

tables 17 and 18 ) Thus in terms of number of readers The pre dose images beat the post dose images by 2 to 1 for both sensitivity and specificity, for the per protocol analysis, and by 2 to 0 in the intent to treat analysis. These results are not statistically significant. It is clear that using the sponsor's definition of sensitivity and specificity, and the sponsor's comparison of the diagnosis, the efficacy of SonoRx has certainly not been demonstrated by this sensitivity and specificity data. The data and the analysis is flawed by the small number of true negatives ( 9 out of 85, 10.5%), by the fact that the same "gold standard" modality was not used to determine the "true" diagnosis, and by the fact that the comparisons of the diagnoses were made by the sponsor instead of by an independent third party. Since these data don't prove anything, these observations are moot for this analysis, but should be considered in the planning of any future study or data analysis.

### 5.7.9 Conclusions

SonoRx is an orally administered contrast agent for abdominal ultrasound imaging. It performs its function as a contrast agent while remaining in the lumen of the digestive tract. 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 117 patients, there was one serious adverse event and 26 non serious adverse events in 20 patients. The one serious adverse event was a case chest pain requiring hospitalization for observation, in a patient in the placebo group. This event was probably not related to the placebo agent. There were 22 adverse events in 17 patients (18%) in the SonoRx group and 3 events in 3 patients (13%) in the placebo group. The difference is not statistically significant ( $p=0.53$ ) The most common adverse events were GI complaints, diarrhea, nausea, and vomiting. These symptoms were self limiting and resolved spontaneously without permanent sequelae. The data on physical examination, vital signs, EKGs, and laboratory monitoring suggest no specific safety concerns. The safety of SonoRx is supported by the results of this study

There are a large number of efficacy endpoints in this study not all of which are related to the proposed indication: "SonoRx is an orally administered 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". The sponsor's primary endpoint is the readers' answer to the question: "Overall did the post dose images provide additional information over the pre dose images?". This question calls for a subjective opinion on the part of the reader. The readers were given little or no guidance on how to answer this question. Although they were later asked to specify the nature of the information, and whether in their opinion, the information could change the diagnosis and/or the management. The readers answers to this question are given in table 12, with the variable being the number of "yes" answers to this question. Since this is not a placebo controlled trial for efficacy, it is not clear what this number of "yes" answers should be compared to. The sponsor claims to show that this number greater than 1% with statistical significance for each for each and every reader with a p value,  $p<0.0001$ . However this value of 1% seems arbitrary and the choice seems to have been made after the data was analyzed so that the sponsor would be able to say that something was shown with statistical significance. 1% is a ridiculously low number. A test that did no better than that would provide additional information in 1 out of 100 cases and would not be clinically useful. If the more reasonable number of 50% had been used, a glance at the confidence intervals in table 12 indicates that the results would be statistically significant for none of the readers. In fact for reader #4, the number of "yes" answers can be shown to be less than 50% with statistical significance. In fact even those "yes" answers that were given, may simply be a result of the fact that in the post dose scans, the stomach was full rather than empty. If this were the case, any liquid or bulk agent could be expected to do as well as SonoRx. (this last remark is applicable to all of the study endpoints).

The conclusion is inescapable that the sponsor has not demonstrated efficacy using the primary outcome variable.

A more clinically meaningful endpoint would be a comparison of the pre dose scans and post dose scans for the readers' ability to make the "correct" diagnosis as determined by some "gold standard" diagnostic modality. The sponsor has attempted to answer this question with the analysis of "sensitivity" and "specificity" (tables 17-24). There are several problems with the sponsor's analysis. The sponsor's definition of "sensitivity" and "specificity" do not correspond to the usual definition because a dichotomous variable is not used. There was no single "gold standard modality." The gold standard actually used was whatever workup, other than ultrasound, imaging that the patient actually had. Needless to say there were large variations in the completeness of that workup from patient to patient. There were too few "true negatives" to assess the ability of readers to distinguish between "normal" scans and scans showing pathology. The determination of whether two diagnoses "matched" was made by the sponsor, rather than by an independent radiologist. Taking all of these problems into account the "sensitivity" and "specificity" as defined by the sponsor, do provide a crude measure of the ability to make a "correct" diagnosis.

The results of this analysis are given in tables 17 and 18. These results are highly variable and reader dependent. For example, in the intent to treat analysis, reader #1 finds a higher sensitivity and specificity for the pre dose scans, whereas in the per protocol analysis, reader #4 found a higher sensitivity for the post dose scans, and equal specificities. There is clearly no advantage for the post dose scans seen in this data. Table 18 shows the number of readers finding higher sensitivities and specificities in the pre dose and post dose scans. It appears that there is an advantage for the pre dose scans but the differences are probably not statistically significant.

Readers were asked to rate the visualization of specific anatomical structures (stomach, stomach wall, pylorus, duodenum, head, body tail and duct of the pancreas) as excellent good poor or none. No guidance as to what characteristics of the image should be used in making this rating, making the question quite subjective. The sum of the number of "excellent" and "good" answers are given in table 14. The readers are almost unanimous in finding better visualization of all mentioned structures in the post dose images than in the pre dose images. Using the Wilcoxin signed rank test these differences, in most cases are highly statistically significant. It appears that there is better visualization of these structures in the post dose images, in the opinion of the blinded readers, however because of the subjective nature of the question it is hard to draw any firm conclusions.

In conclusion there are no clinically significant concerns raised by the data in this study. However, the sponsor has not clearly demonstrated efficacy in this study using the primary outcome variable or any other endpoint considered.

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## 6. Phase 3 Pivotal Trial 42,440-3B

A Phase 3 Clinical Evaluation of the Safety and Efficacy of SonoRx in Patients Highly Suspected of Having Abdominal Pathology (Protocol # 42,440-3B) .

### Reviewer's Comment

The protocol for study 42,440-3B is identical to the protocol for study 42,440-3A and was performed simultaneously with study 42,440-3A by a different group of investigators. There was no overlap between these two studies in investigators blinded readers, or technical reviewers

## 6.1 Description of Study

### 6.1.1 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 determine the efficacy of SonoRx 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

### 6.1.2 Study Design

Protocol 42,440-3B is a Phase 3 Multi-Center Randomized Double Blind Phase 3 Trial.

Protocol (including protocol amendments)

Subjects, Randomization and Dosing

The investigator at each site was to enroll 13 patients who will be randomized to receive either SonoRx or placebo. 10 patients are to receive SonoRx and 3 to receive placebo at each site. Prior to enrollment each patient is randomized to receive either 400 mL SonoRx, or 400 mL of control agent . The entire 400 mL is to be ingested in 15 minutes. If patient is unable to ingest entire 400 mL, the dose actually administered is to be recorded. The patient and the investigator are to be blinded to the agent. Pre dose ultrasound images will be obtained immediately before ingestion of SonoRx.

### Reviewer's comment

Ideally the patient should be enrolled first and then randomized, rather than visa versa. The statement in the protocol may be a mistake or a typo.

As will be noted below, the control agent in this study is SonoRx without 4 ingredients, including the active ingredient which is 22 micron cellulose particles coated with 0.25% Simethicone. These particles are in suspension. Thus while both SonoRx and control will have the same color, it is likely that SonoRx will be cloudy while the control agent will be clear, making blinding problematical.

## 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 6.1 SAFETY MONITORING SCHEDULE

TIME OF TEST					
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	x
Serum Chemistry Screen and CBC	x				x
Urinalysis	x				x
Adverse Events			x	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.

**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 pre dose and post dose 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	Left Kidney
Stomach Wall	Left Renal Artery
Pylorus	Splenic Vein
Duodenum	Superior Mesenteric Artery
Pancreas (Head, Body, Tail)	Liver
Pancreatic duct	Common Bile Duct
Abdominal Aorta	Para-Aortic Lymph Nodes

**Image Interpretation**

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 pre and post dose images at his/her site. In addition two additional readers unaffiliated with any center will read SonoRx images only. 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.

**Reviewer's comment.**

By "SonoRx images" the sponsor means both pre and post dose scans in those patients who received SonoRx and not the post dose images alone, but this should have been explicitly stated. The fact that the placebo images were not used in the efficacy analysis, and that blinding of the investigators may have been less than perfect, would itself seriously undermine the efficacy evaluation in this study. The independent readers will be the only individual readers who will read all the scans in the study

Readers will evaluate the images for the following factors:

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

Primary Efficacy Endpoint

The primary efficacy endpoint of this study will be the reader's answer for each patient, to the question "Overall did the post dose images provide additional information over the pre dose images?"

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

## 6.2 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 6.2 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

The placebo used in this study was SonoRx with the first 4 ingredients omitted

TABLE 6.3 COMPOSITION OF PLACEBO\*

INGREDIENT	gm/L
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

#### Reviewer's Comment:

The active ingredient in SonoRx is the Simethicone coated cellulose. Since the function of the ingredients xanthan gum and sodium laurel sulfate is not stated, it is not clear why these particular ingredients are omitted from the placebo. If they merely effect the appearance, taste or viscosity of the agent, their omission would make it easier to distinguish placebo from active agent without effecting the primary function of the agent. It should be noted that this placebo is different from the placebos used in the phase 1 studies. Since SonoRx is a suspension and placebo is a solution one might expect that SonoRx would appear cloudy and placebo would appear clear. However the sponsor states that SonoRx and placebo are similar in taste and appearance.

The data from the placebo group will be used in the safety analysis only, and will not be used for the analysis of Efficacy. A placebo consisting of some of the ingredients in the preparation but not the active ingredient would be more useful for comparison purposes in an efficacy analysis than in a safety analysis. Only the active ingredient should influence the efficacy, but any ingredient or combination of ingredients could, in principle contribute to toxicity

### 6.3 Subjects

13 patients are to be recruited at each study center

#### 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.

#### 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.

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 ingestion

Known allergy to one or more ingredients in SonoRx or placebo

Determined by investigator to be unsuitable for the study

## 6.4 Evaluation

Safety will be evaluated by monitoring physical examination, vital signs, Serum chemistry, CBC and Urinalysis, on a schedule given in table 1. Adverse events will also be monitored. Efficacy will be monitored by monitoring the readers response to questions about the images listed in the protocol

## 6.6 Results

### 6.6.1 Discrepancies Between Protocol and Study Report

There are several areas where the procedures described in the protocol differ from those actually used in the study and described in the study report. These differences were not specifically listed as protocol amendments. These differences are related mainly to the reading of the images

According to protocol both the investigators and the blinded readers were to be given both static and video images. The sponsor states that after consultation with some of the investigators it was decided that video images were not necessary so readers 1 and 2 were given the static images only. When the results of this study and the identical study, 42,440-3A, were analyzed, the results, in the sponsor's opinion, were inconsistent with those of the phase 2 trial. The sponsor then consulted with radiologists with experience in abdominal ultrasound imaging and was told that in accordance with clinical practice the blinded readers should have had access to the video images, the clinical information, or information from the sonographer who performed the scans. The sponsor then decided to obtain readings from two additional readers, blinded readers 3 and 4. These readers were given both static and video images, were given standardized training prior to image evaluation, and were instructed to limit their reading time to 8 hours per day.

EKGs were obtained on patients at only 1 of 8 sites.

