONCOMEMBRANE, INC.®
Innovation for Global Health

NEW CORRESPONDENCE

1201 Third Ave Suite 3300 Seattle WA 98101 Phone 206 622-6626 Fax 206 622-2259

November 20, 1996

Patricia Y. Love, M.D., M.B.A.
Director
Division of Medical Imaging and Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
Rockville, MD 20857

REVIEWS COMPLETED
DSO ACTION:
LETTER N.A.I.
DATE

Re: NDA 20-292
FerriSeltz™ (ferric ammonium citrate, brown)
Response to FDA action letter dated November 15, 1996

Dear Dr. Love:

We acknowledge receipt of your letter of November 15, 1996, which indicated that the NDA for FerriSeltz is approvable pending the resolution of certain issues. Under 21 CFR 314.110(a)(1), we hereby notify FDA of our intention to file an amendment to provide the information requested in the November 15, 1996 letter. We understand that the notice of intent to file an amendment constitutes an agreement by Oncomembrane to extend the review period for 45 days after the date FDA receives the amendment, to permit the agency to review the amendment.

We also acknowledge requirements to

- Submit three copies of the introductory promotional material that we propose to use for FerriSeltz;
- Provide updated safety information, including results of trials that were still ongoing at the time of the NDA submission and an analysis of digestive system adverse events by time after ingestion and by volume of FerriSeltz ingested; and

We will submit the additional information required on CMC issues, the safety update, and introductory promotional materials as separate amendments to NDA 20-292 and the Phase 4 study information as an amendment to

Sincerely,

Toshihiko Tanaka
CEO & President

ONCOMEMBRANE,INC.®
Innovation for Global Health

1201 Third Ave., Suite 5300, Seattle, WA 98101 Phone: (206) 622-6626 Fax: (206) 622-2259

ORIG AMENDMENT

ORIGINAL
bc

October 17, 1996

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I.

CSO INITIALS DATE

FOOD & DRUG ADMINISTRATION
Attention: Ms. Susan Cusack
Office of Drug Evaluation I
Division of Medical Imaging, Surgical
and Dental Drug Products (HFD-160)
Parklawn Building, Room 18B-09
5600 Fishers Lane
Rockville, MD 20857

RE: FerriSeltz™(ferric ammonium citrate, brown)
NDA #20-292
Amendment: Disbarment Statement

Dear Madam/Sir:

Oncomembrane certifies that it did not and will not use in any capacity the services of any person debarred under subsections "a" or "b" (Section 306 "a" or "b") in connection with this application.

Sincerely,

Toshihiko Tanaka
President

TT/bc

FILE IN THIS WAY
ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
OCT 18 1996
HFD-160

MEMORANDUM OF TELECON

DATE: September 9, 1997

APPLICATION NUMBER: NDA 20-292; FerriSeltz

BETWEEN:

Name: J. Kay Noel, Ph.D.
Phone: 510-525-4250
Representing: J. Kay Noel & Associates (consultant for Oncomembrane, Inc.)

AND

Name: Kim Colangelo
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: Information Request

I phoned Dr. Noel to request an electronic copy of the submitted draft labeling, and of p. 1-37 of the Safety Update dated February 20, 1997. Dr. Noel agreed to submit these items.

Kim Colangelo
Consumer Safety Officer

cc: Original NDA 20-292
HFD-160/Div. File
HFD-160/Kim Colangelo/Paserchia

TELECON

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: September 3, 1997

APPLICATION NUMBER: NDA 20-292; FerriSeltz

BETWEEN:

Name: J. Kay Noel, Ph.D.
Phone: 510-525-4250
Representing: J. Kay Noel & Associates (consultant for Oncomembrane, Inc.)

AND

Name: Kim Colangelo
Division of Medical Imaging and Radiopharmaceutical Drug Products, HFD-160

SUBJECT: PDUFA Goal Date and Environmental Assessment (EA) Issues

I phoned Dr. Noel to verify the PDUFA goal date for this application, since an acknowledgment letter with this information was not sent to the Sponosr. The PDUFA goal date is October 14, 1997. Dr. Noel was aware of the date.

I informed Dr. Noel that the review of the submitted EA was complete, and deficiencies had been noted. Dr. Noel stated that she was aware of the new regulations concerning EA requirements, and the option of requesting a categorical exclusion. I informed Dr. Noel that I would be sending the EA deficiencies via facsimile. Once she and Oncomembrane, Inc., had an opportunity to review them, I requested that she notify me whether they would be addressing the deficiencies or requesting categorical exclusion. Dr. Noel agreed.

APPEARS THIS WAY
ON ORIGINAL

Kim Colangelo
Kim Colangelo
Consumer Safety Officer

cc: Original NDA 20-292
HFD-160/Div. File
HFD-160/Kim Colangelo
HFD-160/Salazar

APPEARS THIS WAY
ON ORIGINAL

TELECON

NDA 20-292

JUL 23 1997

Oncomembrane, Inc.
c/o Otsuka America, Inc.
One Embarcadero Center, Suite 2020
San Francisco, CA 94111

Attention: Kay Noel, Ph.D.

Dear Dr. Noel:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for FerriSeltz® (ferric ammonium citrate, brown).

We also refer to your letter of June 27, 1997, notifying us that the corporate address has been changed from Oncomembrane, Inc., 1201 Third Avenue, Suite 5300, Seattle, WA, 98101 to Oncomembrane, Inc., c/o Otsuka America, Inc., One Embarcadero Center, Suite 2020, San Francisco, CA, 94111.

Our records have been revised to reflect this change.

If you have any questions, please contact Ms. Christy Wilson at (301) 443-3500.

Sincerely yours,

7/21/97

James Cheever, D.M.D.
Associate Director
Division of Medical Imaging and
Radiopharmaceutical Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-292
HFD-160/Div Files
HFD-92/DDM-DIAB
HFD-160/CSO/SCusack
HFD-160/Chow
HFD-160/Salazar
HFD-160/Sadrieh
DISTRICT OFFICE

Drafted by: CWilson/July 21, 1997/n20292.coa
F/T by: CWilson/July 21, 1997

CHANGE OF ADDRESS

APPEARS THIS WAY
ON ORIGINAL