

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20773

MEDICAL REVIEW(S)

JORDAN

SEP 12 1997

NDA#20,773

SonoRx™ Oral Suspension

Simethicone Coated Cellulose Suspension

Dosage: 400 mL P.O. Single Dose

Sponsor: Bracco Diagnostics, Princeton, NJ

Medical Officer Review

M.O. Robert J. Yaes, Sc.D., M.D.

Sponsor's Proposed Indication:

SonoRx is an orally administered ultrasound contrast agent that is indicated for the delineation of anatomy and the detection or exclusion of pathology in the upper abdomen, including the upper gastrointestinal tract and retroperitoneum

Robert J. Yaes, MD., Sc.D., Medical Officer



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Abstract

Ultrasound imaging is an inexpensive, portable diagnostic modality that does not expose the patient to ionizing radiation. Its usefulness in imaging the upper abdomen is limited by the effect of gas shadowing, which results in image degradation. SonoRx is a new, orally administered ultrasound contrast agent which adsorbs and displaces gas in the upper GI tract, and is therefore expected to improve the quality of ultrasound images of the upper abdomen. Since images are to be obtained shortly after ingestion, its effect will be primarily on gas in the stomach. Images of only those structures effected by shadowing by gas in the stomach would be expected to —be improved. These structures are the stomach, gastric wall, duodenum and the head, body and tail of the pancreas.

The sponsor has undertaken two phase 1 trials, one phase 2 dose ranging trial, two pivotal phase 3 trials, and one phase 3 supporting trial, with a total of 426 subjects, in order to demonstrate the safety and efficacy of SonoRx. While these studies were well designed to demonstrate safety, there were major problems with the design and implementation of the pivotal trials in the demonstration of efficacy. Blinded reads were not performed according to protocol. The first pair of readers were not given both static and video images, as the protocol required. A second of readers did not receive the scans from all patients. The questions asked of the readers were highly subjective, and this was reflected in the wide disparity of answers given by the blinded readers. The pivotal trials were not placebo controlled for efficacy.

There does not appear to be any major safety concerns. The active ingredients in SonoRx, cellulose and simethicone, are known to be safe for oral ingestion in the doses given. Pre-clinical studies show that these ingredients remain in the gut and are excreted unchanged in the feces. There were no deaths in any of the studies that could be attributed to the study agent. The number and pattern of adverse events did not raise any particular safety concerns. There was a slight excess of mild adverse events, involving the GI system, such as diarrhea and nausea and vomiting, which would be expected with this type of agent.

The two pivotal trials were identical in design and implementation and were carried out simultaneously. Patients ingested 400 mL SonoRx. Blinded readers compared ultrasound scans taken immediately after SonoRx ingestion (post-dose scan) to scans obtained just before ingestion (pre dose scans). The sponsor's primary outcome variable was the readers answer to the question "Overall did the post dose images provide additional information over the pre- dose images?" The sponsor claims that efficacy has been demonstrated because the percentage of patients for which the answer was yes, was greater than 1% for all blinded readers in both pivotal studies. By pure chance the expected percentage would be 50%.

In conclusion, there are no substantial safety concerns. The sponsor however has not provided substantial evidence of efficacy for the proposed indication, based on the primary outcome variable in the pivotal trials. There is substantial evidence presented in these studies that SonoRx does improve visualization of the stomach duodenum and pancreas, which are those organs whose visualization would be most effected by shadowing by gas in the stomach. The NDA is therefore approvable with the narrower indication.

This reviewer's recommendation is that this NDA is not approvable for the sponsor's desired indication. It is approvable with the much narrower indication "SonoRx is an orally administered ultrasound contrast agent indicated for the improvement of visualization of the stomach, duodenum and pancreas in ultrasound studies of the upper abdomen" Labeling should be modified to reflect this narrower indication, and to indicate that , in the supporting phase 3 trial, where SonoRx was compared directly with water, the results were less favorable to SonoRx than in the pivotal trials.

NDA#20,773
SonoRx™ Oral Suspension
Simethicone Coated Cellulose Suspension
Bracco Diagnostics, Princeton, N.J.

M.O. Robert J. Yaes, Sc.D., M.D.
Document Date;
Date Assigned:
Protocol # 42,440-4

Material reviewed: NDA # 20,773, Volume 1.1 and volumes 1.16 through 1.33 dated Sept 30, 1996.

Proposed Indication:

SonoRx is an orally administered ultrasound contrast agent that is indicated for use in the delineation of anatomy and the detection or exclusion of pathology in the upper abdomen, including the upper gastrointestinal tract and retroperitoneum

Review Team

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1. Introduction

When compared to MRI or CAT scanning, ultrasound imaging has the advantages of low cost, portability and lack of ionized radiation or high magnetic fields. However ultrasound is limited as a screening test for pathology in the upper abdomen, by the image degradation by gas shadowing by gas in the stomach. SonoRx is an ultrasound contrast agent containing ultra small particles of cellulose coated with simethicone, designed to displace and adsorb gas. Gas shadowing by gas in the stomach can be reduced and the stomach can be made transparent to ultrasound, improving visualization of the stomach, and of structures posterior to the stomach, and in particular the pancreas

SonoRx was assessed in 2 phase 1 studies, 1 phase 2 dose ranging studies and 3 phase 3 studies with a total of 426 subjects (see table 1) The 2 pivotal phase 3 studies were *not* placebo controlled for efficacy

Table 1.1 SonoRx CLINICAL STUDIES

| PHASE 1 EFFICACY STUDIES | | | | |
|---------------------------------|-----------------|---|-----------------------|----------|
| NUMBER | DATES | DESIGN | DOSES | SUBJECTS |
| 42,440-1 | 7/93- 7/93 | Phase 1 Single Center Randomized, Placebo Controlled, Double Blind, Parallel, dose Escalating Safety and Efficacy Study in Normal Healthy Adult Male Volunteers | 200-1000ml.....SonoRx | 5 |
| | | | “ Placebo | 3 |
| 42,440-4 | 11/93- 12/93 | Phase 1 Single Center Randomized, Placebo Controlled (Water vs. SonoRx), Single-Blind Crossover Safety and Efficacy Study in Normal Healthy Adult Male Volunteers | SonoRx 800 ml | 24 |
| | | | Placebo 800 ml | 24 |
| PHASE 1 PHARMACOKINETIC STUDIES | | | | |
| 42,440-5 | 11/94- 3/95 | Randomized, Single Dose Placebo Controlled, Double -Blind Study in Male and Female Patients With Impaired Bowel Motility | SonoRx 400ml | 12 |
| | | | Placebo 400 ml | 3 |
| 42,440-6 | 1/95- 1/95 | Randomized, Single Center Single Dose Placebo controlled, Double Blind Study in Normal Volunteers | SonoRx 400 ml | 7 |
| | | | Placebo 400ml | 3 |
| Total Patients | | | SonoRx | 48 |
| | | | Placebo | 33 |

| PHASE 2 DOSE SELECTION STUDY | | | | |
|------------------------------|---------------|---|--------------------|----|
| 42,440-2 | 9/93- 3/94 | Multicenter, Randomized, Uncontrolled, Dose Ranging Study | SonoRx 200-1000 mL | 55 |

| PHASE 3 CLINICAL TRIALS | | | | |
|----------------------------------|----------------|--|----------------------|-----|
| PIVOTAL STUDIES | | | | |
| 42,440-3A | 6/94- 12/94 | Multicenter Randomized Double-Blind Parallel Study | SonoRx 400 mL | 93 |
| | | | Control Agent 400 mL | 24 |
| 42 440-3B | 7/94- 11/94 | Multicenter Randomized Double-Blind Parallel Study | SonoRx 400 mL | 94 |
| | | | Control Agent 400 mL | 28 |
| Total Patients in Pivotal trials | | | SonoRx 400 mL | 187 |
| | | | Control Agent 400 mL | 52 |
| PHASE 3 SUPPORTIVE STUDY | | | | |
| 42,440-7 | 10/94- 2/95 | Multicenter, Randomized, Placebo Controlled, Single-Blind, Crossover Study | SonoRx 400 mL | 51 |
| | | | Water 400 mL | 53 |

Pharm/Tox SonoRx is not pharmacologically active. It is ingested orally and is not absorbed from the gut. It remains in the GI tract and is excreted unchanged in the feces. Mice, rats, dogs and rabbits, given up to 5 times the proposed human dose by body weight, all survived until necropsy without demonstrating any signs or symptoms of toxicity. (see pharm/tox review)

Pharm//Piopharm The active ingredients in SonoRx are simethicone and crystalline cellulose which are ingredients in over the counter antifatulents and laxatives. Both ingredients are eliminated unchanged in the feces within 2 to 3 days.

Focus of review: The focus of this review is on efficacy. An integrated summary of safety, based on the individual study data discussed in this review has been prepared by Dr. Raczkowski.

1.1) Dosage and Formulation

SonoRx is an orally administered ultrasound contrast agent for the delineation of normal anatomy and the detection of pathology in the upper abdomen. The active ingredient is 22 micron fiber length cellulose coated with Simethicone. According to the sponsor the cellulose is manufactured from wood and is considered safe (GRAS). The proposed dose of SonoRx is 400 mL P.O. The sponsor states that the amount of Simethicone in 400 mL SonoRx is 80 mg, which is less than the amount of Simethicone in the maximum recommended doses of common over the counter medications (see pharm-tox review). The composition of SonoRx is given in table 1.2.

TABLE 1.2 COMPOSITION OF SonoRx

| INGREDIENT | gm/L |
|--|------|
| 22 micron cellulose with 0.25% Simethicone coating (active ingredient) | 7.5 |
| Xanthan Gum | |
| Medical anti Foaming Agent A (Simethicone USP) | |
| Sodium Laurel Sulfate NF | |
| Citric Acid USP | |
| Orange Oil Florida Type | |
| FD&C Yellow #6 | |
| Fructose USP | |
| Sodium Benzoate (preservative) NF | |

**APPEARS THIS WAY
ON ORIGINAL**

2. Phase 1 Clinical Trials

2.1 Phase 1 Trial 42,440-1

A Phase 1 Clinical Evaluation of the Safety and Efficacy of SonoRx in Normal Healthy Volunteers
(Protocol # 42,440-1)

2.1.1 Study Objectives:

- . To determine a safe dose range for oral administration of Sonorx
- . To evaluate the efficacy of Sonorx across that same dose range

2.1.2 Study Design

Protocol 42,440-1 is a Phase 1 Single Center Randomized Placebo Controlled Double Blind Parallel Dose Escalating Safety and Efficacy Study in Normal Healthy Adult Male Volunteers.

Eight normal healthy adult male volunteers were entered in this protocol.

Inclusion criteria and exclusion criteria are listed below

Inclusion Criteria:

- Male
- Age 18-50
- Normal physical examination
- Not taking any other medication than indicated in this protocol
- Have not taken any other investigational drug within 60 days
- Signed IRB approved informed consent

Exclusion criteria

Female

- Clinical or laboratory evidence or history of clinically significant organ/system (cardiovascular, renal, hepatic neuromuscular or metabolic) dysfunction
- History of allergy, asthma or anaphylactic reaction to any drug
- Siting blood pressure greater than 135/90 or less than 100/60
- Siting Radial pulse less than 50 bpm or greater than 90 bpm
- Weight differs from ideal body weight for height and build by more than $\pm 15\%$
- History of aspiration or difficulty swallowing
- Recent drug or alcohol abuse

The eight subjects were randomized to either of two groups. One group of five subjects received SonoRx and the second group of three subjects received placebo, which consisted of SonoRx without the active ingredient (22 micron cellulose with 0.25% Simethicone coating) All subjects fasted for 8 hours prior to administration of the drug The 5 volumes given orally were 200 mL, 400 mL, 600 mL, 800 mL and 1000 mL Each subject received all five volumes, sequentially in ascending order on different days, except for one subject in the placebo group who developed infectious epididymitis and dropped out of the study before receiving the 1000 mL dose A washout period of a minimum of 48 hours was allowed between any two volumes ingested

All subjects remained in the clinical research unit from 24 hours before the first ingestion to 24 hours after the last ingestion. Subjects refrained from alcoholic beverages from 48 hours prior to the first ingestion to 24 hours after the last ingestion. Subjects refrained from jogging or other strenuous exercise while residing in the clinical research unit

Ultrasound images of all subjects were obtained immediately before and immediately after ingestion of the agent. Before and after sonograms were evaluated for gas shadowing and visualization of specific regions in the upper abdomen by a single blinded radiologist.

Subjects fasted, for a minimum of eight hours, from midnight until oral administration the following morning. Pre dose ultrasound studies were performed immediately before ingestion. Containers were inverted repeatedly prior to administration to insure complete suspension, and individual doses were measured in a graduated container. Each subject ingested the entire dose within 15 minutes. Post dose ultrasound studies began immediately after ingestion and lasted for no longer than 30 minutes

Subjects

The sample size consisted of eight normal healthy male volunteers between ages of 18 years and 50 years. All subjects met the inclusion criteria and signed the informed consent. Subjects were divided into two groups. One group of five subjects received SonoRx and a second group of 3 subjects received placebo.