All images were evaluated by a designated radiologist (technical reviewer) for complete coverage of the anatomy specified in the protocol and for the use of appropriate imaging parameters. Images were also evaluated for technical quality by each individual blinded reader. Images deemed technically adequate by the technical reviewers were then sent on to the blinded readers for evaluation.

The intent to treat population was defined as patients who received any volume of either SonoRx or placebo and had images of acceptable technical quality. The per protocol population was defined as patients who ingested at least 350 mL SonoRx or placebo, had no significant protocol violations, had pre and post dose images of acceptable technical quality, and had a comparable diagnosis by another acceptable modality. The sponsor inadvertently sent readers 3 and 4 only the images of the per protocol patients instead of all the technically acceptable images. Therefore an intent to treat analysis for readers 3 and 4 was performed for the primary efficacy variable only, with worst case data (i.e. post dose images provided no additional information) imputed to the SonoRx patients and best case data to the placebo patients whose images were not sent to readers 3 and 4. An intent to treat analysis for readers 3 and 4 was not performed for any of the other efficacy variables. The analyses that were performed were intent to treat and per protocol analyses for the primary efficacy variable, and per protocol analysis only for the other efficacy variables, for readers 3 and 4.

Reviewer's comment

The investigators at each site read all of the images at that site, and had access to both static and video images. Blinded readers 1 and 2 received the static images only and did not have access to the video images. Readers 3 and 4 were given both static and video images but, by mistake received images for the per protocol patients only instead of all of the images from all of the patients.. The fact that some of the investigators advised that only the static images should be read, while radiologists with expertise in the area of ultrasound imaging, subsequently consulted by the sponsor, advised that it was common clinical practice to view both video and static images together, would seem to bring into question the investigators' expertise in, or even familiarity with ultrasound imaging and interpretation procedures. Blinded readers 1 and 2 had not read the protocol, while blinded readers 3 and 4 had read the protocol as part of their training. Readers 3 and 4 knew that the patients in the study were highly suspected of having upper abdominal pathology, while blinded readers 1 and 2 did not.

6.6.2 Patient disposition

A total of 123 patients were enrolled at 8 sites. One dropped out before receiving any dose of either SonoRx or placebo. The remaining 122 patients were dosed (94 SonoRx ,28 placebo) and were included in the safety analysis. The demographics of these 122 patients is given in table 4. Three patients randomized to receive SonoRx actually received placebo by mistake. These patients were included in the analyses according to the agent that they actually ingested

6.6.3 Compliance

TABLE 6.4 PATIENT COMPLIANCE IN INGESTING 400 ML SONORX OR PLACEBO

Actual Dose Ingested	SonoRx n=94	Placebo n=28
400	90	27
399-350	1	1
<350	3	0

Reviewer's Comment

Compliance is somewhat better than in study 42,440-3A.

Demographics

TABLE 6.5 DEMOGRAPHICS N=122

agent	AGE (yr)		WEIGHT (kg)		HIGHT (cm)		SEX		RACE			
	mean ±SD	range	mean ±SD	range	mean ±SD	range	M	F	White	Black	Hispan ic	Asian Other
SonoRx N=94	54± 16	23-81	78± 19	27-131	171±1 2	130- 203	56	38	81	8	3	2
placebo N=28	49± 16	22-83	73± 17	46-118	170±9	152- 191	12	116	24	3	1	0

**Reviewer's Comment**

There appear to be no remarkable demographic differences between the SonoRx group and the placebo group. The only apparent difference in this group and the patient population in study 42,440-3A is that there seems to be a higher proportion of Whites and a smaller proportion of Blacks in 42,440-3B. This is probably a result in demographic differences in the populations of the catchment areas of the various treatment centers in the two studies.

**6.6.4 Safety**

**Adverse Events, N=122 (94 SonoRx, 28 placebo)**

**Deaths 0**

**Withdrawals due to adverse events 0**

**Serious adverse events 3 events in 2 patients**

**Severe adverse events\* 0**

\*all non-serious adverse events were classified as mild or moderate. The category of severe non-serious adverse events was not used in this study.

32 adverse events in 21 patients (17%) were reported, 28 adverse events in 17 patients (18%) in the SonoRx group and 4 events in 4 patients (14%) in the placebo group. The most commonly reported adverse events were diarrhea in 4 patients (4%) in the SonoRx group and in 0 patients (0%) in the placebo group, abdominal pain in 4 patients (4%) in the SonoRx group and 1 patient (4%) in the placebo group and nausea in 4 patients in the SonoRx group (4%) and in 1 patient (4%) in the placebo group. The difference in the percentage of adverse events between SonoRx and placebo was not statistically significant ( $p=0.640$ ) There were no trends observed in the incidence of adverse events by age, sex or race.

There were 3 serious adverse events. Patient 316 in the SonoRx group developed chest pain 9 hours after ingestion. Chest pain was relieved with nitroglycerin. This patient had a history of MI and of alcohol and tobacco abuse. This patient had previously experienced nausea, vomiting and chills, 3, 5 and 6.5 hours after ingestion. These events should all be considered to be possibly related to each other and to SonoRx.

Patient 1305, in the SonoRx group experienced two serious adverse events, pneumothorax and chest pain. Pneumothorax developed during placement of a central line and the chest pain was related to the pneumothorax. A chest tube was placed, and subsequently removed 24 hours later when the pneumothorax had resolved

TABLE 6.6 ADVERSE EVENTS

patient no.	agent	event COSTART	body system	intensity	drug related*	permanent sequelae
304	SonoRx	diarrhea	gastrointestinal	mild	possibly	no
307	placebo	eructation	gastrointestinal	mild	possibly	no
311	SonoRx -	melina	gastrointestinal	mild	possibly	no
313	SonoRx	abd. pain	gastrointestinal	mild	possibly	no
316	SonoRx	pain chest nausea vomiting chills	body as whole gastrointestinal gastrointestinal body as whole	SERIOUS mild mild mild	possibly possibly possibly possibly	no no no no
315	SonoRx	dyspepsia	gastrointestinal	mild	definitely	no
317	placebo	back pain	body as whole	mild	no	no
318	SonoRx	back pain	body as whole	mild	no	persistent
401	SonoRx	eructation abd. pain	gastrointestinal body as whole	mild mild	possibly possibly	no no
419	SonoRx	nausea diarrhea abd pain	gastrointestinal gastrointestinal body as whole	moderate mild moderate	possibly possibly possibly	persistent no persistent
606	placebo	nausea	gastrointestinal	mild	possibly	no
608	SonoRx	pharyngitis lymphadeno- pathy	respiratory lympho- reticular	mild mild	no no	no no
612	SonoRx	vomiting	gastrointestinal	mild	definitely	no
1304	SonoRx	hypertonia headache diarrhea nausea	nervous body as whole gastrointestinal gastrointestinal	mild mild mild mild	unknown unknown possibly possibly	no no no no
1305	SonoRx	pneumothorax pain chest	respiratory  body as whole	SERIOUS  SERIOUS	no  no	no  no
1307	SonoRx	abd. pain	body as whole	mild	no	no
1308	placebo	asthenia	body as whole	mild	possibly	no
1313	SonoRx	malaise	body as whole	mild	unknown	no
1810	SonoRx	abd. pain	body as whole	mild	unknown	no
1906	SonoRx	diarrhea	gastrointestinal	moderate	possibly	no
2002	SonoRx	nausea	gastrointestinal	mild	possibly	no

\* the reviewer considers all GI side effects and abdominal pain to be possibly related to SonoRx or placebo

TABLE 6.7 SUMMARY OF ADVERSE EVENTS BY STUDY AGENT AND BODY SYSTEM

Body System	SonoRx N=94			Placebo N=28		
	Patients		Events	Patients		events
Serious Adverse Events						
Body as whole	2	2%	2	0		0
Respiratory	1	1%	1	0		0
Non-Serious Adverse Events						
Body as whole	10	11%	11	2	2	7%
Lymphatic	1	1%	1	0	0	0%
Gastrointestinal	9	10%	13	2	2	7%
Respiratory	2	2%	2	0	0	0%
Nervous	1	1%	1	0	0	0%
TOTAL	17*	18%	28	4	4	14%

\* some patients had multiple adverse events involving multiple organ systems

#### Clinical and Laboratory Monitoring

##### Physical Examination

There were 6 patients in the SonoRx group (6%) with 10 findings on the post dose physical examination that were not present on the pre dose examination. Six of these findings were chest pain, abdominal pain x2, diarrhea, headache, and hypertonia which were reported as adverse events (table 6). Three of the other four findings, new subclavian central venous line, diminished breath sounds and midaxillary puncture wound occurred in the patient who developed pneumothorax during insertion of the central line, and were unrelated to SonoRx. The other change was scattered ronchi. No changes in physical examination were noted for any of the patients in the placebo group.

##### Vital signs

Vital signs taken immediately before and immediately after ingestion were compared. 9 patients experienced changes of greater than  $\pm 20\%$  in systolic BP, 16 in diastolic BP, 19 in heart rate and 20 in respiratory rate (Table 8). None of these changes in vital signs were considered clinically significant by the investigators or the sponsor. Review of vital sign scatter plots by the reviewer indicates no apparent systematic changes from pre dose to post dose values.

TABLE 6.8 CHANGES IN VITAL SIGNS

CHANGES IN VITAL SIGNS OF $\geq 20\%$			
SonoRx N=94			
	No. of pts increased	No. of pts decreased	Range of change
Systolic BP mm hg	4	2	-42 to +44
Diastolic BP mm hg	12	1	-18 to +30
Heart Rate bt/sec	13	3	-31 to +43
Resp. Rate bt/sec	9	9	-8 to +12
Placebo N=24			
Systolic BP mm hg	2	1	-46 to +44
Diastolic BP mm hg	3	0	+11-+25
Heart Rate bt/sec	3	0	+16 to +32
Resp. Rate bt/sec	1	1	-4 to +4

## EKG

Pre and post dose EKGs were performed on 21 patients, (17 SonoRx and 4 placebo) at 1 study center. EKGs were read by a cardiologist. No clinically significant changes were noted on any EKGs. 18 patients had both pre dose and post dose EKGs normal, and 3 patients had both pre and post dose EKGs abnormal (table 9).

TABLE 6.9 EKG CHANGES

EKGs N=21 (17 SonoRx, 4 placebo)		
	pre dose normal	pre dose abnormal
post dose normal	18 (86%)	0 (0%)
post dose abnormal	0 (0%)	3 (14%)

## 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,  $\pm 30\%$

Four SonoRx patients and two placebo patients had CBC changes that exceeded the Sponsor's guidelines. There were 19 serum chemistry value changes that exceeded the sponsor's guidelines, 15 changes in 15 SonoRx patients and 4 changes in 3 placebo patients. These changes are given in table 10-A

TABLE 6.10-A SERUM CHEMISTRY CHANGES

TABLE 10-A SERUM CHEMISTRY CHANGES OUTSIDE OF SPONSOR'S GUIDELINES N=122			
SonoRx			
Test	number of increases	number of decreases	% change
Hemoglobin	1	0	+38%
WBC	3	0	+52 to +69
GGT	1	0	+120%
Glucose	4	5	-28% to +212%
Potassium	5	0	+21% to +24%
Placebo			
WBC	2	0	+106 to +171
BUN	2	0	+120% to +125%
Glucose	0	2	-30% to -39%

None of the serum chemistry changes were considered clinically significant by the sponsor. The most common changes were decreases and increases in serum glucose which may be related to the patient's fasting before ingestion or to the timing of the test in relation to the subject's mealtimes. The fact that large changes were seen in LFTs in 1 patients is consistent with the fact that most of these patients have abdominal pathology. Review of scatter plots of pre and post dose chemistry values, and of mean pre and post dose values by the reviewer revealed no apparent systematic changes from pre dose to post dose values.