Evaluation

Safety was evaluated by monitoring physical examination, vital signs, EKGs Serum chemistry, CBC and Urinalysis, for each dose given. Physical examination was performed at screening, within 24 hours before ingestion and 24 hours after ingestion. Vital signs were monitored at screening, immediately before ingestion, immediately after ingestion, and at 1, 4, 6, and 24 hours post ingestion. Serum chemistry, CBC and urinalysis were obtained at screening within 24 hours pre dose and 24 hours post dose. The timing of these tests is given schematically in table 3

TABLE 2.1.1 SUBJECT MONITORING SCHEDULE

| TEST | TIME OF TEST FOR EACH DOSE ADMINISTRATION | | | | | | |
|--------------------------------|---|---------|-------------|-----------|-------|-------|--------|
| | PRE-DOSE | | | POST-DOSE | | | |
| | screen | <24 hr. | Immediately | 1 hr. | 4 hr. | 6 hr. | 24 hr. |
| History | x | | | | | | |
| Physical | x | x | | | | | x |
| Vitals | x | | x | x | x | x | x |
| Serum Chemistry Screen and CBC | x | x | | | | | x |
| Urinalysis | x | x | | | | | x |
| EKG | x | | | | x | | |
| Ultrasound Imaging | | | x | x | | | |

Ultrasound images were obtained on each subject immediately before and immediately after each dose of SonoRx or placebo. All pre and post dose images were obtained by the same sonographer using the same commercially available ultrasound unit, and the same parameter

settings. Supine, left posterior oblique and right posterior oblique views were obtained and both static and video images were obtained. Pre and post dose images were obtained of the stomach, duodenal bulb, pylorus, liver, pancreas, gallbladder, common bile duct, gastrohepatic ligament and right and left kidneys. The gallbladder was imaged for evaluation of contraction. All images were evaluated by a single blinded board certified radiologist at the enrollment site. The overall image was evaluated with respect to gas shadowing as free of degradation, minor degradation, moderate degradation, marked degradation or uninterpretable. In addition, the image of each anatomical area was rated as excellent (3), good (2), poor (1), or none (0), as described below.

Excellent: Diagnostic Image with excellent visualization of anatomic area of interest

Good: Diagnostic Image. Able to visualize anatomic area of interest

Poor: Marginally Diagnostic Image. Limited visualization of anatomic area of interest

None: Non-diagnostic Image. Can not identify anatomic area of interest

Reviewer's comment:

Because of the 48 hour interval between doses, long term toxicity could not be assessed for any one dose. Because EKG monitoring was not performed at the time of ingestion, the presence or absence of EKG changes during the first hour after ingestion can not be determined

2.1.3 Results

Demographics

Eight normal healthy adult male volunteers who met the inclusion /exclusion criteria were entered in this study. There were 5 subjects in the SonoRx group and 3 subjects in the placebo group. All subjects received all five doses of SonoRx or placebo with the exception of one subject in the placebo group who developed infectious epididymitis and dropped out of the study before receiving the 1000 ml dose. Demographics of the two groups is given in table 2

TABLE 2.1.2 SUBJECT DEMOGRAPHICS

| GROUP | AGE (yr) | | WEIGHT (kg) | | HIGHT (cm) | | RACE | | | |
|---------|--------------|-------|---------------|--------|---------------|-------------|-------|-------|-------|--------------|
| | mean ±SD | range | mean ±SD | range | mean ±SD | range | White | Black | Asian | Native Amer. |
| SonoRx | 24.4 ±1.1 | 23-26 | 82.4 ±13.4 | 65-109 | 179.6 ±6.6 | 172- 187 | 1 | 4 | 0 | 0 |
| placebo | 29.3 ±9.1 | 21-39 | 68.7 ±5.0 | 64-74 | 179.6 ±6.6 | 163- 181 | 2 | 1 | 0 | 0 |

Reviewer's comment

The wide range of ages in the placebo group occurs because of 1 subject age 39. All other subjects were between ages 21 and 28. The average weight is larger in the SonoRx group than in the placebo group, but such a disparity is not unexpected with such a small sample size

1.3.2 Safety

1.3.2.1 Adverse Events

Deaths 0

Withdrawals due to adverse events 1

One patient in the placebo group withdrew from the protocol before receiving the 1000 mg dose because of infectious epididymitis

Serious adverse events 0

Severe adverse events 0

There were three mild and one moderate adverse events, all of which occurred in two subjects in the placebo group. None of these adverse events was considered by the investigator to be related to placebo. Subject A developed indigestion (dyspepsia) two hours after ingesting 600 ml placebo and felt faint at venipuncture (dizziness) 24 hours after ingestion. Subject B felt faint after venipuncture (dizziness) 24 hours after ingesting 800 ml placebo and was found to have infectious epididymitis 35 hours after ingestion. At that point this subject dropped out of the study and was treated with tetracycline with good response. The adverse events are shown in table .3

TABLE 2.1.3 ADVERSE EVENTS

| Drug | Event (COSTART) | Body System | Num. | severity | related to drug | frequency | residual effects |
|---------|-----------------|--------------|------|----------|-----------------|-----------|------------------|
| placebo | epididymitis | GU | 1 | moderate | no | 1/3 33.3% | none |
| placebo | dizziness** | neurological | 2 | mild | no | 2/3 66.6% | none |
| placebo | dyspepsia | GI | 1 | mild | possibly* | 1/3 | none |
| SonoRx | none | | 0 | | | | |

*The investigator did not think that the dyspepsia was related to ingestion of placebo but in the reviewer's opinion, this may not necessarily be the case

** "felt faint during venipuncture"

Clinical and Laboratory Monitoring

Physical Examination

Physical examinations were performed on all eight subjects within 24 hours pre administration and 24 hours post administration. No clinically significant differences between pre and post physical examinations were noted for any subject in this study

EKG

12 lead EKGs were obtained for each subject at screening and at 1 hour post administration of each dose of SonoRx or placebo. All EKGs on all subjects were read as normal. Specific EKG parameters (i.e. Q-T intervals) were not provided in this submission.

Laboratory

Sponsor's guidelines for clinically significant changes in laboratory values (pre vs. post) are as follows:

Hemoglobin, Hematocrit, RBC, Albumin, Calcium $\pm 25\%$
WBC, Platelet Count $\pm 50\%$

Bilirubin, SGOT, SGPT, ASAT, ALAT $\pm 150\%$
 Potassium, Chloride $\pm 20\%$
 BUN, GGT, LDH $+100\%$
 Uric Acid $+75\%$
 Creatinine $+ 50\%$
 Glucose $+100\%$, -25%
 Phosphorus $+100\%$, -40%
 Sodium, $\pm 10\%$
 Total Protein, $\pm 30\%$

One subject in the SonoRx group and two subjects in the placebo group had at least one abnormal laboratory value deviating from guidelines at 24 hours post administration, as shown in table 5 Two subjects developed hypoalbuminemia ant two developed hypoglycemia

TABLE 2.1.4 ABNORMAL LABORATORY VALUES, 24 HOURS POST DOSE

| Subject # agent | Volume (mL) | Test | 24 hr. pre dose | 24 hr post dose | % change | normal range |
|--------------------|-------------|---------|-----------------|-----------------|----------|---------------|
| SonoRx | | | | | | |
| 8 SonoRx | 400 mL | Albumin | 4.5 gm/dL | 2.8 gm/dL | -37.8% | 3.5-4.8 gm/dL |
| Placebo | | | | | | |
| 1 Placebo | 200 mL | Albumin | 4.0 gm/dL | 2.6 gm/dL | -35.0% | 3.5-4.8 gm/dL |
| 1 Placebo | 200 mL | Glucose | 98 mg/dL | 64 mg/dL | -34.7% | 65-110 mg/mL |
| 4 Placebo | 200 mL | Glucose | 81 mg/dL | 54 mg/dL | -33.3% | 65-110 mg/mL |

Vital signs

All changes in vital signs of greater than $\pm 20\%$ were tabulated. There were no changes in vital signs that were considered by the investigator to be clinically significant. Mean values, standard deviations and ranges are given in table 3 for vital signs, immediately pre ingestion and immediately post ingestion for both the SonoRx group and the placebo group for each dose of SonoRx or placebo

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ON ORIGINAL**

TABLE 2.1.5 MEAN±SD and RANGE for IMMEDIATELY PRE INGESTION and IMMEDIATELY POST INGESTION VITAL SIGNS

| Dose | Heart Rate bpm | | Systolic BP mm hg | | Diastolic BP mm hg | | Respiration rate bpm | |
|---------------|----------------|--------|-------------------|---------|--------------------|-------|----------------------|----------|
| | Pre | post | Pre | post | Pre | post | Pre | post |
| SonoRx (n=5) | | | | | | | | |
| 200 ml | 55±11.9 | 54±8.0 | 128±7 | 133±11 | 70±5 | 77±5 | 29±1 | 19±1 |
| range | 43-74 | 46-65 | 122-139 | 118-147 | 64-76 | 71-82 | 18-20 | 18-20 |
| 400 ml | 56±11 | 56±10 | 135±4 | 126±5 | 72±7 | 77±10 | 19±1 | 19±1 |
| range | 47-72 | 47-69 | 130-139 | 119-131 | 65-82 | 68-93 | 18-20 | 18-20 |
| 600 ml | 61±12 | 66±7 | 133±8 | 131±9 | 71±10 | 80±13 | 19±1 | 19±1.1 |
| range | 48-78 | 58-78 | 123-139 | 115-138 | 56-80 | 58-89 | 18-20 | 18-20 |
| 800 ml | 63±9 | 62±8 | 136±8 | 134±9 | 77±7 | 79±6 | 20±0 | 20±0 |
| range | 55-77 | 54-74 | 122-144 | 124-143 | 70-85 | 73-87 | 20-20 | 20-20 |
| 1000 ml | 70±9 | 71±13 | 125±7 | 136±9 | 72±10 | 76±13 | 20±0 | 20±0 |
| range | 58-80 | 57-84 | 115-132 | 129-147 | 60-84 | 53-87 | 20-20 | 20-20 |
| Placebo (n=3) | | | | | | | | |
| 200 ml | 71±3 | 57±2 | 131±5 | 126±9 | 66±10 | 62±10 | 17±1 | 20±0 |
| range | 68-74 | 55-58 | 127-137 | 117-135 | 56-76 | 51-69 | 16-18 | 20-20 |
| 400 ml | 60±2 | 65±2 | 129±1 | 122±3 | 70±2.0 | 67±11 | 19±12 | 20±0 |
| range | 58-62 | 63-67 | 129-131 | 119-125 | 68-72 | 56-79 | 18-20 | 20-20 |
| 600 ml | 62±1 | 65±5 | 124±7 | 127±5 | 71±7 | 70±3 | 19±1 | 19±1 |
| range | 61-63 | 61-72 | 118-132 | 124-133 | 65-79 | 67-73 | 18-20 | 18-20 |
| 800 ml | 68±3 | 75±3 | 120±5 | 122±9 | 65±6 | 71±7 | 20±0 | 20.0±0.0 |
| range | 65-70 | 72-77 | 114-124 | 112-129 | 61-71 | 65-78 | 20-20 | 20-20 |
| 1000 ml | 70±2 | 76±2 | 124±0.7 | 124±9 | 65±9 | 76±2 | 20±0 | 20±0 |
| range | 68-71 | 74-77 | 123-124 | 117-131 | 58-71 | 74-77 | 20-20 | 20-20 |

Urinalysis

No clinically significant deviations from normal were found in either the SonoRx group or the placebo group at any of the times tested

Adverse Events

There were no serious or severe adverse events in either the SonoRx group or the placebo group. There were no adverse events reported in the 5 subjects in the SonoRx group. There were 4 non serious adverse events reported for the 2 subjects in the Placebo. One subject developed "spontaneous infectious epididymitis which was considered moderate in severity and required treatment with tetracycline. The same subject also experienced which was mild in severity. The second subject experienced indigestion and faint "felt after venipuncture" Both were considered to be mild in severity. None of these adverse events were considered to be related to placebo.

Efficacy

Gas Shadowing

The reader was asked to rate each image for gas shadowing artifacts as:

Free of degradation
 Minor degradation
 Moderate degradation
 Marked degradation
 or

Uninterpretable

There was no consistent change in the reader's evaluation of gas shadowing between pre ingestion and post ingestion dose images for subjects receiving SonoRx at any dose level

Organ visualization

For each area of interest, the reader was asked to compare pre dose and post dose images and to state his opinion as to whether visualization was improved on the post dose image compared to the pre dose image. Improved visualization of specific organs was seen by the reader when pre ingestion images were compared to post ingestion images in subjects who received SonoRx. The number of subjects (out of the 5 subjects who received SonoRx) who showed improved visualization of each organ system is shown in table 2.6

TABLE 2.16 IMPROVED VISUALIZATION OF SPECIFIC ORGANS WITH SONORX 5 (SUBJECTS)

| AREA | NUMBER OF SUBJECTS WITH IMPROVED VISUALIZATION FROM PRE TO POST BY AREA AND DOSE | | | | |
|---------------|--|--------|--------|--------|--------|
| | 200 mL | 400 mL | 600 mL | 800 mL | 1000mL |
| stomach | 3 | 3 | 5 | 5 | 5 |
| stomach wall | 2 | 4 | 1 | 2 | 2 |
| head pancreas | 3 | 4 | 3 | 3 | 2 |
| body pancreas | 2 | 3 | 2 | 3 | 3 |
| tail pancreas | 2 | 3 | 4 | 3 | 5 |
| others | 0 | 3 | 4 | 3 | 5 |

Sponsor's Conclusion:

The results of this study demonstrate that orally administered SonoRx is safe at doses 200,400,600,,800 and 1000 mL. Initial efficacy data indicate that SonoRx At these doses is useful in improving ultrasound imaging of structures in the upper abdomen.

2.1.4 Reviewer's Analysis

Safety

There were no serious or severe adverse events reported in this study, Patient monitoring data raised no specific safety concerns at any of the dose levels of SonoRx evaluated in this study.

Efficacy

There is an indication that in this study of five subjects, with scans evaluated by one blinded radiologist, that SonoRx may help in the visualization of the stomach and the pancreas in upper abdominal ultrasound examinations. It is not clear why this radiologist was found no consistent difference in gas shadow degradation between pre and post dose images and yet found a consistently improved visualization of specific organs in the post dose images. However since these evaluations called for subjective evaluations by the radiologist, it is possible for such apparent contradictions to occur

Conclusions

SonoRx is an orally administered contrast agent for abdominal ultrasound imaging. According to the sponsor, all of the active ingredients of SonoRx are chemically inert, remain in the digestive tract and are excreted unchanged in the feces (see pharm-tox and pharmacokinetics reviews). Absorption from the GI tract is negligible. The potential for toxicity is therefore less than with agents that are absorbed or injected. In this study of 8 patients, there were no serious or severe adverse events. The 1 moderate and the 3 mild adverse events all occurred in the placebo group and all were thought by the investigator to be unrelated to the placebo. No clinically significant changes in EKGs or vital signs were noted. Two patients in the placebo group and one in the SonoRx group experienced a > 30% drop in serum albumin and/or serum glucose at 24 hours post infusion but the clinical significance of these changes is unclear. There are no clinically significant safety concerns raised by this data.

In this small group of patients, with scans read by a single blinded reader there is an indication that there may be some improvement in the visualization of the stomach and pancreas with SonoRx compared to pre SonoRx ultrasound images. There was no clear dose-response relationship demonstrated, for either safety or efficacy, in this study.

**APPEARS THIS WAY
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2.2 Phase 1 Study 42,440-4

A Clinical Evaluation of the Safety and Efficacy of SonoRx vs. Water in Normal Healthy Volunteers (Protocol # 42,440-4)

2.2.1 Study Objective:

To evaluate the safety and efficacy of SonoRx vs. water in normal healthy volunteers

2.2.2 Study Design

Protocol 42,440-4 is a Phase 1 Single Center Randomized Placebo Controlled (Water vs. SonoRx) Single Blind Crossover Study in Normal Healthy Adult Male Volunteers.

Twenty four normal healthy adult male volunteers were entered in this protocol. Inclusion criteria and exclusion criteria are listed below

Inclusion Criteria:

- Male
- Age 18-50
- Normal physical examination
- Not taking any other medication than indicated in this protocol
- Have not taken any other investigational drug within 60 days
- Signed IRB approved informed consent

Exclusion criteria

Female

- Clinical or laboratory evidence or history of clinically significant organ/system dysfunction (cardiovascular, renal, hepatic neuromuscular or metabolic)
- History of allergy, asthma or anaphylactic reaction to any drug
- Sitting blood pressure greater than 135/90 or less than 100/60
- Sitting Radial pulse less than 50 bpm or greater than 90 bpm
- Weight differs from ideal body weight for height and build by more than $\pm 15\%$
- History of aspiration or difficulty swallowing
- Recent drug or alcohol abuse
- Has consumed alcohol within 48 hours before or 24 hours after any administration

The 24 subjects were randomized to two groups of 12 subjects each. The subjects in the first group ingested a single dose of 800 mL SonoRx. At a subsequent occasion these subjects ingested a single dose of 800 mL tap water (placebo). For the second group, the order of the agents was reversed. The second group ingested a dose of 800 mL tap water, and then on a separate occasion, 800 ml SonoRx. Subjects fasted for at least 6 hours before ingestion. All subjects ingested the entire 800 mL of SonoRx or water within 15 minutes. A washout period of at least 48 hours was allowed between administrations.

Pre dose ultrasound images were obtained, of the stomach duodenum, pylorus and pancreas, immediately before each dose administration, and within 30 minutes after ingestion of the agent. Images were evaluated by two blinded readers, one of whom was affiliated with the study center and one of whom was not. Pre dose images were compared to post dose images for both SonoRx and water, and in addition the post dose images for SonoRx and water were

compared to each other. Images were evaluated for the ability to visualize each of the above mentioned anatomical structures and for the overall effect of gas shadowing.

Dosage and Formulation

SonoRx is an orally administered ultrasound contrast agent for the intended use of delineating normal anatomy and detecting pathology in the upper abdomen. The active ingredient is 22 micron fiber length cellulose fibers coated with simethicone. The cellulose is manufactured from wood and is considered safe (GRAS). Simethicone is a component of several over the counter medications. Both simethicone and cellulose components of SonoRx are considered by the sponsor to be chemically inert, to not be absorbed from the GI tract and to be excreted unchanged in the feces (see pharm-tox and pharmacokinetics reviews). The composition of SonoRx used in this study is given in table 1 below

TABLE 2.2.1 COMPOSITION OF SonoRx

| INGREDIENT | gm/L |
|--|------|
| 22 micron cellulose with 0.25% simethicone coating (active ingredient) | 7.5 |
| Xanthan Gum | |
| Medical anti Foaming Agent A (Simethicone USP) | |
| Sodium Laurel Sulfate NF | |
| Citric Acid USP | |
| Orange Oil Florida Type | |
| FD&C Yellow #6 | |
| Fructose USP | |
| Sodium Benzoate (preservative) NF | |

The mixture is brought to a volume of 1 liter with purified water USP

The placebo used in this study was ordinary tap water from the study institution.

Subjects

The sample consisted of 24 normal healthy adult male volunteers between ages of 18 years and 50 years. All subjects met the inclusion criteria and signed the informed consent. Subjects were divided into two equal groups of 12 subjects each. All subjects received 800 mL SonoRx and 800 mL tap water on separate occasions. The first group received SonoRx first and water second. For the second group, the order of the agents was reversed.

Evaluation

Safety was evaluated by monitoring physical examination, vital signs, Serum chemistry, CBC and Urinalysis, for each dose given. Physical examination was performed at screening, within 24 hours before ingestion and 24 hours after ingestion. Vital signs were monitored at screening, immediately before ingestion, immediately after ingestion, and at 24 hours post ingestion. Serum chemistry, CBC and urinalysis were obtained at screening within 24 hours pre dose and 24 hours post dose. The timing of these tests is given schematically in table 2

TABLE 2.2.2 SUBJECT MONITORING SCHEDULE

| TIME OF TEST FOR EACH DOSE ADMINISTRATION* | | | | | |
|--|----------|---------|-------------|------------|--------|
| TEST | PRE-DOSE | | | POST -DOSE | |
| | screen | <24 hr. | Immediately | | 24 hr. |
| History | x | | | | |
| Physical | x | x | | | x |
| Vitals | x | | x | x | x |
| Serum Chemistry Screen and CBC | x | x | | | x |
| Urinalysis | x | x | | | x |
| Ultrasound Imaging | | | x | x | |

Reviewer's comment: EKGs were not monitored in this study

Ultrasound images were obtained on each subject immediately before and immediately after each dose of SonoRx or placebo. All images were obtained using the same commercially available ultrasound unit by two qualified sonographers. Optimal position and settings were determined by the sonographers for each subject's body habitus. Whether the same settings were used for pre and post dose images is unclear. The protocol states: "The sonographer should use his/her own best judgment to determine the optimal imaging parameters for each pre and post dose scan depending on the individual subjects body habitus" The study report states: "Optimal imaging parameters were used for each set of pre and post dose images, for each subject per each evaluation performed depending on the individual subjects body habitus"

Reviewer's Comment

Each of these two statements seem open to interpretation. These statements would seem to imply that the same parameters were used for pre and post dose scans but one can not be certain. It is uncertain whether the parameters for the pre and post dose images were the same for each individual subject, or whether pre and post dose image parameters were optimized independently. Since the protocol instructions seem somewhat ambiguous to me, they may have seemed ambiguous to the sonographer as well.

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Static and video pre and post dose images for both SonoRx and water were evaluated by two blinded readers. The overall image was evaluated with respect to gas shadowing as: 1) not obscured, 2) mildly obscured, 3) moderately obscured, 4) markedly obscured or 5) completely obscured. The 8 specific anatomical areas or functions evaluated were the stomach, stomach wall, pancreatic head, pancreatic body, pancreatic tail, pylorus and duodenum. Gastric motility was also evaluated. Each pre dose image and each post dose image was evaluated by each reader. The image of each anatomical area was rated as: excellent (3), good (2), poor (1), or none (0) as described below.

Excellent: Diagnostic Image with excellent visualization of anatomic area of interest

Good: Diagnostic Image. Able to visualize anatomic area of interest

Poor: Marginally Diagnostic Image. Limited visualization of anatomic area of interest

None: Non-diagnostic Image. Can not identify anatomic area of interest

The post dose images for each anatomical area for both water and SonoRx were compared to the pre dose images by both blinded readers and rated as: markedly better (3), slightly better (2), same (1) or worse (0). There were a total of 48 comparisons of pre and post dose images for each region of interest (two readers each reading scans on 24 subjects). The principal efficacy variable for this study was the number of readings, for each anatomical area, for which the post dose scan showed improved visualization (markedly better or slightly better) than the pre dose scan.

Reviewer's comment:

Because a different placebo was used and because of differences in study design the results of this study can not be compared directly with the results of study 42,440-1

2.2.3 Results

Demographics

Twenty four normal healthy adult male volunteers who met the inclusion/exclusion criteria were entered in this study. All subjects received 800 ml SonoRx and 800 ml water on separate occasions. Demographics of the group is given in table 3

TABLE 2.2.3 DEMOGRAPHICS

| AGE (yr) | | WEIGHT (kg) | | HEIGHT (cm) | | RACE | | | |
|--------------|-------|---------------|----------------|---------------|-----------------|-------|-------|--------------|-------|
| mean ±SD | range | mean ±SD | range | mean ±SD | range | White | Black | Hispani c | Other |
| 28.8 ±1.1 | 19-41 | 78.0 ±10.7 | 62.7- 103.6 | 179.2 ±8.2 | 165.1- 192.0 | 12 | 9 | 3 | 0 |

Safety

Adverse Events

Deaths 0

Withdrawals due to adverse events 0

Serious adverse events 0

Severe adverse events 0

There were two mild and one moderate adverse events, all of which occurred after ingestion of SonoRx. Subject #4 had pharyngitis of moderate severity (this was described by the investigator as "common cold not related to drug"). This was present before dosing and therefore considered not related to the SonoRx. Subject #1 developed diarrhea of mild severity with bright orange liquid stools, 1 hour and 30 minutes after ingestion of SonoRx, which lasted for 4 hours. Subject #5 develop mild diarrhea 1 hour, 18 minutes after ingestion of sonoRx, which lasted for 5 hours and which was considered by the investigator to be possibly related to SonoRx. These adverse events are tabulated in table 4

TABLE 2.2.4 ADVERSE EVENTS

| Drug | Event (COSTART) | Body System | NO. | severity | related to drug | frequency | residual effects |
|--------|-----------------|-------------|-----|----------|-----------------|-----------|------------------|
| SonoRx | Diarrhea | GI | 2 | mild | yes* | 2/24=8% | no |
| SonoRx | pharyngitis | RES | 1 | moderate | no | 1/24=4% | no |

* In the reviewer's opinion, both cases of diarrhea should be regarded as related to the drug

6.2.2) Clinical and Laboratory Monitoring

Physical Examination

Physical examinations were performed on all 24 subjects within 24 hours pre administration and 24 hours post administration for both water and SonoRx. No clinically significant differences between pre and post physical examinations were noted for any subject in this study

Laboratory

There were no laboratory values either pre dose or post dose that were outside of the laboratory normal range, for both SonoRx or water, except for changes in SGOT and SGPT in one subject. These changes are given in table 5A below. These changes were not considered by the sponsor to be clinically significant. Therefore in the sponsor's opinion, there were no clinically significant change in laboratory values