#### Urinalysis

Mean values of pre and post dose urine pH and specific gravity (S. G.) and values are shown in table 10-B

TABLE 6.10-B URINALYSIS RESULTS

TABLE 6.10-B URINALYSIS						
Test	SonoRx			placebo		
	pre dose	post dose	change	pre dose	post dose	change
pH	5.7	5.8	0.1	5.6	5.8	0.2
S.G.	1.0	1.0	0	1.0	1.0	0

There are no clinically significant changes in these urinalysis results. A total of 17 urinalysis deviations in 12 patients (11 SonoRx, 1 placebo) were noted by the investigators. There were 2 urinalyses positive for glucose, 1 positive for ketones, 9 positive for protein, 4 positive for blood and one abnormally high specific gravity.

#### 6.6.4 Efficacy

##### Patient disposition

Data obtained from readings of the scans from the 28 patients who received placebo were listed in the summary tables but were not included in the sponsor's efficacy analysis. Thus efficacy data on the placebo patients were not included in the study report but were available in the supplementary tables. This was the original intent of the sponsor as stated in the protocol, and the study was not powered for comparison of efficacy between placebo and SonoRx. Of the 95 patients randomized to receive SonoRx, one dropped out before dosing. The remaining 94 patients

were included in the intent to treat analysis of the investigator's readings (each of the 8 investigators read the images from his/her center only). The scans of these 94 patients were reviewed by the technical reviewers, and 9 images were excluded for technical reasons. The scans on 1 patient were miscoded for blinded readers 1 and 2. The images of 84 patients were sent to blinded readers 1 and 2 and were included in the intent to treat analysis for these 2 blinded readers. In an apparent error, the scans of 4 patients who had ingested less than 350 mL SonoRx, had drug left standing for <2 minutes or who fasted for <4 hours (protocol violations) were not sent to blinded readers 3 and 4. For the purpose of intent to treat analysis of these blinded readers, the worst case scenario (no additional information provided by the post dose images) was assigned to these patients. An intent to treat analysis, of 85 patients, was performed for readers 3 and 4 for the primary efficacy variable only. For the per protocol analysis there were 88 patients for the investigators, 80 patients for blinded reader 1, 78 for blinded reader 2 and 80 for blinded readers 3 and 4.

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TABLE 6.11 PATIENT DEPOSITION FOR EFFICACY ANALYSIS	
Total Number of patients planned	100
Total Number of patients enrolled	123
Dropped Out Before Ingestion	1 ( SonoRx)
Patients Available For Safety Analysis (SonoRx 94 ) (Placebo 28 )	123-1=122
Patients Available For Efficacy Analysis (SonoRx patients only*)	122-28=94
Intent to Treat Analysis By Investigators	94
Technically inadequate per technical reviewer (8))	9
Intent to Treat Analysis By Blinded readers 3 and 4	94-9=85
1 image miscoded for readers 1 and 2	1
Intent to Treat Analysis By Blinded readers 1 and 2	85-1=84
Intent to Treat Analysis By Blinded readers 3 and 4 (primary efficacy endpoint only)	85
Patients Who Ingested <350 mL	3
Per Protocol Analysis By Investigators	88**
Per Protocol Analysis By Blinded reader 1	80**
Per Protocol Analysis By Blinded reader 2	78**
Per Protocol Analysis By Blinded readers 3 and 4	81**

\*placebo data used for safety analysis only

\*\* Images were evaluated for technical acceptability by both the technical reader and the individual blinded readers. The number of images excluded as technically unacceptable varied from reader to reader.

#### Primary Efficacy Endpoint

The primary efficacy endpoint of this study was the reader's answer for each patient, to the question "Overall did the post dose images provide additional information over the pre dose images?" The possible answers were yes or no. The sponsor's analysis of results for each reviewer are given in table 12A

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TABLE 6.12A SPONSOR'S PRIMARY EFFICACY VARIABLE

TABLE 12A ADDITIONAL INFORMATION: POST DOSE IMAGE vs. PRE DOSE IMAGE						
Per Protocol						
Response	blinded readers					
	investigators N=88	reader #1 N=80	reader #2 N=78	reader #3 N=81	reader #4 N=81	
yes	66 75%	55 69%	33 42%	61 75%	52 65%	
no	22 25%	25 31%	45 58%	20 25%	29 35%	
confidence interval %	66.0%-84.0%	58.6%-78.9%	31.3%-53.3%	65.9%-84.7%	53.8%-74.6%	
Binomial test yes≤1%	p=0.0001**	p=0.0001**	p=0.0001**	p=0.0001**	p=0.0001**	
Intent To Treat						
Response	investigators N=94*	reader #1 N=84	reader #2 N=84	reader #3 N=85	reader #4 N=85	
	yes	71* 76%	58 69%	36 43%	61 72%	52 61%
no	22* 23%	26 31%	48 57%	24 28%	33 39%	
confidence interval %	66.8%-84.2%	59.2%-78.9%	32.3%-53.4%	62.2%-81.3%	50.8%-71.5%	
Binomial test yes≤1%	p=0.0001**	p=0.0001**	p=0.0001**	p=0.0001**	p=0.0001**	

\* one patient was not imaged post dose

\*\* all of the p values cannot be exactly identical. The sponsor probably means p<0.0001

Reviewer's Comment

The entries in table 12 were taken directly from the sponsor's tables S, T, AA and AB, (pgs.66, 67, 80 and 82, vol.29). The statistical analysis was also performed by the sponsor. The sponsor's null hypothesis is that the reader would agree that the post dose scan provided additional information in 1% or less of the cases. The null hypothesis would be false if the readers gave a positive answer for more than one patient out of 100. Given the fact that the question is really asking for a subjective opinion from the reader, that SonoRx is not being tested against a placebo, but against nothing (i.e. against an empty stomach) and that even if the post dose scan did provide more information than the pre dose scan, that information might not necessarily be clinically useful, a rejection of the sponsor's null hypothesis would be an extremely weak demonstration of efficacy. If 50%, the number of "yes" answers that would be obtained by pure chance, were used instead of 1%, the confidence intervals indicate that the null hypothesis could be rejected for 3 out of 4 blinded readers and for the investigators. The value 1% seems to have been used here because the same value was used in study 42,440-3A. The study had originally been powered assuming 75% "yes" answers.

Although not used in the sponsor's statistical analysis, comparative data between SonoRx and placebo is available in the summary tables for the blinded readers. This data for the sponsor's primary efficacy endpoint, the readers' answer to the question "Overall did the post dose images provide additional information over the pre dose images?" for SonoRx and placebo is given in table 12B

**TABLE 6.12B ADDITIONAL INFORMATION: POST DOSE IMAGE vs. PRE DOSE IMAGE  
SonoRx vs placebo, Blinded readers per protocol analysis**

	Blinded Reader #1				Blinded Reader #2				Blinded Reader #3				Blinded Reader #4			
	SonoRx		placebo		SonoRx		placebo		SonoRx		placebo		SonoRx		placebo	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
yes	55	69	19	86	33	42	11	50	61	75	12	57	52	65	17	81
no	25	31	3	14	45	58	11	50	20	25	9	41	29	35	4	19
total	80	100	22	100	78	100	22	100	81	100	21	100	81	100	21	100
Confidence interval-yes	58.6%-78.9%		72.0%-100.0%		31.3%-53.3%		29.1%-70.9%		65.9%-84.7%		36.0%-78.3%		53.8%-74.6%		64.2%-97.7%	

The SonoRx entries in table 12B are the same as the corresponding entries for the per protocol analysis in table 12A. The confidence intervals for SonoRx and placebo overlap for each of the 4 blinded readers. Since the study was not powered to show a statistically significant difference between SonoRx and placebo, it should not be surprising that a statistically significant difference is not seen for any of the blinded readers. However there does not even seem to be a trend in favor of SonoRx in this data.

Three out of four readers, readers 1, 2 and 4 answered "yes" for a higher percentage of placebo images than of SonoRx images.

**Reviewer's Comment**

In comparing the results in table 12A and 12B to the results in the corresponding tables for study 42,440-3A it appears that readers are finding additional information in the post dose scans in a higher percentage of cases in this study than in the previous study. This, however seems to be the case for both SonoRx and placebo, with 3 out of 4 readers finding a higher percentage with more information in the placebo group than in the SonoRx group. The difference is not statistically significant and may just represent the difference between imaging with a full stomach or an empty stomach. The differences in the results between this study and the identical study, 42,440-3A may be a result of the subjective nature of the question asked, and the consequent high variability in the answers of different readers.

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## Nature of Additional Information

Readers were asked to specify the nature of the additional information in those cases where the post dose scan did provide additional information. The possible choices were:

- Improved delineation of abdominal anatomy
- Improved confidence in exclusion of pathology
- Improved delineation of pathology
- Improved evaluation of extent of disease pathology seen

The most common choice was Improved delineation of abdominal anatomy. The results were given in table 13

TABLE 6.13 TYPE OF ADDITIONAL INFORMATION GIVEN BY POST DOSE SCAN

TABLE 6.13 NATURE OF ADDITIONAL INFORMATION					
	Investigators N=66*	Blinded Readers			
		Reader#1 N=55*	Reader#2 N=33*	Reader#3 N=61*	Reader#4 N=52*
Improved delineation of abdominal anatomy	57	55	30	56	52
Improved confidence in exclusion of pathology	39	37	10	45	24
Improved delineation of pathology	32	9	5	17	7
Improved evaluation of extent of disease pathology seen	17	7	2	12	2
Other	4	2	0	1	0

\*N=number of patients with additional information according to each individual reader

Readers were asked to estimate their confidence in the diagnosis (from 0% to 100%) for pre dose and post dose scans. There was a statistically significant increase in confidence from pre dose to post dose for reader #1, with a change of  $+13\pm 18\%$ ,  $p=0.0001$ ,  $N=80$  and a statistically significant increase in confidence from pre dose to post dose for reader #3, with a change of  $-8\pm 15\%$ ,  $p=0.0001$ ,  $N=81$ . The increase in confidence for readers #1 and #4 was not statistically significant (per protocol analysis)

## Visualization of Specific Structures

The visualization of the stomach, stomach wall, pancreatic head, pancreatic body, pancreatic tail, pancreatic duct, pylorus and duodenum were evaluated for each scan 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 sum of the number of ratings of "excellent" and of "good" are given for each structure and for each reader in table 14

Structure	Investigators		Blinded Readers							
	N=87		Reader #1 N=80		Reader #2 N=78		Reader #3 N=81		Reader #4 N=81	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Stomach	3	42	11	44	0	0	15	48	4	28
Gastric Wall	4	30	11	44	1	1	14	55	7	38
Pylorus	1	24	3	34	0	0	20	55	6	31
Duodenum	2	29	2	23	0	0	11	32	1	15
Pancreatic Head	32	65	26	48	16	20	34	61	51	62
Pancreatic Body	44	68	42	67	15	22	47	67	40	50
Pancreatic Tail	7	34	2	21	3	5	21	38	14	27
Pancreatic Duct	12	25	24	44	4	7	41	59	16	19