TABLE 2.2.5A ABNORMAL LABORATORY VALUES

| Subject # | Agent | Test | Normal Range | Pre Dose Value | Post Dose Value |
|-----------|--------|------|--------------|----------------|-----------------|
| 18 | Water | SGPT | 5-50 u/L | 49 | 54 |
| 18 | SonoRx | SGPT | 5-50 u/L | 54 | 67 |
| 18 | SonoRx | SGOT | 15-47 u/L | 34 | 44 |

Reviewers Comment

There may be a typographical error in the sponsor's table 10 (table 5A above) the normal ranges in the table do not correspond to the normal ranges given in Attachment 111, Subject Data Listings. The values for the subject (subject 18) do correspond (note that in the last row of table 5A the subject's values are not outside the table's normal range)

Vital signs

Post dose vital signs that changed from baseline by more than $\pm 20\%$ are given in table 5B
TABLE 2.2.5B POST-DOSE CHANGES IN VITAL SIGNS FROM BASELINE of $\geq 20\%$

| Vital Sign | SonoRx, N=24 | | | | | | | |
|------------------------|--------------|------------|-------|------------|----------|-------------|----------|-------------|
| | Increase | | | | Decrease | | | |
| | number | change | range | %change | number | change | range | %change |
| Heart rate (bpm) | 6 | 19 \pm 6 | 12-28 | 32 \pm 9 | 0 | | | |
| Systolic B (mm hg) | 1 | 33 \pm 0 | 33-33 | 33 \pm 0 | 0 | | | |
| Diastolic BP (mm hg) | 8 | 17 \pm 4 | 14-27 | 27 \pm 7 | 0 | | | |
| respiration rate (bpm) | 1 | 6 \pm 0 | 6-6 | 33 \pm 0 | 0 | | | |
| | Water, N=24 | | | | | | | |
| | Increase | | | | Decrease | | | |
| | number | change | range | %change | number | change | range | %change |
| Heart rate (bpm) | 3 | 17 \pm 2 | 15-18 | 27 \pm 1 | 2 | -17 \pm 1 | -17, -16 | -26 \pm 1 |
| Systolic B (mm hg) | 2 | 29 \pm 6 | 25-33 | 28 \pm 3 | 0 | | | |
| Diastolic BP (mm hg) | 1 | 19 \pm 0 | 19-19 | 38 \pm 0 | 1 | -18 \pm 0 | -18, -18 | -24 \pm 0 |
| respiration rate (bpm) | 1 | 4 \pm 0 | 4-4 | 22 \pm 0 | 0 | | | |

Reviewers comment:

A relatively small number of subjects had large ($\geq 20\%$) changes in vital signs post dose, in both the SonoRx group, and the placebo group. Heart rate, blood pressure, and respiratory rate tended to increase rather than decrease. This may be due to the volume ingested irrespective of the type of agent

None of the changes in vital signs was considered by the sponsor to be clinically significant.

Urinalysis

No clinically significant deviations from normal were found either post SonoRx or post placebo at any of the 24 subjects.

Efficacy

Images were evaluated by two blinded readers, one of which was associated with the study center and one of which was not. Pre dose images were evaluated for visualization of each area of interest. Pre dose images were compared to post dose images for both SonoRx and water, and in addition the post dose images for SonoRx and water were compared to each other. Images were evaluated for the ability to visualize each of the above mentioned anatomical structures and for the overall effect of gas shadowing.

Gas Shadowing

There was no consistent change in the evaluation of either reader of image degradation from gas shadowing between pre ingestion and post ingestion dose images for subjects receiving SonoRx and those receiving water

Organ visualization

When the readers were asked "what do you consider to be an advantageous result of post dose evaluation compared to pre dose?" a consistent improvement in visualization of specific abdominal structures was seen in subjects who received SonoRx. The number of subjects (out of the 24 subjects who received SonoRx) who showed improved visualization of each organ system is shown in table 6. The majority of subjects also showed improved visualization with water but the percentage of subjects showing improvement was larger for SonoRx than for water

TABLE 2.2.6 IMPROVED VISUALIZATION (PRE DOSE SCANS COMPARED TO POST DOSE SCANS) OF SPECIFIC ORGANS WITH SonoRx OR WATER (24 SUBJECTS)

| AREA | NUMBER OF SUBJECTS WITH IMPROVED VISUALIZATION FROM PRE TO POST BY AREA , AGENT and READER | | | | | | | | | | | |
|------------------|--|--------|----------------|--------|----------------|--------|---------------|--------|-------------------|----------------|------------------|----------------|
| | Reader #1 N=24 | | | | Reader #2 N=24 | | | | Both Readers n=48 | | | |
| | SonoRx** | | Water** | | SonoRx** | | Water** | | SonoRx | | Water | |
| | worse/ same | better | worse/ same | better | worse/ same | better | worse same | better | improved* No. | improved* % | improved* No. | improved* % |
| stomach | 0 | 24 | 0 | 24 | 0 | 24 | 1 | 23 | 46 | 96 % | 37 | 77 % |
| pylorus | 6 | 18 | 9 | 15 | 0 | 24 | 1 | 23 | 32 | 67 % | 32 | 50 % |
| duodenum | 3 | 21 | 2 | 22 | 5 | 19 | 9 | 15 | 28 | 58 % | 30 | 63 % |
| head pancreas | 0 | 24 | 9 | 15 | 10 | 14 | 11 | 13 | 32 | 67 % | 22 | 46 % |
| body pancreas | 4 | 18 | 11 | 13 | 10 | 14 | 11 | 13 | 28 | 58 % | 19 | 40 % |
| tail pancreas | 4 | 20 | 7 | 17 | 3 | 21 | 10 | 14 | 38 | 79 % | 26 | 54 % |

*Readers were asked "what do you consider to be an advantageous result of post dose evaluation compared to pre dose" The numbers do not exactly correspond to the results when readers were asked to rate post dose images compared to pre dose images as: worse, same, slightly better, markedly better

**comparison of post dose to pre dose scan as (worse(0), same(1), slightly better(2) or markedly better (3)) Readers were also asked to compare overall post dose images for SonoRx with overall post dose images for water for overall visualization of abdominal anatomy and the results are shown in table 7

TABLE 2.2.7 READER'S DIRECT COMPARISON OF POST DOSE SCANS SonoRx vs. WATER

| Response | Reader #1, n=24 | | Reader #2 n=24 | | combined n=48 | |
|-----------------|-----------------|---------|----------------|---------|---------------|---------|
| | number | percent | number | percent | number | percent |
| SonoRx better | 21 | 88% | 17 | 71% | 38 | 79% |
| Can't determine | 1 | 4% | 2 | 8% | 3 | 6% |
| water better | 2 | 8% | 5 | 21% | 7 | 15% |

Sponsor's Conclusion:

The results of this study demonstrate that SonoRx is safe for use of an abdominal ultrasound contrast agent. The efficacy data indicate that SonoRx is more efficacious than water in improving the ultrasonic visualization of structures located in the upper abdomen

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2.4 Reviewer's Analysis

Safety

There were no serious or severe or serious adverse events reported in this study. The only adverse events reported were two cases of mild and self limiting diarrhea in the SonoRx group. A small number of patients experienced changes of >20% in heart rate, blood pressure or respiratory rate after either SonoRx or water (with increases outnumbering decreases). This is more likely related to ingestion of a large volume rather than to the specific agent, and these changes do not appear to be clinically significant. Unfortunately, EKG monitoring was not performed during ingestion. Overall the data does not raise any substantial safety concerns, and ingestion of 800 mL SonoRx by normal healthy volunteers appears to be safe.

Efficacy

From the responses of both readers given in table 4, it is clear that ingestion of 800 mL of either water or SonoRx improves the visualization of specific structures in the upper abdomen. However both readers found improved visualization in post dose scans vs. pre dose scans, for most structures, in more subjects with SonoRx than with water. In a direct comparison of post dose SonoRx images with post dose water images, both readers considered the SonoRx images to provide better visualization of abdominal anatomy than the water images in a large majority of subjects. According to the sponsor's analysis the differences between SonoRx and water in table 5 are statistically significant. In general according to the interpretation of the two blinded readers, 800 ml SonoRx does provide better visualization of abdominal anatomy than 800 ml tap water in the majority of subjects. Whether the differences between the water images and the SonoRx images are large enough to be clinically significant can not be determined from this study.

It appears that SonoRx may have some advantage over water as a contrast agent. However since the readers were asked so many different questions and to compare the images in so many different ways it is impossible to draw any firm overall conclusion.

Conclusions

SonoRx is an orally administered contrast agent for abdominal ultrasound imaging. All of the ingredients of SonoRx remain in the digestive tract and are excreted in the feces. Absorption from the GI tract is negligible (see pharm-tox and pharmacokinetic reviews). The potential for toxicity is therefore less than with agents that are absorbed or injected. In this study of 24 subjects, there were no serious or severe adverse events. There were two mild and self limiting cases of diarrhea which were probably related to SonoRx. No clinically significant changes in EKGs or vital signs were noted although ingestion of 800 mL of either SonoRx or water did have a tendency to increase heart rate, blood pressure and respiratory rate in a relatively small number of subjects. There are no clinically significant safety concerns raised by this data.

In this study of 24 subjects, in the opinion of the two blinded readers, 800 mL SonoRx does seem to provide better visualization of upper abdominal structures in more patients than does 800 mL tap water. The magnitude of the differences between the SonoRx images and tap water images can not be determined from the results of this study.

3 Phase 2 Clinical Trial 42,440-2

A Phase 2 Clinical Evaluation of the Safety and Efficacy of SonoRx in Patients Highly Suspected of Having Abdominal Pathology (Protocol # 42,440-2)

3.1 Study Objectives:

To expand the initial safety profile established in phase 1 trials using a broader population of patients highly suspected of having abdominal pathology

To determine the efficacy of SonoRx in the delineation of pathology using a range of dose volumes

To determine the optimal imaging time point post-administration

3.2 Study Design

Protocol 42,440-2 is a Phase 2 Multi-Center Randomized Open Label Dose Ranging Study in Patients Highly Suspected of Having Abdominal Pathology

103 patients were entered in this study at 6 study centers. Three patients withdrew prior to dosing and one withdrew after "tasting" 10 mL SonoRx and refusing to sign an informed consent. Inclusion criteria and exclusion criteria are given below:

Inclusion Criteria:

Age 18 years or Greater

Referred for Abdominal Ultrasound

Highly Suspected of Having At Least One of the Following Abdominal pathologies:

Stomach/Duodenal disease

Pancreatic Disease,

Extrahepatic Biliary Disease,

Left Kidney Mass

Could Be Examined by Accepted Comparable Modality (e.g. CAT Scan, MRI, Nuclear Medicine Scan, Plain X-ray, Endoscopy, Laparoscopy, Biopsy), For Comparison to the Ultrasound Images

Signed IRB approved informed consent

Exclusion criteria

Pregnant or Nursing Female

History of aspiration or difficulty swallowing

Suspected Gastrointestinal obstruction

Likely to Require Abdominal Surgery Within 8 Hours of SonoRx

Determined by Investigator to be Unsuitable for the Study

Protocol

Subjects were randomized to receive one of 5 doses of SonoRx :200 mL, 400 mL, 600 mL, 800 mL or 1000 mL. It was intended that all dose groups would have an equal number of patients. Patient and investigator were blinded to the dose ingested which was given in an unmarked plastic cup.

Reviewer's comment

It is difficult to totally blind both patient and investigator to the volume of SonoRx ingested, the same way as blinding to SonoRx or Placebo. Both the patient and the investigator could probably tell whether they were receiving a large dose or a small dose

Patients fasted for at least 8 hours before ingestion and were told to ingest the entire volume in 15 minutes .At each site all images were obtained by the same sonographer using the same commercial ultrasound unit. The optimal transducer for each patient's body habitus was chosen by the sonographer. Patients were imaged in the supine, left posterior oblique and right posterior oblique positions. Patients were also imaged in the erect position if deemed necessary. Both static and video images were obtained Pre dose ultrasound images were obtained, of the stomach, stomach wall duodenum, pylorus pancreas, common bile duct, left kidney, left renal artery, splenic vein, superior mesenteric artery, abdominal aorta and para-aortic lymph nodes, immediately before each dose administration, and within 30 minutes after ingestion of the agent. The same imaging parameters were used for both pre dose and post dose images. Three additional post dose images were obtained. A second post dose image was obtained immediately afterward, with parameters optimized, by the sonographer for the presence of the contrast agent. Using these optimized parameters ,two delayed images were obtained at between 30 and 45 minutes post ingestion, and between 45 and 60 minutes post ingestion. Thus for each patient 5 images were obtained, one pre dose image and 4 post dose images. The post dose images were numbered in the order that they were taken as images: 1, 2 ,3 and 4 as specified below:

- 1) Same parameters as pre dose
- 2) Optimized parameters
- 3) First delayed image
- 4) Second delayed image

The reader placed the pre dose images and post dose images side by side and then evaluate the pre dose first. Pre dose images were then compared to post dose images. Images at each site were read by the investigator at that site, who was a board certified radiologist who has been blinded to the dose administered. The same investigator read all scans at any one site. Each pre dose and post dose image was evaluated on a scale of 0 to 4 (0=none, 1=poor, 2=fair, 3=good, 4=excellent) as described below;

- 4) Excellent: Diagnostic Image with excellent visualization of anatomic area of interest
- 3) Good: Diagnostic Image. Good visualization of anatomic area of interest
- 2) Fair: Diagnostic image. Adequate visualization of anatomic area of interest

1) Poor: Marginally Diagnostic Image. Limited visualization of anatomic area of interest

0) None: Non-diagnostic Image. Can not identify anatomic area of interest

This evaluation was performed for each of the following characteristics:

Technical quality
 Visualization of specific abdominal anatomy
 Effect of gas shadowing artifacts
 Ultrasound diagnosis
 Change in patient diagnosis
 Change in patient management

Reviewer's comment

The readers apparently did not evaluate each image separately but had all images for each subject available to them during the entire evaluation procedure. Readers were asked whether the post dose images would have changed the diagnosis that would have been made using the pre dose scans only. They were not asked whether the pre dose scans would have changed the diagnosis that would have been made using the post dose scans only. There is thus no information on whether the contrast agent might have obscured some of the anatomy and/or pathology visible in the pre dose scan. In clinical practice, both pre and post dose scans would have to be performed on each patient to obtain all clinically relevant information. Changes in diagnosis and changes in patient management would be the endpoints with the most clinical significance.

Post dose images were compared to pre dose images on a scale of 0 to 3 (0=worse, 1=same, 2=slightly better, 3=markedly better). The overall effect of gas shadowing was scored for each image as: completely obscured, markedly obscured, moderately obscured, mildly obscured or not obscured. The reader was asked to rate the level of confidence in the diagnosis, for pre dose images and for post dose images 1 and 2. Post dose image 1 and post dose image 2 were compared to determine the optimal image, and for additional information provided compared to the pre dose image. The overall diagnosis pre SonoRx was compared to the post SonoRx diagnosis

Reviewer's comment

Although the protocol is not precisely clear on this point, it appears that the pre SonoRx diagnosis would be based on the clinical information and the pre dose scan, while the post SonoRx diagnosis would be based on the clinical information, the pre dose scan and the post dose scan

Formulation

SonoRx is an orally administered ultrasound contrast agent for the intended use of delineating normal anatomy and detecting pathology in the upper abdomen. The active ingredient is 22 micron fiber length cellulose fibers coated with simethicone. The cellulose is manufactured from wood and is considered safe (GRAS). Simethicone is a component of several over the counter medications. Both simethicone and cellulose components of SonoRx are considered by the sponsor to be chemically inert, to not be absorbed from the GI tract and to be excreted unchanged in the feces (see pharm-tox and pharmacokinetics reviews). The composition of SonoRx used in this study is given in table 1 below

TABLE 3.1 COMPOSITION OF SonoRx

| INGREDIENT | gm/L |
|--|------|
| 22 micron cellulose with 0.25% simethicone coating (active ingredient) | 7.5 |
| Xanthan Gum | |
| Medical anti Foaming Agent A (Simethicone USP) | |
| Sodium Laurel Sulfate NF | |
| Citric Acid USP | |
| Orange Oil Florida Type | |
| FD&C Yellow #6 | |
| Fructose USP | |
| Sodium Benzoate (preservative) NF | |

The mixture is brought to a volume of 1 liter with purified water USP

Placebo

The placebo used in this study was ordinary tap water from the study institution. There is no indication that any attempt was made to make the water look like or taste like SonoRx.

Subjects

The sample consisted of 99 evaluable patients enrolled by six different investigators at six different study centers. All patients were over the age of 18 years, had suspected abdominal pathology and had been referred for an abdominal ultrasound study for further evaluation.. Patients were randomized to five equally sized groups receiving five different doses of SonoRx. The doses used were 200 mL, 400 mL, 600 mL, 800mL and 1000 mL. Compliance was not 100%, and some patients were unable to ingest the entire dose that they were assigned. The results were analyzed according to the dose that the patients had actually ingested, not the dose to which they had been assigned by randomization.

Evaluation

Safety was evaluated by monitoring physical examination, vital signs, Serum chemistry, CBC and Urinalysis, for each dose given. Physical examination was performed at screening, within 24 hours before ingestion and 24 hours after ingestion. Vital signs were monitored at screening, immediately before ingestion, immediately after ingestion, and at 24 hours post ingestion. Serum chemistry, CBC and urinalysis were obtained at screening within 24 hours pre dose and 24 hours post dose. The timing of these tests is given schematically in table 2

TABLE 3.2 SAFETY MONITORING SCHEDULE

| TIME OF TEST FOR EACH DOSE ADMINISTRATION* | | | | | |
|--|----------------|-------------|------------|--------|---|
| TEST | PRE-DOSE | | POST -DOSE | | |
| | within 24 hrs. | Immediately | 1 hr. | 24 hr. | |
| History | x | | | | |
| Physical | x | | | | x |
| Vitals | | x | x | x | x |
| Serum Chemistry Screen and CBC | x | | | | x |
| Urinalysis | x | | | | x |
| Adverse Events | | | x | x | x |

Reviewer's comment: EKGs were not monitored in this study

Ultrasound images were obtained on each subject immediately before and immediately after each dose of SonoRx or placebo. An additional post dose image was obtained with parameters optimized for the presence of contrast. Two additional delayed post dose images were obtained at 30 to 45 minutes post ingestion and at 45 to 60 minutes post ingestion, respectively. All images were obtained using the a single commercially available ultrasound unit by a single qualified sonographer at each individual study center. Anatomical regions imaged were:

| | |
|-----------------------------|----------------------------|
| Stomach | Left Kidney |
| Stomach Wall | Left Renal Artery |
| Pylorus | Splenic Vein |
| Duodenum | Superior Mesenteric Artery |
| Pancreas (Head, Body, Tail) | Common Bile Duct |
| Abdominal Aorta | Para-Aortic Lymph Nodes |

Immediately after ingestion, ultrasound images were obtained of the same anatomy, Using the same equipment and parameter settings (Transducer, gain factor etc.) A second post dose image was taken immediately afterward, with the parameters optimized by the sonographer for the presence of contrast. Two additional "delayed" post dose images, at between 30 and 45 minutes post ingestion and at between 45 and 60 minutes post ingestion, respectively, of the stomach, duodenum, and pancreas only were taken. There were thus a total of 5 images taken for each subject, a single pre dose image, and 4 separate post dose images. The 4 post dose images were labeled 1, 2, 3 and 4, in the order in which they were taken as described below.

- 1) Same parameters as pre dose
- 2) Optimized parameters
- 3) First delayed image
- 4) Second delayed image

Images were evaluated by the investigators at each site. There were no blinded readings. Readers were instructed to evaluate the images according to the following criteria:

Pre dose image

Visualization of anatomy

Technical quality of the Image as a whole

Visualization of individual abdominal structures on a scale of 1 to 4:

- 4) Excellent: Diagnostic Image with excellent visualization of anatomic area of interest
- 3) Good: Diagnostic Image. Good visualization of anatomic area of interest
- 2) Fair: Diagnostic image. Adequate visualization of anatomic area of interest
- 1) Poor: Marginally Diagnostic Image. Limited visualization of anatomic area of interest
- 0) None: Non-diagnostic Image. Can not identify anatomic area of interest

Post dose images

Technical quality of images

Visualization individual abdominal structures compared to pre dose image on a scale of 0 to 3

- 0-Worse
- 1-Same
- 2- Slightly Better
- 3-Markedly better

Gas Shadowing

Readers evaluated the effect of gas shadowing artifacts using the following categories:

- Completely obscured
- Markedly obscured
- Moderately obscured
- Mildly obscured
- Not obscured

Diagnosis

Readers were asked to make a diagnosis and specify confidence in that diagnosis, on a scale of 1 to 5 (1= least confident, 5= most confident)

- After pre dose scan
- After first post dose scan
- After second post dose scan

Additional comparisons

Readers were asked to compare post dose scan 1 with post dose scan 2 for most optimal image
The sponsor's primary efficacy parameter was the comparison of the post dose scans 1 and 2 to the pre dose scan for providing additional information. Readers were also asked to specify:

Nature of additional information

Post dose diagnosis

Most optimal post dose image for pancreas, duodenum and stomach

Comparison of post dose images 1 and 2 to post dose images 3 and 4

Readers were asked to make a diagnosis and specify;

Overall clinical diagnosis excluding SonoRx

Post SonoRx diagnosis

Comparison of pre SonoRx diagnosis to pre SonoRx diagnosis

Reviewer's comment

There were 5 separate ultrasound images for each patient. Readers were asked to make a large number of subjective judgments about each image and a number of subjective comparisons between these five images. The large number of efficacy endpoints is confusing rather than enlightening, even before the actual data is analyzed. Some of the readers may also have been confused. While the results of this study might provide guidance in designing phase 3 trials it would be difficult to draw any firm conclusions concerning efficacy from a study with this design

The sponsor's primary endpoint is the comparison of the pre dose image to post dose images 1 and 2, with the question being whether the post dose scans provide additional information that would not be obtained from the pre dose image alone. This judgment is subjective and may not be clinically relevant. A more clinically significant endpoint would be the number of patients for whom the post dose scans changed the pre dose diagnosis to the correct diagnosis as determined by a "gold standard", such as biopsy.

3.3 Results**Patient disposition**

A total of 103 patients were entered in the study. Three patients withdrew before dosing, and a fourth withdrew after "tasting" 10 mL SonoRx. The safety analysis was performed on the remaining 99 patients. Of these 99 patients, 93 were evaluable for the efficacy analysis.

Compliance

Only 77 patients ingested the dose of SonoRx to which they were randomized. Of the remaining 22 patients, 4 ingested more than their assigned volume due to dosing errors by the investigators. 19 patients ingested less than the assigned dose because of inability to swallow the whole amount. Patient compliance was defined as ingesting an equal or greater volume of SonoRx than the volume assigned by randomization. Compliance was dose dependent, and was 100% at 200 mL, 75% at 800 mL and 57% at 1000 mL.

Reviewer's Comment

Compliance may have depended on the diagnosis and the severity of the abdominal pathology.

Demographics

TABLE 3.3 DEMOGRAPHICS (BY DOSE INGESTED) N=99

| Dose (mL) | AGE (yr) | | WEIGHT (kg) | | HIGHT (cm) | | SEX | | RACE | | | |
|-----------|-------------|-------|-------------|--------|-------------|---------|-----------|-----------|-----------|-----------|--------------|---------|
| | mean ±SD | range | mean ±SD | range | mean ±SD | range | M | F | White | Black | Hispan ic | Asian |
| 200 | 53± 15 | 26-81 | 85± 20 | 45-118 | 173±9 | 154-188 | 18 | 4 | 17 | 4 | 1 | 0 |
| 201-400 | 57± 16 | 21-81 | 70± 18 | 40-104 | 166±9 | 152-185 | 11 | 10 | 17 | 2 | 1 | 1 |
| 401-600 | 58± 13 | 30-76 | 76± 16 | 54-108 | 170±1 1 | 148-200 | 16 | 8 | 17 | 7 | 0 | 0 |
| 601-800 | 51± 12 | 30-73 | 74± 14 | 48-100 | 171±1 1 | 158-193 | 10 | 9 | 15 | 2 | 2 | 0 |
| 801-1000 | 59± 13 | 38-82 | 71±24 | 44-119 | 167±1 1 | 152-188 | 3 | 7 | 9 | 1 | 0 | 0 |
| >1000 | 45± 19 | 29-66 | 64± 6 | 59-70 | 170±1 0 | 160-173 | 1 | 2 | 3 | 0 | 0 | 0 |
| ALL | 55 ±14 | 21-82 | 76 ±18 | 40-119 | 170 ±10 | 148-200 | 59 60% | 40 40% | 78 79% | 16 16% | 4 4% | 1 1% |

Reviewer's Comment

There appear to be no dose-related trends in the demographic data

Safety

Adverse Events, N=99

Deaths 0

Withdrawals due to adverse events 0

Serious adverse events 1

Severe adverse events 0

There were a total of 14 adverse events in 11 of the 99 patients who ingested various doses of SonoRx (11%). There was 1 serious adverse event, eight mild and six moderate adverse events. Subject # 608 developed a severe nosebleed (epistaxis) 10 hours after ingesting 200 mL SonoRx. Epistaxis lasted for 8 days, required hospitalization, and resolved without permanent sequelae after surgical intervention. This event was characterized as serious. Since this patient has a history of severe nosebleeds, his epistaxis is considered to be the result of a pre-existing condition unrelated to SonoRx. Patient #204 developed bradycardia followed by tachycardia, hypertension and chest pain, in the first hour after ingestion of 400 mL SonoRx. These 4 events for this one patient were all characterized as moderate in severity. This patient, had a history of hypertension, and did not take his antihypertensive medication as scheduled. His signs and

symptoms resolved within 30 minutes on taking his medication. These events were not considered by the investigator to be related to SonoRx. However the close proximity in time between the development of these cardiovascular symptoms and SonoRx ingestion might seem to indicate that SonoRx may have lead to a worsening of the patient's underlying condition. The patient had ingested 400 mL of the sonoRx suspension which consisted mostly of water. Absorption of a significant part of this water from the gut in a short period of time could have caused these symptoms in a patient with underlying cardiovascular dysfunction. The one patient who developed moderate hypoglycemia had a history of insulin dependent diabetes, and this event was considered to be not related to SonoRx All other adverse events were mild.