A statistical analysis was performed by the sponsor using the excellent, good, poor, none, rating system, comparing the pre dose and post dose scans using the Wilcoxin signed rank test. The p values for each structure and for each reader are given in table 15. NS means not statistically significant

Structure	Investigators*		Blinded Readers			
	N=79		Reader #1 N=80	Reader #2 N=78	Reader #3 N=81	Reader #4 N=81
Stomach	p=0.0001		p=0.0001	p=0.0001	p=0.0001	p=0.0001
Gastric Wall	p=0.0001		p=0.0001	NS	p=0.0001	p=0.0001
Pylorus	p=0.0001		p=0.0001	p=0.0001	p=0.0001	p=0.0001
Duodenum	p=0.0001		p=0.0001	p=0.0001	p=0.0001	p=0.0001
Pancreatic Head	p=0.0001		p=0.0001	p=0.0001	p=0.0001	p=0.0001
Pancreatic Body	p=0.0001		p=0.0001	p=0.0001	p=0.0001	p=0.0001
Pancreatic Tail	p=0.0001		p=0.0001	p=0.0035	p=0.0001	p=0.0001
Pancreatic Duct	p=0.0001		p=0.0001	NS	p=0.0001	p=0.0313

\*the p values for the investigators were obtained by comparing the numbers in table 14, not using the Wilcoxin test on the ranks

#### Reviewer's Comment

The results in tables 13, 14 and 15 regarding delineation of abdominal anatomy are impressive. The assignment of a rating of excellent, good, poor or none to the visualization of a structure, without further guidance for assigning the rating can be considered subjective. However the responses of the readers are remarkably consistent. Using reader consistency as an operational definition of objectivity, the data indicates that this question is not as subjective as it would first appear. Thus in table 13 all readers found that better delineation of anatomy was the most common source of additional information. In tables 14 and 15, all 4 blinded readers and the investigators were asked to rate the visualization of 8 different anatomical structures, resulting in 40 comparisons of pre dose to post dose images. In table 14 for 38 of those 40 comparisons, readers found the visualization excellent or good in a larger number of post dose images than pre dose images. In the remaining two cases, the numbers were equal. In table 15 it is shown that in 38 out of 40 cases the difference in the number of excellent or good ratings between post and pre dose images is statistically significant.

## 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 reader and scan is given in table 16.

Gas Shadowing	Investigators		Blinded Readers							
	N=88		Reader #1 N=73		Reader #2 N=73		Reader #3 N=64		Reader #4 N=64	
	Pre Dose	Post Dose	Pre Dose	Post Dose	Pre Dose	Post Dose	Pre Dose	Post Dose	Pre Dose	Post Dose
Completely Obscured	6	0	0	0	9	4	9	2	0	0
Markedly Obscured	25	5	25	6	18	20	22	7	7	2
Moderately Obscured	41	22	32	23	32	32	26	20	30	13
Mildly Obscured	16	49	22	45	17	19	16	26	39	49
Not Obscured	0	12	1	6	2	3	8	26	5	17

Other than the wording of the question, the readers were given no guidance as to how to rate the scans. The question must be regarded as highly subjective. In the sponsor's opinion, the mechanism of action of SonoRx is the displacement or dispersion of gas in the upper digestive tract, so that gas shadowing is reduced and visualization of abdominal anatomy is improved. Thus any improvement in image quality produced by SonoRx should be a result of decreased gas shadowing. The differences in reader response for pre dose and post dose scans was statistically significant for the investigators and for all four blinded readers, using the Wilcoxin signed rank test.

## Diagnoses (Sensitivity and Specificity)

Readers were asked to make diagnoses based on the pre dose scans and on the post dose scans. Blinded readers were not given the clinical information or information from any of the other diagnostic studies, but such information was probably available to the investigators at the institutions where the patients were recruited. These diagnoses were compared to the diagnosis from the "comparable modality" and the diagnoses from the scans were rated as "matched" to the comparable modality diagnosis, or as not matched. Where a patient had multiple diagnostic procedures other than ultrasound, the comparable diagnosis was the diagnosis made using the totality of these other procedures. On the basis of these comparisons, the sponsor has prepared tables of what are called the "sensitivity" and "specificity" for the pre dose scans and the post dose scans. The sponsor's results are shown in table 17

## Reviewer's Comment

Review of the patient data listings have indicated that the "comparable modality" has ranged from a hepato-biliary nuclear medicine scan only, to a CT, MRI and endoscopy with biopsy. The other modality procedures may have been done before the ultrasound imaging, after the ultrasound imaging, or some procedures before and others after. In the cases where the workup was virtually complete before the ultrasound images were done, the final diagnosis may have already been made and have been known to the investigator. Therefore there is no point in comparing the investigator's diagnosis to the comparable modality diagnosis. In many cases the diagnoses from the comparable modality and from the ultrasound images involved multiple pathological findings, some of which might be the same and some different. It is not clear what criteria were used to decide if diagnoses matched or not in these cases, or in cases where the diagnoses may be very similar, but not identical.

TABLE 6.17 "SENSITIVITY" AND "SPECIFICITY"

BLINDED READERS (PER PROTOCOL)				
	Reader #1	Reader #2	Reader #3	Reader #4
Pre SonoRx				
Sensitivity	34.3%	33.8%	38.0%	29.6%
Specificity	70.0%	70.0%	50.0%	60.0%
Post SonoRx				
Sensitivity	47.1%	46.2%	42.3%	42.3%
Specificity	60.0%	70.0%	50.0%	60.0%
BLINDED READERS (INTENT TO TREAT)*				
Pre SonoRx				
Sensitivity	35.6%	33.8%	*	*
Specificity	63.6%	72.7%	*	*
Post SonoRx				
Sensitivity	47.9%	42.5%	*	*
Specificity	54.5%	72.7%	*	*

- Because all scans were not sent to readers 3 and 4, intent to treat analysis is available for readers 1 and 2 only

For the per protocol analysis, sensitivity is greater in the post dose scans for all four readers. The specificity is greater for the pre dose scans for reader 4, and equal for readers 2, 3 and 4. For the intent to treat analysis sensitivity is greater in the post dose scans for both readers 1 and 2. The specificity is greater for the pre dose scan for reader 1 and equal for reader 2. For the sensitivity and specificity the way that the sponsor has defined it, there is no clear advantage for the post dose scans in specificity although there is an indication of an advantage in sensitivity. However these results are not statistically significant (see statistical review).

TABLE 6.18 NUMBER OF READERS FINDING HIGHER VALUE

	Per protocol		intent to treat*	
	sensitivity	specificity	sensitivity	specificity
Pre dose	0	1	0	1
post dose	4	0	2	0
both equal	0	3	0	1

\* intent to treat analysis not performed for readers 3 and 4

Table 17 is in turn obtained from tables of comparable diagnoses for each of the four blinded readers Schematically the tables will have the form of table 19, for the pre dose scan only

TABLE 6.19 COMPARISON OF DIAGNOSES (SCHEMATIC)

Pre Dose Diagnosis	Comparative Modality Diagnosis		
	Pathology Found	Pathology Not Found	Total
Pre Dose Scan			
Same Pathology Found	True Positives (TP)	False Positives (FP)	TP+FP
Same Pathology Not Found	False Negatives (FN)	True Negatives (TN)	TN+FN
Total	TP+FN	FP+TN	TP+FN+ FP+TN

**Reviewer's comment**

In the case where no pathology is found by the comparable modality, it is not clear what "same pathology found" and "same pathology not found" mean. However from the numbers in the following tables for the calculation of sensitivity and specificity, the true and false positives are as given in the table above. Thus for no pathology found by the comparable modality, 'same pathology found' would mean "pathology found" and "same pathology not found" would mean "pathology not found"

The sponsor then uses the usual definitions of sensitivity and specificity:

$$\text{Sensitivity} = \text{TP}/(\text{TP}+\text{FN}), \quad \text{Specificity} = \text{TN}/(\text{TN}+\text{FP})$$

**Reviewer's Comment**

It should be noted that the sponsor's definition of "sensitivity" does not really correspond to the usual definition of this term. This term, as usually defined, applies only to a situation where a test has either a positive or a negative answer (the patient either is HIV positive or the patient is not HIV positive). This is not the case where a test is used to make an open ended diagnosis (the ultrasound scan is supposed to determine the type of pathology, not merely confirm or rule out a specific pathology) In the sponsor's definition, a "true positive" is not the case where the ultrasound and the comparable modality both find pathology, it is the case only when they both find the same pathology. Thus if both the other modality and the ultrasound scans find pathology but the pathologies are not the same (For example, in the investigator reading of patient 207[vol 27 pg216] the comparable modality reading was ulcerated leiomyoma of the stomach", while the ultrasound reading was "left renal cyst" Since the pathologies are not the same this would be called a "false negative") It is for this reason that some of the sensitivities will be <50%, the number that would result from pure chance.

The determination of whether the pre dose diagnosis or the post dose diagnosis matched the comparable diagnosis was made by a physician employed by the sponsor on the basis of information contained in the case report forms. Since multiple pathological findings may be found for one patient and since diagnoses may be similar but not identical (e.g. mass in the gastric antrum vs. tumor of the gastric antrum) considerable clinical judgment is involved in making this determination. This determination should have been made by an independent blinded third party, rather than by the sponsor.

Tables corresponding to table 17 for both pre dose and post dose scans are given below for the 4 blinded readers, to show the numbers from which the "sensitivities" and "specificities" were calculated.