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TABLE 3.4 ADVERSE EVENTS (BY DOSE INGESTED*)

| Dose* mL | Event COSTART | Body System | No. of patients | severity | related to*** SonoRx | Frequency | perm- anent sequelae |
|---------------------------------------|------------------------|--------------------|--------------------|----------|----------------------------|----------------------------------|----------------------------|
| 200 | epistaxis | RESP. | | serious | no | | no |
| 200 | nausea | GI | | mild | possibly | | no |
| 200 | diarrhea | GI | | mild | possibly | | no |
| Total 200 (22 pts) | | | 3 | | | 3/22, 13% | 0/22 |
| 201-400 | abd. pain | GI | | mild | possibly | | no |
| 201-400 | hyper- tension** | cardio vascular | | moderate | possibly | | no |
| 201-400 | tachy- cardia ** | cardio vascular | | moderate | possibly | | no |
| 201-400 | brady- cardia** | cardio vascular | | | possibly | | no |
| 201-400 | chest pain** | cardio vascular | | moderate | possibly | | no |
| Total 201-400 (21 pts) | | | 2 | | | 2/21, 10% | 0/21 |
| 401-600 | diarrhea | GI | | mild | yes | | no |
| 401-600 | nausea | GI | | mild | possibly | | no |
| Total 401-600 (24 pts) | | | 2 | | | 2/24, 8% | 0/24 |
| 601-800 | nausea | GI | | mild | yes | | no |
| 601-800 | diarrhea | GI | | mild | possibly | | no |
| 601-800 | hypo- glycemia | meta- bolic | | moderate | no | | no |
| Total 601-800 (19 pts) | | | 3 | | | 3/19, (16%) | |
| 801-1000 (10 pts) | diarrhea | GI | 1 | mild | possibly | | no |
| >1000 (3 pts) | None | | 0 | | | 0/3, 0% | 0/3 |
| Grand Total all doses SonoRx, N=99 | | | 14 vent 11 pts | | | 14 events. 11/99 pts (11%) | 0/99 |

*Dose actually ingested, NOT necessarily the same as dose assigned by randomization

**Same Patient This patient had a history of hypertension and missed a dose of antihypertensive medication. On taking the medication symptoms resolved in 30 minutes. However these events began within 1 hour after ingestion. Because of this proximity in time the reviewer thinks that these events may be related to SonoRx

*** Reviewer regards ALL GI Adverse Events as possibly related to SonoRx whether or not the investigator does

Clinical and Laboratory Monitoring

Physical Examination

Physical examinations were performed on all 99 subjects within 24 hours pre administration and 24 hours post administration for both water and SonoRx. There were 5 changes from normal to abnormal on physical examination. Two of these findings were, anal skin tags and puncture sites in the left groin were probably missed on the first examination. All other findings were also recorded as adverse events. Subject 608 developed severe nosebleeds which

was recorded as a serious adverse event. Patient 312 complained of weakness secondary to diabetic hypoglycemia. Pt 401 had post-dose diarrhea and patient 508 complained of RUQ abdominal pain.

Laboratory

Sponsor's guidelines for clinically significant changes in laboratory values (pre vs. post) are as follows:

Hemoglobin, Hematocrit, RBC, Albumin, Calcium $\pm 25\%$
 WBC, Platelet Count $\pm 50\%$
 Bilirubin, SGOT, SGPT, ASAT, ALAT $\pm 150\%$
 Potassium, Chloride $\pm 20\%$
 BUN, GGT, LDH $+100\%$
 Uric Acid $+75\%$
 Creatinine $+50\%$
 Glucose $+100\%$, -25%
 Phosphorus $+100\%$, -40%
 Sodium, $\pm 10\%$
 Total Protein, $\pm 30\%$

Comparison was made between CBCs serum chemistries taken 24 hours before and 24 hours after ingestion. Blood was not drawn for chemistries or CBC at or near to the time of infusion. Sponsor's guidelines for CBC changes in Hgb, Hct and RBC were $\pm 25\%$ and for WBC was $\pm 50\%$. 3 patients had changes outside of these guidelines. All changes were increases. One patient had increases in WBC Hgb, Hct and RBC from low to normal range. Two other patients had increases in WBC only, from 7.4 to 11.6, and from 7.8 to 12.2. None were considered to be clinically significant.

There were 17 patients in whom changes in routine serum chemistry values exceeded the sponsor's guidelines. Three patients experienced increases in serum potassium from the normal range (3.5 to 4.5 mEq/L) to 4.6, 4.8 and 5.2 respectively. Changes exceeding sponsor's guidelines also occurred in SGOT, alk.phos., glucose, and phosphorus. None of these were considered by the sponsor or the investigators to be clinically significant. Blood was not drawn for chemistry or CBC at the time of ingestion.

Vital signs

Vital signs taken immediately before and immediately after ingestion were compared. Nine patients experienced changes of greater than $\pm 20\%$ in systolic BP, 17 in diastolic BP, 14 in heart rate and 29 in respiratory rate. None of these changes in vital signs were considered clinically significant by the investigators or the sponsor.

TABLE 3.5 CHANGES IN VITAL SIGNS

| CHANGES IN VITAL SIGNS OF $\geq 20\%$ | | | |
|---------------------------------------|----------------------|----------------------|-----------------|
| | No. of pts increased | No. of pts decreased | Range of change |
| Systolic BP mm hg | 6 | 3 | -67 to +42 |
| Diastolic BP mm hg | 9 | 8 | -28 to +54 |
| Heart Rate bt./sec | 14 | 0 | +25 to +58 |
| Resp. Rate bt./sec | 22 | 7 | -17 to +10 |

Urinalysis

No clinically significant deviations from normal were found either post SonoRx or post placebo at any of the 99 subjects.

Efficacy

Patient disposition

Of the 99 patients who received SonoRx, 6 patients were excluded from the efficacy analysis for the following reasons:

- #310 Post dose 2 images technically inadequate
- #315 Ultrasound analysis confirming diagnosis 2 years old
- #501 Post dose 2 images technically inadequate
- #604 Pre dose images technically inadequate
- #610 Patient received over 1000 mL
- #615 Patient received over 1000 mL

There were 93 evaluable patients remaining for the efficacy analysis.

Primary Efficacy Endpoint

The sponsor's primary efficacy variable is the Reader's determination of whether the early post dose images (image 1 and 2) provide additional information than the pre dose image. The Readers were also asked whether post dose image 1 or post dose image 2 individually provided additional information. The results of this analysis were analyzed for a dose related trend.

TABLE 3.6 PRIMARY EFFICACY ENDPOINT BY DOSE INGESTED
 "Does the immediate post dose images provide additional information over the pre dose image?"

| DOSE | 200 mL N=20 | 201-400 mL N=20 | 401-600 mL N=24 | 601-800 mL N=19 | 801-1000 mL N=10 | All Doses N=93 |
|------------------|--------------------------------|--------------------|--------------------|--------------------|---------------------|-------------------|
| | Reader's Response (% response) | | | | | |
| YES, post scan 1 | 1 (5%) | 1 (5%) | 2 (8%) | 2 (11%) | 1 (10%) | 5 (5%) |
| YES, post scan 2 | 2 (10%) | 0 (0%) | 1 (4%) | 0 (0%) | 0 (0%) | 3 (3%) |
| YES, Both scans | 16 (80%) | 18 (90%) | 21 (88%) | 18 (95%) | 10 (100%) | 83 (89%) |
| NO | 4 (20%) | 2 (10%) | 3 (12%) | 1 (5%) | 0 (0%) | 10 (10%) |
| TOTAL | | | | | | 93 (100%) |

For a total of 83 out of 93 evaluable patients (89%), the readers said that additional information was provided by the post dose images (post dose scans 1 and 2), compared to the pre dose image. It appears that both post dose scans 1 and 2 were needed to obtain this additional information since either post dose scan alone provided additional information in only a small number of cases. There were no statistically significant differences between subgroups when patients were stratified by dose, age, sex, body weight or body surface area.

Change in Diagnosis and Management

The readers were also asked, for those 83 patients with additional information post dose, if the additional information obtained with the SonoRx scans could change the diagnosis or patient management. Their responses are given in table 7

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 "Could the additional information obtained with SonoRx change the diagnosis or patient management?"

TABLE 3.7 CHANGE IN DIAGNOSIS AND MANAGEMENT

| DOSE | 200 mL N=16 | 201-400 mL N=18 | 401-600 mL N=21 | 601-800 mL N=18 | 801-1000 mL N=10 | All Doses N=83 |
|--------------------------------|-------------|-----------------|-----------------|-----------------|------------------|----------------|
| Reader's Response (% response) | | | | | | |
| change diagnosis | 7 (44%) | 8 (44%) | 7 (33%) | 7 (39%) | 5 (50%) | 34 (41%) |
| no change | 9 (56%) | 10 (56%) | 14 (67%) | 11 (61%) | 5 (50%) | 49 (59%) |
| (61%) | | | | | | |
| change management | 4 (25%) | 7 (39%) | 8 (38%) | 7 (39%) | 7 (70%) | 33 (40%) |
| no change | 12 (75%) | 11 (61%) | 13 (62%) | 11 (61%) | 3 (30%) | 50 (60%) |

Thus of the 93 evaluable patients, in the opinion of the readers, the additional information obtained with SonoRx could change the diagnosis in 34 patients (37%) and the management in 33 (36%)

When readers were asked whether the post dose diagnoses have actually changed from the pre dose diagnoses, The answer was yes for only 6 patients

TABLE 3.8 Readers' response to " is the post dose diagnosis the same as the pre dose diagnosis"

| TABLE 3.8 "IS THE POST DOSE DIAGNOSIS THE SAME AS THE PRE DOSE DIAGNOSIS" | | | | | | |
|---|-------------|-----------------|-----------------|-----------------|------------------|----------------|
| DOSE | 200 mL N=20 | 201-400 mL N=20 | 401-600 mL N=24 | 601-800 mL N=19 | 801-1000 mL N=10 | All Doses N=93 |
| YES | 19 (95%) | 20 (100%) | 20 (83%) | 18 (95%) | 9 (90%) | 86 (93%) |
| NO | 1 (5%) | 0 (0%) | 4 (17%) | 1 (5%) | 1 (5%) | 6 (7%) |

When readers were asked whether the post dose diagnoses have actually changed from the pre dose diagnoses, The answer was yes for only 6 patients. Readers were also asked whether the post dose diagnosis

Reviewer's Comment

In the reviewer's opinion, the most clinically significant endpoint would be whether there is a change in diagnosis between the pre dose scan and the post dose scans and whether these diagnoses agree with the final diagnosis after the entire work-up is complete. This information can only be obtained by comparing the actual diagnoses, patient by patient. This comparison would give more concrete information than simply asking the reviewers for their opinion as to whether the additional information obtained from the post dose scans could change the diagnosis or patient management

Diagnoses

In reviewing the patient data listings for individual patients, the reviewer found 17 out of 93 evaluable patients (18%) for whom the pre dose diagnosis appeared to differ from the diagnosis after one or both of the two immediate post dose scans. These patients and the corresponding diagnoses, and the final (and presumably "correct") diagnosis are listed in table 9. The patient number, the dose received, the diagnosis after the pre dose scan the diagnosis after the first post dose scan, the diagnosis after the second post dose scan and the final diagnosis are given for each of these 17 patients. The correspondence between these diagnoses is also given.