TABLE 6.20 COMPARISON OF DIAGNOSES READER # 1 N=84 INTENT TO TREAT			
Ultrasound Diagnosis	Comparative Modality Diagnosis		
Pre Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	26	4	30
Same Pathology Not Found	47	7	54
Total	73	11	84
Sensitivity 35.6%		Specificity=63.6%	
Post Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	35	5	40
Same Pathology Not Found	38	6	44
Total	73	11	84
Sensitivity 47.9%		Specificity=54.5%	

TABLE 6.21 COMPARISON OF DIAGNOSES READER # 1 N=73 PER PROTOCOL			
Ultrasound Diagnosis	Comparative Modality Diagnosis		
Pre Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	24	3	27
Same Pathology Not Found	46	7	53
Total	70	10	80
Sensitivity 34.3%		Specificity=70.0%	
Post Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	33	4	37
Same Pathology Not Found	37	6	43
Total	70	10	80
Sensitivity 47.1%		Specificity=60.0%	

TABLE 6.22 COMPARISON OF DIAGNOSES READER # 2 N=84 INTENT TO TREAT			
Ultrasound Diagnosis	Comparative Modality Diagnosis		
Pre Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	24	3	27
Same Pathology Not Found	47	8	55
Total	73	11	84
Sensitivity 38.2%		Specificity=55.6%	
Post Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	31	3	34
Same Pathology Not Found	42	8	50
Total	73	11	84
Sensitivity 33.8%		Specificity=72.7%	

TABLE 6.23 COMPARISON OF DIAGNOSES READER # 2 N=78 PER PROTOCOL			
Ultrasound Diagnosis	Comparative Modality Diagnosis		
Pre Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	23	3	26
Same Pathology Not Found	45	7	52
Total	68	10	78
Sensitivity 33.8%		Specificity=70.0%	
Post Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	29	3	32
Same Pathology Not Found	39	7	46
Total	68	10	78
Sensitivity 42.6%		Specificity=70.0%	

TABLE 6.24 COMPARISON OF DIAGNOSES READER # 3 N= 81 PER PROTOCOL			
Ultrasound Diagnosis	Comparative Modality Diagnosis		
Pre Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	27	5	32
Same Pathology Not Found	44	5	49
Total	71	10	81
Sensitivity =38.0%		Specificity =50.0%	
Post Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	30	5	35
Same Pathology Not Found	41	5	46
Total	71	10	81
Sensitivity 42.3 %		Specificity50.0 %	

TABLE 6.25 COMPARISON OF DIAGNOSES READER # 4 N= 81 PER PROTOCOL			
Ultrasound Diagnosis	Comparative Modality Diagnosis		
Pre Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	21	4	25
Same Pathology Not Found	50	6	56
Total	71	10	81
Sensitivity =29.6%		Specificity =60.0%	
Post Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	30	4	34
Same Pathology Not Found	41	6	47
Total	71	10	81
Sensitivity 42.3%		Specificity 60.0%	

**Reviewer's comment**

A screening test that is used to find suspicious cases that require further workup should have a high sensitivity, but a relatively low specificity would be acceptable, since the true negatives would be separated from the false positives by that further workup. Because of its relatively low cost and its non-invasiveness, it is likely that Ultrasound will be used as such a screening modality. All of the sensitivities for all readers for both pre dose and post dose scans for both the per protocol and intent to treat analysis, are less than 50%. Conversely, all of the specificities, for all of the readers for both pre dose and post dose scans, for both the per protocol and intent to treat analysis, are greater than 50%. For all readers for both the intent to treat and the per protocol analysis, the sensitivity is higher for the post dose scans than for the pre dose scans. The specificity, on the other hand, is higher for the pre dose scans for reader #1 for both the per protocol and intent analysis, and is equal for both scans for all other readers for both the per protocol and intent to treat analysis.

There are several reasons for these low values for sensitivity and specificity. Firstly, as previously noted, the sponsor's definition of sensitivity differs from the usual definition, so a comparison with the results of pure chance is not really warranted. Secondly there was no single "gold standard" for determining the "true" pathology, with which the ultrasound scans can be compared. The "gold standard" that was actually used was whatever workup, other than ultrasound, that each particular patient happened to have. This workup ranged from CAT scan, MRI and endoscopy with biopsy, to nothing more than hepato-biliary nuclear medicine scan. It is difficult to compare diagnoses because different modalities would have different capabilities of detecting specific pathologies (for example, a renal cyst might be found on an ultrasound scan or a CAT scan, but it could not be detected on an upper GI series or a plain abdominal x-ray). The low values for the specificities could be the result of the relatively small number of true negatives, and of a tendency to over-read the scans if the reviewers knew that most of these patients were "highly suspected of having abdominal pathology"

**6.65 Sponsor's Conclusion:**

The results of this clinical trial clearly show that SonoRx is a safe oral contrast agent that is well tolerated by a diverse group of patients highly suspected of having abdominal pathology. SonoRx is efficacious in improving the delineation of abdominal anatomy, and in providing additional information to assist in the diagnosis of abdominal pathology.

**6.7 Reviewer's Analysis****6.71 Safety**

122 patients (94 SonoRx, 28 placebo) were evaluable for safety analysis

**Adverse events**

There were 32 adverse events in 21 patients out of 122 patients (17%), 28 adverse events in 17 patients (18%) in the SonoRx group and 4 events in 4 patients in the placebo group (14%) (table 6). 21 events in 14 patients (11%), in the reviewer's opinion were definitely possibly, or of unknown relationship to SonoRx or placebo (The reviewer considered all gastrointestinal events to be possibly related to the ingested agent even if the sponsor did not). In the sponsor's opinion 9 adverse events in 7 patients were definitely possibly or of unknown relationship to the agent. There were three serious adverse events in two patients. Patient 316 in the SonoRx group experienced nausea vomiting and chills followed by chest pain relieved by nitroglycerin. This patient had a history of myocardial infarction. The reviewer considers these events to be possibly related to each other and to SonoRx. Patient 1305 in the SonoRx group developed pneumothorax with accompanying chest pain during the placement of a subclavian line. These events are not related to SonoRx. The category of severe non serious adverse events was not used in the analysis of results of this study. All non serious adverse events were classified as moderate or mild. There

were 3 events in two patients classified as moderate by the investigators. One patient in the SonoRx group developed nausea and abdominal pain, both of which were classified as moderate and another patient in the SonoRx group developed diarrhea that was classified as moderate. All three moderate adverse events were possibly related to SonoRx. There were no moderate adverse events in the placebo group. The most common adverse events were diarrhea (4 patients, 4 SonoRx and 0 placebo) and nausea (5 patients, 4 SonoRx, and 1 placebo)

This pattern of adverse events does not raise any clinically significant safety concerns. Of the 3 serious adverse events two were definitely not related to SonoRx. The third event was chest pain of cardiac origin in a patient with a history of MI which was relieved by nitroglycerin. Since this same patient also experienced nausea vomiting and chills this event is considered by the reviewer to be possibly related to SonoRx. The cardiac load or electrolyte imbalance caused by nausea could have caused cardiac ischemia in an already compromised cardiovascular system. The majority of the other adverse events involved the gastrointestinal system, the most common being diarrhea or nausea, usually mild in severity. Since there was no statistically significant difference between SonoRx and placebo in the number of adverse events, these events may be related to the rapid ingestion of 400 ml of fluid rather than to SonoRx itself. Even mild vomiting or diarrhea might be of concern in patients who are severely debilitated, but this problem is best dealt with the labeling.

#### 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 8. There were 53 such changes in the 94 patients in the SonoRx group for an average of 0.56 changes per patient. There were 11 such changes among the 24 placebo patients for an average of 0.46 changes per patient. More increases in heart rate and blood pressure than decreases were seen in the SonoRx patients. None of these changes were considered to be clinically significant. EKG monitoring was not performed during infusion so EKG tracings can not be correlated with the observed changes in heart rate and blood pressure. These changes may also be correlated with the ingestion of 400 mL fluid rather than with SonoRx itself.

#### Physical Examination

There were 10 changes in 6 patients noted on physical examination. Six of these changes have already been discussed as adverse events. Three others, diminished breath sounds, central line and mid axillary puncture wound occurred in patient 1305 who developed pneumothorax and chest pain during placement of that line. The other change was scattered ronchi.

#### Laboratory Monitoring

Four SonoRx patients, and 2 placebo patients had changes in CBC outside of the sponsor's guidelines (RBC  $\pm 25\%$ , WBC  $\pm 50\%$ ). There were 3 increases in WBC and one increase in hemoglobin in the SonoRx group and 2 increases in WBC in the placebo group. None of these changes were considered to be clinically significant by the investigators. Changes in routine serum chemistries outside of the sponsor's guidelines included changes in potassium, GGT, and glucose. None of these changes were considered to be clinically significant or to be related to SonoRx. There were no clinically significant changes in urinalysis.

#### EKG

EKGs were obtained on 21 patients (17 SonoRx, 4 placebo) at one center. 18 patients had normal pre dose and post dose EKGs. 3 patients had abnormal pre dose and post dose EKGs. No patient with a normal pre dose EKG developed an abnormal post dose EKG.

## 6.72 Efficacy

Efficacy was evaluated for the SonoRx group only. The results for the patients who ingested placebo were not reported in the sponsor's efficacy analysis. 94 SonoRx patients were available for the intent to treat analysis by the investigators, 9 patients whose scans were not of acceptable quality were not sent to the blinded readers, leaving 85 remaining SonoRx patients for the intent to treat analysis by blinded readers 1 and 2. When patients who had ingested less than 350 ml SonoRx and those with images of unacceptable quality as determined by the readers were excluded, there were 80 patients remaining for the per protocol analysis by blinded readers 1 and 78 patients for analysis by reader 2. These two readers were given the static images only, not both the static and video images as stated in the protocol. Blinded readers 3 and 4 read both the static and video images. An intent to treat analysis was not possible for readers 3 and 4, so a per protocol analysis only was reported for 81 patients for blinded readers 3 and 4 (see table 11). There were thus 3 different groups of readers, the investigators, blinded readers 1 and 2 and blinded readers 3 and 4. Each group read a different number of scans under different circumstances, making a comparison of the results from the different groups difficult, and an analysis and interpretation of the results from a combination of groups problematical. The readings of the investigators should be given little weight since they were probably aware of the patients medical history and the results of other diagnostic tests at the time of their readings. Neither the readings of readers 1 and 2 nor those of readers 3 and 4 were strictly in accordance with the protocol. A per protocol analysis only was available from readers 3 and 4 which might be expected to give more favorable results than an intent to treat analysis. Even though, when making a diagnosis, blinded readers read the pre dose images and the post dose images separately and were not told which was which, they could tell which was which by whether the stomach was empty or full, since patients were required to fast before ingestion.

The sponsor's primary endpoint was the readers' answer to the question "does the post dose image provide additional information over the pre dose image". In order to answer this question, the readers would have had to evaluate both images 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. Readers were given little or no guidance on what criteria and what characteristics of the image to use in making their judgment. If a correct 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 likely to be used 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. False negatives would be of particular concern since these might involve patients with serious illnesses who might have no further workup because of a negative ultrasound scan. This problem might be exacerbated, if radiologists felt that they might be more confident in a negative image because a contrast agents used. In other words, sensitivity may be more important in evaluating the clinical value of the ultrasound images than specificity. The best way to determine whether radiologists could correctly identify true negatives would be to have a study where scans from normal healthy volunteers were mixed in with scans from patients with known abdominal pathology, on the basis of CT, MRI, or other imaging modality (one can not expect ultrasound to compete with endoscopy in identifying small lesions or in making a histological diagnosis) For consistency the same gold standard modality should be used for all subjects. Obviously this study was not designed in this way and therefore may not give a good estimate of either the sensitivity or specificity of the pre dose scan or of the post dose scan.

The "gold standard" was not the same for all patients in this study. The "gold standard" that was actually used was whatever workup, other than the ultrasound studies, was actually done. This ranged from a CAT scan, MRI, and endoscopy with biopsy, for one patient, to a nuclear medicine hepato-biliary scan for another. One could probably have more confidence in the fact

that the correct diagnosis had been made by the "gold standard" when that gold standard involved an extensive workup.