| TABLE 3.9 | | | PRE AND POST DOSE DIAGNOSES N=17 | | | | same as final ? | | |
|-----------|-----|---------|---|--------------------------------------|---------------------------------------|-------------------------------|-----------------|--------|--------|
| # | Pt# | dose mL | diagnosis after pre dose scan, PR | Diagnosis after post dose scan 1 PO1 | diagnosis after post dose scan 2, PO2 | Final Diagnosis, F | PR =F | PO1 =F | PO2 =F |
| 1 | 203 | 600 | not seen | not seen | pancreatitis, dilated CBD | diverticulitis, fatty liver | No | No | No |
| 2 | 211 | 200 | GB sludge | not seen | L kidney cyst | L renal cyst | No | No | Yes |
| 3 | 409 | 600 | not seen | focal gastric thickening | focal gastric thickening | gastric ulcer, ventral hernia | No | No | No |
| 4 | 411 | 625 | liver lesions | not seen | not seen | liver mets pelvic malignancy | Yes | No | No |
| 5 | 417 | 350 | not seen | celiac adenopathy gastric tumor | celiac adenopathy gastric tumor | carcinoma, GE junction | No | Yes | Yes |
| 6 | 424 | 200 | cyst L lobe liver, renal cysts | not seen | not seen | renal cysts | Yes | No | No |
| 7 | 427 | 400 | renal/adrenal mass, gastric wall thickening | gastric tumor | gastric tumor | gastric malignancy | No | Yes | Yes |
| 8 | 428 | 1000 | not seen | not seen | pancreas tail mass | liver lesions (cysts) | No | No | No |
| 9 | 429 | 490 | L retroperitoneal cystic mass | pancreatic pseudocyst | pancreatic pseudocyst | chronic calcific pancreatitis | No | Yes | Yes |
| 10 | 430 | 400 | not seen | abdominal aortic aneurism | abdominal aortic aneurism | abdominal aortic aneurism | No | Yes | Yes |
| 11 | 502 | 725 | pancreatic mass, liver mass | pancreatic mass, liver mass | not seen | liver mass, pancreatic mass | Yes | Yes | No |
| 12 | 505 | 600 | L adrenal nodule | l adrenal nodule | not seen | prob. adrenal adenoma | Yes | Yes | No |
| 13 | 515 | 800 | not seen | not seen | normal pancreas | possible cholangio-carcinoma | No | No | No |
| 14 | 607 | 600 | negative | enlarged pancreas head | enlarged pancreas head | enlarged pancreas head | No | Yes | Yes |
| 15 | 612 | 600 | normal | peripelvic echogenicity | peripelvic fat | peripelvic echogenicity | No | Yes | Yes |
| 16 | 616 | 1000 | excess gas, no dx | L renal stone | L renal stone | L renal stone | No | Yes | Yes |
| 17 | 619 | 800 | excess gas no dx | small L kidney | small L kidney | Small L kidney | No | Yes | Yes |
| Total yes | | | | | | | 3 | 10 | 9 |

The numbers in table 7, 8 and 9 do not agree. In table 7 readers were asked their opinion as to whether the additional information would change the diagnosis. In table 8 the readers were asked whether the post dose diagnosis agreed with the pre dose diagnosis. In table 9, the actual diagnoses were compared by the reviewer to see whether the diagnosis had in fact changed and which diagnosis agreed with the final diagnosis.

Of the 17 patients for whom the pre dose and post dose diagnoses disagreed, the pre dose scan diagnosis agreed with the final diagnosis in 5 patients, the first post dose scan diagnosis agreed with the final diagnosis in 10 patients, and the second post dose diagnosis agreed with the final diagnosis in 9 patients. Thus it appears that the post dose scans agreed with the final diagnosis in a larger number of patients than the pre dose scans in cases where the pre and post diagnoses differ. However because these differences in diagnoses only occurred in a small number of patients, these differences in the number of diagnoses are probably not statistically significant.

For 6 patients, the pre dose scan was non diagnostic, and the first post dose scan detected pathology, which agreed with the final diagnosis and in two additional cases, the pre dose scan, and the first post dose scan were both negative or nondiagnostic and the second post dose scan detected pathology, which agreed with the final diagnosis

Interestingly the post dose scans for which the parameters were optimized for the presence of contrast did not seem to give better results than the post dose scans where the post dose scans remained the same.

Readers were asked if the overall clinical diagnosis agreed with the results of the SonoRx procedure.

Visualization of Anatomical structures

Images were assessed for visualization of individual anatomical structures to determine whether visualization was better on the post dose images.. Post dose images were compared to pre dose images on a scale of 0 to 3 (0=worse, 1=same, 2=slightly better, 3=markedly better). If visualization was rated slightly better or markedly better, visualization can be considered to be improved. The combined number of images rated slightly better or markedly better, by structure and dose is given in table 10

TABLE 3.10 SLIGHTLY OR MARKEDLY IMPROVED VISUALIZATION

| IMPROVED VISUALIZATION POST DOSE vs. PRE DOSE SCANS | | | | | | |
|---|------------------|----------------------|----------------------|-----------------------|-------------------|------------------|
| Post Dose Scan 1 | | | | | | |
| DOSES organs | 200 (mL) N=20 | 401-600 (mL) N=20 | 601-800 (mL) N=24 | 801-1000 (mL) N=19 | 1000 (mL) N=10 | ALL (mL) N=93 |
| Stomach | 14 | 16 | 17 | 17 | 9 | 73 (78%) |
| Duodenum | 10 | 14 | 12 | 16 | 6 | 58 (62%) |
| Head Pancreas | 12 | 11 | 12 | 12 | 6 | 53 (57%) |
| Body Pancreas | 10 | 12 | 14 | 12 | 6 | 54 (58%) |
| Tail Pancreas | 9 | 15 | 16 | 15 | 6 | 61 (66%) |
| Post Dose Scan 2 | | | | | | |
| Stomach | 13 | 16 | 18 | 19 | 9 | 75 (80%) |
| Duodenum | 9 | 13 | 11 | 16 | 7 | 56 (60%) |
| Head Pancreas | 11 | 14 | 13 | 12 | 5 | 55 (59%) |
| Body Pancreas | 12 | 14 | 13 | 12 | 5 | 56 (60%) |
| Tail Pancreas | 9 | 11 | 12 | 12 | 7 | 51 (55%) |

Gas Shadowing

The overall image was evaluated with respect to gas shadowing as: 1) not obscured, 2) mildly obscured, 3) moderately obscured, 4) markedly obscured or 5) completely obscured. The number of scans rated mildly obscured or not obscured, by dose and scan is given in table 9 for the pre dose scan and the 4 post dose scans .

| | 200 mL N=20 | 201-400 mL N=20 | 401-600 mL N=24 | 601-800 mL N=19 | 801-1000 mL N=10 | TOTAL N=93 |
|-------------|-------------|--------------------|--------------------|--------------------|---------------------|------------|
| Pre Dose | 4 | 5 | 9 | 5 | 4 | 27 (29%) |
| Post Dose 1 | 13 | 12 | 15 | 12 | 8 | 60 (64%) |
| Post Dose 2 | 13 | 13 | 16 | 14 | 8 | 64 (69%) |
| Post Dose 3 | 10 | 11 | 15 | 11 | 6 | 53 (57%) |
| Post Dose 4 | 9 | 11 | 14 | 10 | 6 | 50 (54%) |

Sponsor's Conclusion:

The results of this clinical trial indicate that SonoRx is a safe oral contrast agent for use in a diverse group of patients suspected of having abdominal pathology. SonoRx is efficacious in providing additional information over uninanced images at doses from 200 mL to 1000 mL. The most substantial increase in efficacy was observed between the 200 and 400 mL dose groups. Based on the results of this study, the 400 mL volume was selected as the minimum effective dose to be further evaluated in the phase 3 trials

3.4 Reviewer's Analysis

Safety

99 patients were evaluable for safety

Adverse events

There were 14 adverse events in 11 out of 99 patients (11%) in this study (table 4). 12 events in 9 patients (9%), in the reviewer's opinion were possibly related to SonoRx. In the sponsor's opinion 7 adverse events were definitely or possibly related to SonoRx. Two events were considered to be definitely related by the sponsor and the investigators. There was one serious adverse event, a severe nosebleed that required hospitalization, but this event was not related to SonoRx. One patient had 4 moderate cardiovascular events (hypertension, bradycardia followed by tachycardia, and chest pain). These events began within 1 hour after ingestion of 400 mL SonoRx. The sponsor has attributed these events to a missed dose of antihypertensive medication. However because of the close proximity in time, to ingestion, the reviewer feels that the SonoRx may have been a contributing factor (if a large proportion of the water in the 400 mL SonoRx had been absorbed from the gut the cardiovascular system could have been overloaded) It is also possible that dehydration secondary to pre dose fasting could have contributed to these events. EKGs, which could have further characterized these events were not monitored in this study. The reviewer considered all GI events (diarrhea, nausea, abdominal pain) as possibly related to SonoRx.

Vital signs

Vital signs immediately before ingestion and immediately after ingestion were compared. Changes in vital signs by more than $\pm 20\%$ are given in table 5. Increases in heart rate, respiratory rate, systolic blood pressure and diastolic blood pressure were seen more often than decreases in these parameters. None of these changes were considered to be clinically significant. EKG monitoring was not performed during infusion so there are no EKG tracings that can be correlated with the observed changes in heart rate and blood pressure.

Physical Examination

Changes noted on physical examination, such as anal skin tags and puncture sites in the left groin resulting from previous catheterization, were probably missed on the original physical examination. Other than for those patients reported as having experienced adverse events, no clinically significant changes were noted.

Laboratory Monitoring

Three patients had changes in CBC outside of the sponsor's guidelines (RBC $\pm 25\%$, WBC $\pm 50\%$). All changes were increases. In one patient both RBC and WBC increased from low to normal. The two other patients had increases in WBC. None of these changes were considered to be clinically significant. Changes in routine serum chemistries outside of the sponsor's guidelines included changes in potassium, SGOT, alkaline phosphatase, glucose, and phosphorus. None of these changes were considered to be clinically significant or to be related to SonoRx. There were no clinically significant changes in urinalysis.

Efficacy

93 patients were evaluable for efficacy. The evaluation of efficacy in this study is complicated by the large number of scans to be compared, and the large number of endpoints that the readers were asked to evaluate. The sponsor's primary endpoint was the readers' answer to the question "does the immediate post dose images provide additional information over the post dose image?" In order to answer this question, the readers would have had to evaluate them together rather than separately. The answer to this question calls for a subjective judgment by the reader, and this judgment may not be clinically significant. If a final diagnosis can be made from the pre dose scan alone, it doesn't matter whether the post dose images provide additional information or not. If a diagnosis can not be made from the pre dose scan then additional information per se is not particularly valuable unless that information helps the reader to make a diagnosis. Since the ultrasound examination is a screening test, and any positive result will be followed up by confirmatory tests (CT scan, biopsy, etc.) the most important clinical indicator is the ability of the ultrasound image to allow the reader to detect pathology. In other words sensitivity may be more important in evaluating the clinical value of the ultrasound images than specificity.

Sponsor's Primary Endpoint

The sponsor's primary endpoint is the reader's answer to the question "Do the immediate post dose images 1 (images 1 and 2) provide additional information over the pre dose image" (table 6). The readers' positive response for 83 patients (89%) would seem to be an indication of efficacy. However, the question calls for a subjective judgment on the part of the readers that may not be clinically relevant. The readers were also asked, for those 83 patients with additional information, whether that additional information could change the diagnosis (table 7). They said that the information would change the diagnosis in 34 patients (41%) and would not change the diagnosis in 49 patients (59%). However, when the readers were asked whether the post diagnosis was the same as the pre dose diagnosis (table 8), they answered yes for 86 patients (93%) and no for 6 patients (7%). Even though the readers found additional information in 83 cases (89%), they found that the diagnosis changed for only 6 patients. It thus appears that, for most patients, even if there was additional information obtained from the post dose scans, that additional information did not change the diagnosis or management.

Change in Diagnosis

The readers were asked if the additional information could change the diagnosis in those cases where there was additional information. They responded that it could change the diagnosis in 34 patients (41%) and the management in 33 patients (40%) (table 7). Readers were asked if the pre dose diagnosis is the same as the post dose diagnosis. The answer was yes for 86 patients (93%) and no for 6 patients (7%). The reviewer reviewed the patient data tables for pre dose diagnosis, post dose diagnoses, and final (and presumably "correct") diagnosis and identified 17 patients for whom the pre dose diagnosis differed from either the diagnosis after post dose scan 1 or the diagnosis after post dose scan 2. The pre dose diagnosis agreed with the final diagnosis for 3 patients, the post dose scan 1 diagnosis for 10 patients, the post dose scan 2 diagnosis agreed with the final diagnosis for 9 patients, and the two post dose scans agreed with each other for 9 patients. The reason for the discrepancy in the numbers in tables 7, 8 and 9 is not clear, but it may be due to the way the questions were worded, and lack of agreement on which diagnoses that seemed similar were the same and which were different. In any event, it appears that the pre dose diagnosis differs from the post dose diagnosis in a relatively small number of patients, and for the majority of these patients, the post dose diagnosis agrees with the final diagnosis in the majority of cases.

Visualization of Individual Organs

Readers were asked whether there was better visualization of individual anatomic structures in the post dose scans than in the pre dose scans. The readers replied that visualization was slightly better or markedly better the stomach in 73 patients (78%), of the duodenum in 58 patients, of the head of the pancreas in 53 patients of the body of the pancreas in 53 patients (57%), and of the tail of the pancreas in 61 patients (66%).

Gas Shadowing

In evaluating images for gas shadowing, readers rated the pre dose scans as mildly obscured for 27 patients (29%). Post dose scans 1 and 2 were rated as mildly obscured or not obscured in 60 patients (64%), and in 64 patients (69%) respectively.

Dose-Response

From the point of view of safety, there is no clear dose-response relationship in number of adverse events or changes in vital signs or laboratory values. From the point of view of efficacy

there seems to be a small but consistent increase in efficacy between the 200 mL Group and the 201-400 mL group for visualization of the stomach, duodenum, and head, body and tail of the pancreas (table 10), in both scans providing additional information (table 6), and in additional information that would change management (table 7). The number of cases where the post dose scans actually changed the diagnosis were too small to draw any conclusions about any dose response relationship. It is not clear from the data that there is any clear dose response relationship for doses above the 201-400 ml range. It is on the basis of these observations that the sponsor decided on the 400 mL dose for further evaluation in the phase 3 studies.