The readers were asked whether in their opinion the additional information would change the diagnosis or change the management. This question again calls for a subjective judgment. A more objective way to approach the same issue would be to determine the number of cases for which the post dose diagnosis differed substantially from the pre dose diagnosis and agreed with the final diagnosis made by a "gold standard" diagnostic modality. This question is addressed in the sponsor's analysis of "sensitivity and specificity"

#### 6.7.2.1 Sponsor's Primary Endpoint

The sponsor's primary endpoint is the reader's answer to the question "Do the post dose images provide additional information over the pre dose image" (table 12 ) The number of positive answers to this question were highly reader dependent, ranging from 75% (Reader #3) to 42 % (reader #2) in the per protocol analysis and from 72%(Reader #2) to 43 % (reader #2) in the intent to treat analysis. The number of positive responses if the readers would have been asked to flip a coin instead of looking at the images at all, would be 50%. From the confidence intervals in table 12 it is clear that 50% could be excluded for readers 1,3and 4 and the investigators, for both the intent to treat analysis and the per protocol analysis. 50% would fall within the confidence interval only for reader 2 . The sponsor's statistical analysis has demonstrated with a  $p < 0.0001$  that the number of yes answers is greater than 1% for all readers. However readers finding additional information in 1% or more of the post dose images is an extremely weak endpoint of questionable clinical significance. It is conceivable that readers would find more information in 1% of second images, if the second images were taken without contrast several minutes after the first. It is possible that the sponsor has chose4n the value of 1% simply because 1% was used in the analysis of study 42,440-3A

It should be noted that the results for the sponsor's primary efficacy variable are much more favorable for SonoRx than the comparable results in study 42,440-3A. This may simply be a result of the subjective nature of the question asked and the consequent high variability in the reader's responses.

The results for patients who received placebo were not included in the sponsor's efficacy analysis, but the data is available in the supplementary tables The results for SonoRx and placebo are shown in table 12B. 3 out of four readers found more information in a higher percentage of post-dose placebo images than post dose SonoRx images.

#### 6.7.2.2 Nature of Additional Information

For those patients where readers had said that the post dose scans provided additional information, readers were asked to specify the nature of the additional information. The most common response for all readers was "improved delineation of abdominal anatomy" (table 12B).

#### 6.7.2.3 Visualization of Individual Anatomical Structures

Readers were asked to rate the visualization of individual anatomical structures as "excellent", "good", "poor" or "none". The sum of the number of responses of "excellent" and "good" are tabulated in table 14. The results appear to consistently favor the post dose images. Except for reader #2, all readers consistently favored the post dose images for all structures listed in tables 14 and 15 (stomach, stomach wall, pylorus, duodenum, and pancreatic head body tail and duct) Reader #2 found no good or excellent images of the stomach pylorus and duodenum, and one stomach wall. For all readers the , using the Wilcoxin rank sign test, the differences were statistically significant for the stomach, pylorus, duodenum and the head, body, tail and duct of the pancreas (table 15). For reader # 2 the differences were not statistically significant for the stomach wall and the pancreatic duct.

While the results appear to consistently favor the post dose images, and the differences between pre dose and post dose images, in most cases, are statistically significant, interpretation of this result are confounded by the fact that the question asked requires a subjective judgment on the part of the readers, and little or no guidance was given to the readers as to what characteristics of the image to use in determining whether visualization of a structure was excellent, good poor or none. In addition, readers could not be blinded as to which images were pre dose and which were post dose because on the pre dose images the stomach empty and on the post dose images the stomach was full. There is no way to tell whether the improvement in visualization was due to the SonoRx itself or just due to the fact that the stomach was full instead of empty on the post dose scans. If SonoRx had been tested against placebo, the stomach would have been distended in both cases..

#### 6.7.2.4 Gas Shadowing

In evaluating images for gas shadowing, readers rated the pre dose and post dose scans as not obscured, mildly obscured, moderately obscured, markedly obscured or completely obscured. The results are given for all readers in table 16. There is a clear trend in favor of the post dose scans. The differences in reader response for pre dose and post dose scans was statistically significant for the investigators and all 4 blinded readers, using the Wilcoxin signed rank test.

Once again the results are difficult to interpret because of the subjective nature of the question, the lack of guidance given to the readers and the difficulty in blinding the readers to which scans were pre dose and which were post dose.

#### 6.7.2.5 Diagnoses (Sensitivity and Specificity)

The diagnoses for the pre dose scan the post dose scan and for the comparable modality, as stated on the case report forms were compared by a physician employee of the sponsor to determine whether the diagnoses "matched". There were no specific written instructions as to how to determine a match or a non match when there were multiple positive findings, all of which were not exactly identical or where diagnoses were similar but not identical (e.g. gastric mass vs. gastric tumor). The results of this analysis are given in tables 20 through 25. Sensitivity, as defined by the sponsor (see table 19 and accompanying discussion) is higher for the post dose scans for all readers for both the per protocol and intent to treat analyses. These results are not statistically significant. On the other hand, sensitivity for the pre dose scans is either equal to or higher than the sensitivity for the post dose scans for all readers in both analyses. These results are more favorable to SonoRx than the corresponding results of study 42,440-3A The data and the analysis is flawed by the small number of true negatives ( 11 out of 84, 13% for the intent to treat analysis), by the fact that the same "gold standard" modality was not used to determine the "true" diagnosis for all patients, and by the fact that the comparisons of the diagnoses were made by the sponsor instead of by an independent third party.

#### 6.7.3 Conclusions

SonoRx is an orally administered contrast agent for abdominal ultrasound imaging. It performs its function as a contrast agent while remaining in the lumen of the digestive tract. 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 122 patients, there were 3 serious adverse events in 2 patients in the SonoRx group and 29 non serious adverse events in 21 patients. Two serious adverse events were

pneumothorax and chest pain that developed in a patient during placement of a subclavian line. This was not related to SonoRx. A second patient developed nausea vomiting and chills, followed by chest pain. This patient had a history of MI and his chest pain resolved with nitroglycerin. Since the nausea and vomiting may have been caused by SonoRx, and the cardiac chest pain may have resulted from fluid and electrolyte imbalances caused by the nausea and vomiting, this event is considered by the reviewer to be possibly related to SonoRx. There were 28 adverse events in 17 patients (18%) in the SonoRx group and 4 events in 4 patients (14%) in the placebo group. The difference is not statistically significant ( $p=0.64$ ). The most common adverse events were GI complaints, diarrhea, nausea, and abdominal pain. These symptoms were self limiting and resolved spontaneously in most cases without permanent sequelae (two SonoRx patients had persistent abdominal pain and nausea at the time of final evaluation). The data on physical examination, vital signs, EKGs, and laboratory monitoring suggest no specific safety concerns. The safety of SonoRx is supported by the results of this study.

There are a large number of efficacy endpoints in this study not all of which are directly related to the proposed indication: "SonoRx is an orally administered 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". The sponsor's primary endpoint is the readers' answer to the question: "Overall did the post dose images provide additional information over the pre dose images?". This question calls for a subjective opinion on the part of the reader. The readers were given little or no guidance on how to answer this question. Although they were later asked to specify the nature of the information, and whether in their opinion, the information could change the diagnosis and/or the management. The readers answers to this question are given in table 12 A, with the variable being the number of "yes" answers to this question. Since this is not a placebo controlled trial for efficacy, it is not clear what this number of "yes" answers should be compared to. The sponsor claims to show that this number greater than 1% with statistical significance for each for each and every reader with a p value,  $p<0.0001$ . However this value of 1% seems arbitrary and the choice seems to have been made after the data was analyzed so that the sponsor would be able to say that something was shown with statistical significance in both pivotal trials. 1% is a ridiculously low number. A test that did no better than that would provide additional information in 1 out of 100 cases and would not be considered clinically useful in comparison to other imaging modalities. If the more reasonable number of 50% had been used, a glance at the confidence intervals in table 12A indicates that 50% is excluded from the confidence interval for the investigators and for 3 out of the 4 blinded readers.

These results are considerably more favorable to SonoRx than those of study 42,440-3A. However, those "yes" answers that were given, may simply be a result of the fact that in the post dose scans, the stomach was full rather than empty. If this were the case, any liquid or bulk agent could be expected to do as well as SonoRx. (this last remark is applicable to all of the study endpoints). This hypothesis is supported by the results shown in table 12B. Three out of four blinded readers found additional information in a higher percentage of placebo images than SonoRx images. Because this study was not powered to test the efficacy of SonoRx compared to placebo the differences are not statistically significant. However it is interesting to note that the trend favors placebo rather than SonoRx.

A more clinically meaningful endpoint would be a comparison of the pre dose scans and post dose scans for the readers' ability to make the "correct" diagnosis as determined by some "gold standard" diagnostic modality. The sponsor has attempted to address this question with the analysis of "sensitivity" and "specificity" (tables 17-25). There are several problems with the sponsor's analysis. The sponsor's definition of "sensitivity" and "specificity" do not correspond to the usual definition because a dichotomous variable is not used. There was no single "gold standard modality". The gold standard actually used was whatever workup, other than ultrasound, imaging that the patient actually had. Needless to say there were large variations in the completeness of that workup from patient to patient. There were too few "true negatives" to assess the ability of readers to distinguish between "normal" scans and scans showing pathology. The determination of whether two diagnoses "matched" was made by the sponsor, rather than by an independent

radiologist. Taking all of these problems into account the "sensitivity" and "specificity" as defined by the sponsor ,do provide a crude measure of the ability to make a "correct" diagnosis.

The results of this analysis are given in tables 17 and 18. There appears to be consistency among the readers, as all readers find a higher sensitivity for the post dose scans, and the majority of readers find equal specificity for both scans. Table 18 shows the number of readers finding higher sensitivities and specificities in the pre dose and post dose scans. It appears that there is an advantage for the post dose scans but the differences are probably not statistically significant. The results are more favorable to SonoRx than the results of study 42,440-3A

Readers were asked to rate the visualization of specific anatomical structures (stomach, stomach wall, pylorus, duodenum, head, body tail and duct of the pancreas) as excellent, good, poor or none. No guidance as to what characteristics of the image should be used in making this rating, making the question quite subjective. The sum of the number of "excellent" and "good" answers are given in table 14. The readers are almost unanimous in finding better visualization off all mentioned structures in the post dose images than in the pre dose images. Using the Wilcoxin signed rank test these differences, in 38 out of 40 cases are statistically significant. It appears that there is better visualization of these structures in the post dose images, in the opinion of the blinded readers, however because of the subjective nature of the question it is hard to draw any firm conclusions.

In conclusion there are no clinically significant concerns raised by the data in this study. However, the sponsor has not clearly demonstrated efficacy in this study using the primary outcome variable or any other endpoint considered. There is a consistent , statistically significant difference between SonoRx and placebo in the answers to the questions concerning individual anatomical structures. However the subjectivity of the question asked, and the fact that placebo patients were not included in the efficacy analysis makes it difficult to draw any firm conclusion.