Conclusions

SonoRx is an orally administered contrast agent for abdominal ultrasound imaging. According to the sponsor, all of the active ingredients of SonoRx are chemically inert, remain in the digestive tract and are excreted unchanged in the feces (see pharm-tox and pharmacokinetics reviews). Absorption from the GI tract is negligible. The two active ingredients in SonoRx are known to be safe in the doses administered in this study. The potential for toxicity is therefore less than with agents that are absorbed or injected. In this study of 99 patients, there was one serious adverse event and no severe adverse events. The one serious adverse event was a case of epistaxis requiring hospitalization, in a patient with a history of severe nosebleeds. This event is not related to SonoRx. Of concern is the one patient in the 201-400 mL group who experienced a sequence of 4 moderate cardiovascular adverse events. Since this patient was hypertensive and had missed a dose of his antihypertensive medication, the sponsor has concluded that these events were not related to SonoRx. However since these events began within the first hour post ingestion, this conclusion may be questionable. Unfortunately, EKG monitoring, which could have elucidated the etiology of these changes was not performed in this study. The only other moderate adverse event was hypoglycemia in a patient who was diabetic, which was not related to SonoRx. There were no safety concerns raised by the results of monitoring vital signs or laboratory studies.

There is only one safety concern raised by this study. Although it is not possible to draw any firm conclusions on the basis of one patient, there is a possibility that SonoRx may pose a danger to patients with pre-existing cardiovascular pathology and careful monitoring may be necessary for such patients.

Because of the large number of efficacy endpoints in this study, it is difficult to draw any firm conclusions without determining which endpoint is the most clinically relevant. For a majority of the patients, readers, when asked to make subjective judgments, felt that the post dose scans provided additional information, better visualization of the stomach, duodenum and pancreas, and less gas shadowing when compared to the pre dose scans. However the post dose scans actually changed the diagnosis in a relatively small number of patients. However the fact that SonoRx does change the diagnosis in some patients, and that the post dose diagnosis does agree with the final diagnosis, is probably the best indication of the clinical usefulness of this agent. Because the diagnosis is changed in only a small number of patients it is unlikely that this clinical advantage can be shown with statistical significance.

4. Phase 3 supportive trial 42,440-7

The Clinical Evaluation of the Safety and Efficacy of SonoRx vs. Water in Patients Highly Suspected of Having Abdominal Pathology (Protocol # 42,440-7)

Reviewer's Comment

This study can not be considered independent of studies 3A and 3B since 3 out of the 6 investigators were also either investigators or blinded readers for either study 3A or study 3B, and two of the 4 blinded readers were also either investigators or blinded readers for either study 3A or study 3B. The technical reviewer was the same for all 3 phase 3 studies

Description of Study

4.1 Study Objectives:

The objective of this study is to evaluate the safety and efficacy of SonoRx as an ultrasound contrast agent in patients highly suspected of having abdominal pathology. Specifically the goals are:

To expand the initial safety profile established in phase 1, and Phase 2

To compare the efficacy of SonoRx versus water in the delineation of abdominal anatomy and to assist in the detection or exclusion of pathology in a broad spectrum of patients undergoing abdominal ultrasound

4.2 Study Design

Protocol 42,440-7 is a Phase 3 Multi-Center Randomized Single Blind (investigator blinded) Placebo Controlled Crossover Trial.

Protocol (including protocol amendments)

Subjects, Randomization and Dosing

The investigator at each of 6 sites was to enroll 8 patients. All patients will receive both 400 mL SonoRx and 400 mL water, in a crossover fashion, with patients randomized as to which agent to receive first. A washout period of 1 to 4 days will be allowed between agents. The investigator only is blinded to the agent (the subject can obviously tell from the appearance and taste). All subjects will fast a minimum of 4 hours before ingestion. Patients will be monitored for safety for 24 hours after ingestion.

Safety Monitoring

The following evaluations for safety monitoring will be obtained

History and Physical: A complete history and physical will be obtained within 24 hours prior to ingestion. Physical examination will be repeated at 24±3 hours after ingestion

Vital Signs: Vital signs will be obtained immediately before ingestion, immediately after ingestion, 1 hour after ingestion, and 24±3 hours after ingestion. Vital signs to be monitored are: radial pulse, blood pressure, respiration rate and temperature.

Clinical Laboratory: Serum laboratory assays will be obtained at 24 hours prior to ingestion and 24±3 hours after ingestion. These include CBC, chem-screen panel, electrolytes, LFTs and routine urinalysis. All laboratory values are to be reviewed by the investigator and any changes found by the investigator to be remarkable are to be entered on the case report forms.

Reviewer's Comment

Reviewers were given no guidance from the sponsor, in the case report form as to what changes should be considered to be "remarkable". This seems to have been left entirely to the clinical judgment of the individual investigator. The threshold for a change in a laboratory value to be considered "remarkable would probably vary from investigator to investigator. The sponsor did have a list of " Sponsor guidelines for screening pre vs post administration laboratory changes" but these seem to have been used mainly by the sponsor to analyze data submitted by the investigators. These tables were not given in the case report forms and investigators were not specifically told to adhere to them in deciding which changes were remarkable.

EKG: 12 lead EKGs will be obtained within 24 hours prior to ingestion and at 1hour±10 minutes post ingestion.

TABLE 4.1 SAFETY MONITORING SCHEDULE

| TEST | TIME OF TEST | | | |
|--------------------------------|----------------|-------------|------------|--------|
| | PRE-DOSE | | POST -DOSE | |
| | within 24 hrs. | Immediately | 1 hr. | 24 hr. |
| History | x | | | |
| Physical | x | | | x |
| EKG* | x | | x | |
| Vitals | | x | x | x |
| Serum Chemistry Screen and CBC | x | | | x |
| Adverse Events | | | x | x |

* EKGs were obtained at only 1 of 8 sites

Adverse Events

All events involving appearance or worsening of illnesses, signs or symptoms after implementation of study procedures will be reported. Adverse events will be classified as serious if they are life threatening or permanently disabling, require hospitalization or a prolongation of hospitalization or result in death, cancer, congenital abnormality, or overdose. Non serious adverse events will be classified as moderate if they require medication or other treatment by a physician, and will be classified as mild if they are self resolving without treatment. Adverse events will be monitored

Proposed Indication:

Reviewer's comment

There is no category of severe but non serious adverse events in the case report forms.

Efficacy

Imaging

A commercially available ultrasound unit will be used at each site. The transducer used will be the one that in the sonographer's opinion provides the best image for the patient's body habitus. The same ultrasound unit, the same transducer and the same parameter settings will be used for both SonoRx and water images on each patient. All attempts will be made to use the same sonographer throughout the study at each study site. The investigator or a designated sub investigator must be available in the vicinity during all the entire study evaluation.

Each patient should be imaged in the supine, right posterior oblique and left posterior oblique positions. Erect images will be obtained if needed. Static and video images will be obtained Pre dose images will be obtained immediately before dosing of the following structures

- | | |
|---|--------------------------|
| Stomach Pylorus Pancreas (Head, Body, Tail) | Stomach Wall Duodenum |
|---|--------------------------|



Image Interpretation

Pre dose images were obtained on all patients for patient management purposes but these pre dose images will not be evaluated as part of this trial. The investigator at each site will be a qualified radiologist who will be blinded to the identity of the drug administered. The investigator will evaluate all SonoRx and water images at his/her site. In addition two additional readers, unaffiliated with any center, will read the SonoRx and water images. These readers will be blinded to patient identity and all clinical information. For all readings, static and video images for each patient will be placed side by side for review.

Readers will evaluate the images for the following factors:

- Technical quality
- Delineation of specified abdominal anatomy
- Effect of gas shadowing artifacts
- Ultrasound diagnosis
- Level of confidence in making ultrasound diagnosis
- Potential change in patient's diagnosis (investigators only)
- Potential change in patient's management/therapy
- Comparison to results from other procedures (investigators only)
- Overall performance (visualization of anatomy and providing diagnostic information)

Reviewer's Comment

All of the above endpoints require a subjective judgment on the part of the reader. Endpoints for investigators only should be discounted since investigator's responses must be considered the least unbiased.

Primary Efficacy Endpoint

The primary efficacy endpoint of this study will be the reader's answer for each patient, to the question "Overall which images provided more diagnostic information SonoRx, water or both equal?"

Reviewer's Comment

If the aim is to determine the percentage of cases for which SonoRx images provided more information than water images, then the number of "SonoRx" answers should be compared to the sum of the number of "water" answers and the number of "equal" answers

Visualization of specific abdominal anatomy

The following scoring system will be used for to evaluate the pre and post dose images for the visualization of each listed anatomical area on a scale of 0 to 4 (0=none, 1=poor, 2=fair, 3=good, 4=excellent)

- 4) Excellent: Diagnostic Image; excellent delineation; high confidence in detecting or excluding pathology
- 3) Good: Diagnostic Image; Good delineation; good level of confidence in detecting or excluding pathology
- 2) Fair: Diagnostic image. Fair delineation; fair confidence in detecting or excluding pathology
- 1) Poor: Marginally Diagnostic Image. Limited delineation; low level of confidence in detecting or excluding pathology
- 0) None: Non-diagnostic Image. Cannot identify area of interest; cannot detect nor exclude pathology

Reviewer's comment

The words excellent, good, fair and poor seem to be defined in terms of themselves. Without more guidance from the protocol these words are likely to mean different things to different readers

Effect of gas shadowing artifacts

The overall effect of gas shadowing will be evaluated on a scale from 0 to 4

- 0=completely obscured
- 1=markedly obscured
- 2=moderately obscured
- 3=mildly obscured
- 4=not obscured

Formulation

SonoRx is an orally administered ultrasound contrast agent for the intended use of delineating normal anatomy and detecting pathology in the upper abdomen. The active ingredient is 22 micron fiber length cellulose fibers coated with Simethicone. The cellulose is manufactured from wood and is considered safe (GRAS). Simethicone is a component of several over the counter anti-flatulence medications. Both Simethicone and cellulose components of SonoRx are considered by the sponsor to be chemically inert, to not be absorbed from the GI tract and to be excreted unchanged in the feces (see pharm-tox and pharmacokinetics reviews). The composition of SonoRx used in this study is given in table 1 below

TABLE 4.2 COMPOSITION OF SonoRx*

| INGREDIENT | gm/L |
|--|------|
| 22 micron cellulose with 0.25% Simethicone coating (active ingredient) | 7.5 |
| Xanthan Gum | |
| Medical anti Foaming Agent A (Simethicone USP) | |
| Sodium Laurel Sulfate NF | |
| Citric Acid USP | |
| Orange Oil Florida Type | |
| FD&C Yellow #6 | |
| Fructose USP | |
| Sodium Benzoate (preservative) NF | |

*The mixture is brought to a volume of 1 liter with purified water USP

TABLE 4.3 COMPOSITION OF PLACEBO

| INGREDIENT |
|---|
| Degassed water if available or tap water left standing for 30 minutes |

Subjects

8 patients are to be recruited at each study center, for a planned total of 48 patients

Inclusion Criteria:

Age 18 years or greater

Scheduled for ultrasound examination

Highly suspected of having upper abdominal pathology including but not limited to pancreatic disease, stomach/duodenal disease, extrahepatic biliary pathology and/or a left kidney mass

Patients must have or be scheduled to undergo a comparative diagnostic modality other than ultrasound which includes but is not limited to; computed tomography, magnetic resonance imaging, nuclear medicine imaging, standard abdominal x ray, endoscopy, laparoscopy, biopsy, and/or surgery for comparative purposes.

Signed IRB approved informed consent

Signed IRB approved informed consent

Agreed to undergo both post SonoRx and post water ultrasound scans

Reviewer's comment

The third inclusion criterion seems to contradict the fourth. A patient who is scheduled for a comparative diagnostic modality may be said to be highly suspected of having abdominal pathology, but, a patient who has already had other studies, is likely to be definitely known to have or to not have abdominal pathology. If other imaging studies are done before the patient is referred to the investigator for the protocol ultrasound studies, results of the other studies may be known to the investigator and/or the sonographer at the time that the ultrasound scan is performed and interpreted. Ideally the patients should have been "fresh" referrals who would have their ultrasound first and the rest of the diagnostic workup later. Since that was not to be done in every case, those patients for whom the ultrasound was the first imaging study, and patients for whom it was not should be clearly identified and analyzed separately. The number and type of other studies, will vary from patient and will be dependent on the patient's condition and the inclination of the referring physician.

Exclusion criteria

Pregnant or Nursing Female

History of aspiration or difficulty swallowing

Suspected gastrointestinal obstruction

Likely to require abdominal surgery within 8 hours of ingestion

Known allergy to one or more ingredients in SonoRx or placebo

Determined by investigator to be unsuitable for the study