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## Integrated Efficacy Review

### 7.1 Overview

#### 7.1.1 Desired indication:

The desired indication is "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" This indication has two distinct and independent components. The first component is the delineation of anatomy, and the second is the detection or exclusion of pathology. The first part of the indication relates directly to the quality of the images, and its evaluation should not depend too much on the sophistication of the reader. The second part of the indication calls for a clinical judgment on the part of the reader, and can be expected to be at least as dependent on the skill and training of the reader, as on the quality of the images. In order to properly assess the efficacy of the agent for the second part of the indication, a generally accepted "gold standard" diagnostic modality would be required, to which the ultrasound diagnoses could be compared. This efficacy analysis will therefore concentrate on what was demonstrated in the clinical trials and how this is related to each of the two components of the desired indication

#### 7.1.2 Clinical Trials

Efficacy of 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 7.1 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 " Placebo	5 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 Placebo 800 ml	24 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 Placebo 400 ml	12 3
42,440-6	1/95-1/95	Randomized, Single Center Single Dose Placebo controlled, Double Blind Study in Normal Volunteers	SonoRx 400 ml Placebo 400ml	7 3
Total Patients			SonoRx Placebo	48 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 Control Agent 400 mL	93 24
42 440-3B	7/94-11/94	Multicenter Randomized Double-Blind Parallel Study	SonoRx 400 mL Control Agent 400 mL	94 28
Total Patients in Pivotal trials			SonoRx 400 mL Control Agent 400 mL	187 52
PHASE 3 SUPPORTIVE STUDY				
42,440-7	10/94-2/95	Multicenter, Randomized, Placebo Controlled, Single-Blind, Crossover Study	SonoRx 400 mL Water 400 mL	51 53

## 7.2 Demonstration of efficacy in Pivotal Studies, Protocols 42,440-3A and 42,440-3B

### 7.2.1 primary endpoint

Protocols 42,440-3A and 42,440-3B are Phase 3 multi-center randomized phase 3 trials of identical protocol design.

The sponsor's pivotal studies were studies 42,440-3A and 42,440-3B which were of identical design. There were a total of 239 patients entered into these two studies, 187 who ingested SonoRx and 52 patients who ingested the placebo, (which was SonoRx without the active ingredients). 117 patients (93 SonoRx and 24 placebo) participated in study 24,440-3A, at 10 study centers, and 122 patients (94 SonoRx and 28 placebo) participated in study 42,440-3B at 8 study centers. The placebo patients were used in the sponsor's safety analysis only. The studies were not powered for the use of these patients in the efficacy analysis. Thus, for the purpose of efficacy analysis these studies were not placebo controlled.

Since the pivotal phase 3 trials were not placebo controlled for efficacy, scans obtained after SonoRx ingestion (post dose scans) were compared to scans obtained with an empty stomach, just before SonoRx was ingested, (pre dose scans). Patients had fasted for 4 hours before the scans were taken. Since scans with a full stomach were compared to scans with an empty stomach, it was not possible to blind the readers as to which were pre dose scans and which were post dose scans. Even if these studies demonstrated an efficacy advantage for SonoRx, it would not be clear whether this advantage was due to the specific properties of SonoRx, or whether any agent that would distend the stomach would display the same advantage.

There were problems with the blinded reads. The readings by the investigators can be discounted because of biases that might result from the facts that the investigators may have had diagnostic information available to them from the patient's medical record or the referral slips and that other biases may occur in readings at the centers where the study was performed. Readings by the two groups of blinded readers, readers #1 and #2 and readers #3 and 4, in both pivotal studies, were flawed. Video images were not sent to readers #1 and #2, along with the static images as required by the protocol. When the results of this first blinded reading were found to be unsatisfactory by the sponsor, the sponsor consulted with a group of experts in ultrasound imaging and were advised that the reading of both static *and* video images together is standard clinical practice. Both video and static images were then sent to a second set of blinded readers, readers #3 and #4. However in the interim, video images for 9/93 (10%) of patients who ingested SonoRx in study 42,440-3A had been lost or were unreadable. In addition, by error, only scans for the "per protocol" patients were sent to readers #3 and #4. The sponsor performed an intent to treat analysis for the primary efficacy variable, assigning "worst case" data to those patients whose scans were not sent to readers #3 and #4. In the intent to treat analysis for all blinded readers, scans that were found to be "technically unacceptable" by a "technical reviewer" were excluded. Thus none of the blinded reads were performed according to protocol, there was no reading that included static and video images on all intent to treat patients and in each trial, each group of readers read a different number of scans.

The sponsor's primary efficacy endpoint is the readers' answer to the question "Overall, did the post dose images provide additional information over the pre dose images?" The readers were to answer this question yes or no. To answer this question, readers reviewed both pre dose and post dose images for each patient side by side, after previously performing independent evaluations of the scans. Other than the question itself, readers were given no additional specific instructions, in the protocol, as to what criteria, or specific properties of the images should be used as the basis for their answer to this question. Readers 3 and 4 were given "training" but the nature of this training is not described in detail in the study report.

The subjective nature of this question is clear, and is reflected in the disparity in readers' responses. Among the blinded readers, in study 42,440-3A, the percentage of patients for whom the answer was "yes" ranged from 99% for reader #2 to 20% for reader #4 in the intent to treat analysis. In study 42,440-3B the percentage of "yes answers ranged from 72% for reader #3, to 43 % for reader #2.

The sponsor claims to have shown, with statistical significance with a p value of 0.0001, that the number of "yes" answers is greater than 1% for all blinded readers in both studies ( the sponsor's null hypothesis is that the percentage of "yes" answers is  $\leq 1\%$ ) This value of 1% is extremely low. In the initial study design, the sample size was calculated to give 95% confidence intervals within 10% of the percentage of interest which was assumed to be 75%, which would seem to imply that the sponsor's original objective was to show, with 95% confidence that the number of "yes" answers was greater than 67% If the readers had not looked at the scans at all, but flipped a coin instead, the percentage of "yes" answer would have been 50%. If the readers knew absolutely nothing about how to read an ultrasound image, and had to guess , or if the quality of both the post dose scans and the pre dose scans were so poor as to make them unreadable, the readers would still have had to choose between "yes" and "no" and the percentage would have also been 50%. If they had been so inclined, the sponsor could have virtually guaranteed an answer substantially higher than 1% just by using a group of very inexperienced readers, or a group of very poor quality images.

The sponsor has not demonstrated substantial evidence of efficacy, for the desired indication, based on the primary efficacy endpoint in the 2 pivotal studies. The studies were poorly designed, and the readings were not carried out in accordance with the protocol . In both pivotal studies, readers 1 and 2 did not have access to the video images. Some of the video images were lost or unreadable, in study 42,440-3A., and thus could not be sent to readers 3 and 4. Only the "per protocol" scans were sent to blinded readers 3 and 4 in both studies. The primary efficacy question was too subjective and this subjectivity is confirmed by the widely divergent responses of the different blinded readers. The endpoint that the sponsor has demonstrated with statistical significance is not clinically meaningful. The sponsor's null hypothesis would be rejected if there was additional information in the post dose scans in more than 1 case out of a hundred, irrespective of what that information was or whether it would have been useful in making a diagnosis. This would be the case if for 99% of patients, the SonoRx scans would produce no additional information, over that which would be obtained by scanning the patient on an empty stomach. It could not be ascertained from the data from these studies whether even this 1% of cases with additional information resulted from the unique properties of SonoRx or whether any ingestible substance that would distend the stomach would give an equivalent result. A diagnostic test with only a 1% success rate in providing new diagnostic information would not be of much use in the clinic.

Although the placebo patients were not included in the sponsor's efficacy analysis, and the study was not powered for such an analysis, the placebo patients were scanned, the scans were read and the readings were included in the patient data tables. While statistically significant conclusions can not be made by comparing the SonoRx data to the placebo data, it is still interesting to compare these data using the sponsors primary efficacy variable. In Study 42,440-3A, one blinded reader answered "yes" in a higher percentage of SonoRx patients than placebo patients, while the other three readers answered "yes" in a higher percentage of placebo patients than SonoRx patients. In study 42,440-3B, also, one reader answered "yes" for a higher percentage of SonoRx patients than placebo patients, while the other three answered "yes" for a higher percentage of placebo patients than SonoRx patients. While these results are not statistically significant, they do not lend support to the proposition that SonoRx is more effective than SonoRx without its active ingredients.

## 7.2.2 Pivotal Trials Secondary Endpoints

Reviewers were asked to specify the additional information provided in those post dose scans that provide additional information. The choices were: Improved delineation of abdominal anatomy, Improved confidence

in exclusion of pathology, Improved delineation of pathology, or improved evaluation of extent of pathology seen. For all four blinded readers in both pivotal trials, the answer given most frequently was Improved delineation of abdominal anatomy.

Readers were asked to rate their confidence, from 0% to 100% in their diagnosis from the pre dose scan and from the post dose scan for each patient. Confidence in a diagnosis is also highly subjective, and may have more to do with a reader's confidence in his/her own clinical skills than with the images themselves. In study 42,440-3A, there was a statistically significant increase in confidence, from pre dose to post dose, for one blinded reader, a statistically significant decrease in confidence for a second blinded reader, and no statistically significant change for the other two blinded readers. In study 42,440-3B, there was a statistically significant increase in confidence for two out of four blinded readers, and no statistically significant change for the other two blinded readers.

Readers were asked to rate the image as a whole for the effect of gas shadowing as: 1) not obscured, 2) mildly obscured, 3) moderately obscured, 4) markedly obscured or 5) completely obscured. These ratings are important because the presumed mechanism of action of SonoRx is the adsorption and displacement of stomach and bowel gas, creating uniform echogenicity and eliminating gas shadowing. Since the post dose scans are obtained within 10 minutes of SonoRx ingestion, this effect should be seen primarily for gas in the stomach, rather than for gas in the small or large intestine. SonoRx would therefore be expected to improve only the visibility of the stomach and organs which would be obscured by shadowing by gas in the stomach, such as the pancreas. The readers are given no specific instructions as to how the properties of the image are to be used answer this question, or where to draw the line, for example, between mildly obscured and moderately obscured. In study 42,440-3A the reader's responses showed a consistent advantage for the post dose images. Using the Wilcoxin signed rank test, the differences between the pre dose images and the post dose images were statistically significant for 3 out of 4 blinded readers. In study 42,440-3B there was also a consistent advantage for the post dose scans over the pre dose scans, and the differences were statistically significant for all four blinded readers.

Readers were asked to make a diagnosis from the pre dose scans and from the post dose scans. Pre dose scans and post dose scans for all of the patients were mixed together in one group and identified by a number only, so that pre dose scans and post dose scans for each individual patient would be evaluated separately. These diagnoses were then compared to the "comparable modality" diagnosis. There was no single "gold standard" comparable modality, but rather, for each patient, the comparable modality was whatever workup, other than the ultrasound scans, that the patient happened to have. This workup ranged from CAT scan, endoscopy and biopsy, to a plain film of the abdomen only. For each patient, the diagnoses from the pre dose scan and from the post dose scan, were compared by the sponsor to the diagnosis from the comparable modality, as reported on the case report forms, to determine if they matched. The sponsor did not specify which particular employee of the sponsor made this determination, what the credentials of this person were, and even if only one person made this determination for all patients. The sponsor did not specify what criteria were used to determine whether the diagnoses "matched" when they were similar but not identical (e.g. mass in the head of the pancreas vs. cancer of the head of the pancreas), or if more than one positive finding was seen, and some but not all of these findings were the same.

The sponsor used the results of this comparison to determine what was called "sensitivity and specificity" The sponsor's definition of sensitivity and specificity do not correspond to the conventional definition of these terms because a true positive is said to occur when the ultrasound and the "comparable modality" indicate *the same* pathology. If they each find different pathologies it will be called a false negative. It is because of this definition that sensitivities and specificities of less than 50% were found. Because only patients with a high suspicion of abdominal pathology were entered in the study, there were relatively few "true negatives", patients for whom no pathology was found by comparable modality (e.g. 9/73=12% for the per protocol analysis by readers 1 and 2 in study 42,440-3A). The sensitivities found in these studies may not be a good estimate of the "true" values. Nevertheless, in the per protocol analysis for study 42,440-3A, the sensitivity was higher in the pre dose scans for 2 readers, higher in the post dose scan for 1 reader and equal for 1 reader. The specificity was higher in the pre dose scan for 2 readers, higher in the post dose scan for 1 reader and equal for 1 reader. In study 42,440-3B, the sensitivity was higher in the post dose scans for all 4 readers, while the specificity was higher for the pre dose scans for 1 reader and equal for 3 readers. These results are mixed and do not demonstrate a clear advantage for the post dose scans.

The readers were asked about the visualization of specific anatomical structures. Data is presented on the reader's rating of the visualization of the following anatomical structures:

Stomach  
Stomach wall  
Head of the pancreas  
Body of the pancreas  
Tail of the pancreas  
Pancreatic duct  
Pylorus  
Duodenum

as excellent, good, poor or none. The organs listed above are precisely those whose visualization might be expected to be most effected by shadowing by gas in the stomach. (In the protocol, readers were also asked to rate the visualization of the abdominal aorta, left kidney, left renal artery, splenic vein, superior mesenteric artery, liver, common bile duct and the para-aortic lymph nodes as well. The sponsor has apparently only presented data for those anatomical structures for which the results were favorable to SonoRx.) While the decision of where to place the line, for example, between "excellent" and "good", could be expected to vary from reader to reader, if a consistency were found in the rank order of the ratings, among all 4 blinded readers, it is likely that this rank order would reflect actual inherent properties of the images themselves. Such consistency could be considered to provide objective evidence of the objectivity of the question that is asked, whereas a lack of such consistency could be considered to be objective evidence of the contrary.

In study 42,440-3A, the total number of excellent or good ratings for the post dose images were greater than or equal to the corresponding number for the pre dose images for all blinded readers for all structures listed above. Using the Wilcoxin signed rank test, the differences between the post dose scans and the pre dose scans were statistically significant, for all four blinded readers, for the stomach, pylorus and duodenum, for three out of four blinded readers for the gastric wall, the head of the pancreas, and the tail of the pancreas, for two out of four blinded readers for the body of the pancreas and for one out of four blinded readers for the pancreatic duct. For study 42,440-3B, the number of images rated excellent or good for the post dose images was greater than or equal to the corresponding number for the pre dose images for all four blinded readers for all anatomical structures listed above. Using the Wilcoxin signed rank test, the differences between the post dose images and the pre dose images were statistically significant for all four blinded readers for the stomach, the pylorus, duodenum, pancreatic head, pancreatic body and pancreatic tail, and for three out of four blinded readers for the gastric wall and pancreatic duct. This data indicates that the blinded readers appear to be consistent in finding improved visualization of these structures in the post dose scans compared to the pre dose scans.

### 7.3 Supporting Phase 3 Trial, protocol 42,440-7

Protocol 42,440-7 is a phase 3 multi-center randomized single blind (investigator blinded) placebo controlled crossover trial. This trial differs in design from the two pivotal trials in certain key aspects:

- 1) This trial is placebo controlled for the assessment of efficacy. The placebo is tap water. Post dose SonoRx scans are compared to post dose water scans. Pre dose scans are used for diagnostic purposes only and are not used in the evaluation of efficacy in this study.
- 2) This is a crossover study. The same patients received both SonoRx and water in a randomized order.
- 3) The specific anatomical structures evaluated are limited to the stomach, pylorus, stomach wall, duodenum and pancreas (head, body and tail).
- 4) The question asked of the readers to assess the primary efficacy endpoint has 3 possible answers instead of two. The question is "Overall, which images provide more diagnostic information, SonoRx, Water or both equal?" This raises questions as to how the "both equal" category should be handled in the statistical analysis.

The design is otherwise similar to that of the two pivotal studies, and problems with the pivotal studies are similar to the problems with this study.

53 patients were entered into this study. Two patients who were randomized to water first, dropped out before ingesting SonoRx, leaving 53 patients who ingested water and 51 who ingested SonoRx for the intent to treat analysis. Additional patients were excluded from the per protocol analysis because < 350 ml were ingested, images were found to be technically inadequate by the technical reviewer or by the individual blinded reader, or because they had not ingested SonoRx. For three patients the video images were missing or unreadable and those patients were excluded from both the intent to treat analysis and the per protocol analysis by blinded readers 3 and 4. An intent to treat analysis was performed for the primary efficacy variable only. Per protocol analyses were performed for the secondary outcome variables.

The sponsor's primary outcome variable in this study is the reader's answer to the question: "Overall, which images provide more diagnostic information, SonoRx, water or both equal?" For the purpose of the intent to treat analysis, for the primary outcome variable, these two patients were assigned "worst case data", i.e. water provides more information than SonoRx. The sponsor's null hypothesis was that the percentage of patients for which the readers would say that SonoRx provided more information was less than 50% (the study has been powered assuming a value of 70%). Using the binomial test, which would be most appropriate in this case, the sponsor's null hypothesis was rejected with statistical significance for none of the blinded readers. The sponsor also performed a statistical analysis using the equal split test (where the "equal" answers were equally split between the other two categories), and the sign test. Among the blinded readers, the null hypothesis was rejected with statistical significance in the intent to treat analysis for the sign test for blinded reader 3 only and in the per protocol analysis, for the equal split test for blinded reader 3 and 4 only. In the intent to treat analysis, the percentage of patients for which the readers said that the SonoRx scans provided more diagnostic information ranged from 51% for reader #3 to 38% for readers #2 and 4. For the per protocol analysis the percentages ranged from 55% for reader #3 to 38% for reader #2. It should be clear from these percentages, why the difference between the percentages and 50% was not statistically significant for any reader. Since it is well known by radiologists that a fluid filled stomach can provide an ultrasound "window" for imaging the pancreas, that this test of SonoRx against water is more clinically relevant than the test of SonoRx against an empty stomach in the pivotal studies. Using the sponsor's primary outcome variable and the sponsor's statistical analysis, this supporting study does not provide substantial evidence of efficacy for the desired indication.

In this study, all 4 blinded readers found that the most common additional information was improved delineation of abdominal anatomy. "Sensitivity and specificity" were defined in the same way as in the pivotal trials in terms of comparison of the ultrasound diagnoses with the "comparable modality" diagnosis, by the sponsor. For SonoRx, sensitivity ranged from 65% for reader #3 to 27.5% for reader #4, and specificity ranged from 100% for readers #1, #2 and #4. For water, sensitivity ranged from 67.5% for reader #3, to 30.2% for reader #2, and specificity ranged from 100% for reader #2 to 50% for reader #3. Overall, 2 blinded readers found a higher sensitivity for SonoRx than for water, and 2 readers found a higher sensitivity for water than for SonoRx. Two readers found a higher specificity for SonoRx than for water, while the other two readers found an equal specificity for both water and SonoRx.

Readers were asked to rate the visualization of the stomach, gastric wall, pylorus, duodenum, head of the pancreas, body of the pancreas, tail of the pancreas and pancreatic duct as excellent, good poor or none. The number of excellent and good ratings was greater for SonoRx than for water for all readers for the gastric wall, duodenum, head of the pancreas, tail of the pancreas and pancreatic duct, for 3 out of 4 readers for the pylorus and body of the pancreas, and for 2 out of 4 readers for the stomach. Using the Wilcoxin signed rank test, the differences between SonoRx and water are statistically significant for 2 out of 4 blinded readers for the stomach, gastric wall and tail of the pancreas, and for one out of four readers for the gastric wall, pylorus and head of the pancreas. In comparison to the comparable results of the pivotal trials where SonoRx was compared to an empty stomach, the results of this study where SonoRx is compared to water, seem less favorable to SonoRx.

Readers were asked to rate the effect of gas shadowing on the visualization of these same anatomical structures as: not obscured, mildly obscured, moderately obscured, markedly obscured or completely obscured (In the pivotal studies, the question concerning the effect of gas shadowing was asked

about the image as a whole rather than about the image of individual structures.) In the sponsor's analysis of these rankings of the effect of gas shadowing, a statistically significant advantage was seen for SonoRx for 3 out of 4 blinded readers for the stomach, gastric wall and duodenum, for 2 out of 4 blinded readers for the pylorus, body of the pancreas and tail of the pancreas, and for 1 blinded reader for the head of the pancreas.

This supporting study has not demonstrated substantial evidence of efficacy for the desired indication, based on the sponsor's primary efficacy variable and the sponsor's statistical analysis. This study does provide support for the conclusion that SonoRx does aid in the visualization of specific abdominal structures by reducing the effect of gas shadowing.

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#### 7.4 Phase 2 Dose Ranging Study

The optimal dose of SonoRx was determined in the dose ranging phase 2 study, 42,440-2. This was a phase 2 multi-center randomized open label dose ranging study in patients highly suspected of having abdominal pathology. 99 evaluable patients were enrolled in this study, at 6 study centers. 6 subjects were subsequently excluded from the analysis because of technically inadequate images ingestion of more than the prescribed dose or lack of recent "comparable modality" study leaving 93 subjects for the efficacy analysis. Subjects were randomized to orally ingest one of 5 doses of SonoRx: 200 mL, 400 mL, 600 mL, 800 mL, or 1000 mL. Each pre and post dose image was evaluated. Images were evaluated by the investigators at each site. There were no blinded readings.

No significant differences were seen between the post dose images taken immediately after ingestion with the same parameters as the pre dose scans, and scans obtained with parameters "optimized for the presence of the contrast agent or scans obtained after a short delay, or after a short delay. When the readers were asked whether the post dose images provided additional information over the pre dose images, The percentage of yes answers were 80% for 200 mL, 90% for 400 mL, 88% for 600 mL, 95% for 800 mL and 1200% for 1000 mL. On the other hand, compliance ( the ability of the patient to ingest the entire dose) was 100% at 200 mL, 88% at 400 mL, 89% at 600 mL, 75% at 800 mL, and 57% at 1000 mL. Although these differences were not statistically significant, the sponsor concluded that the largest increase in efficacy occurred between 200 mL and 400 mL, with only a small drop in compliance, and no apparent increase in the number of adverse events, so that 400 mL would be the the optimal dose.

This study is the only study in which the sponsor's analysis contained a direct comparison of the pre dose diagnosis and the post dose diagnosis to each other as well as to the "comparable modality" diagnosis. When the readers were asked if the additional information obtained with SonoRx could change the diagnosis, they answered "yes" for 34 patients (41%). When they were asked if the post dose diagnosis was the same as the pre dose diagnosis, they answered "no" for only 6 patients (7%). When the reviewer compared the diagnoses listed in the patient data tables, 7 patients were found where the post dose diagnosis agreed with the "comparable modality" diagnosis" while the pre dose diagnosis did not, and 2 patients for whom the pre dose diagnosis matched the "comparable modality" diagnosis, and the post dose diagnosis did not. The differences between these numbers can be explained by the subjective nature of the first question, and a disagreement between the reviewer and the investigators, in a small number of cases as to whether diagnoses that were similar, but not identical should be considered to be the same.

Readers were asked to rate the visualization of individual anatomical structures including the stomach duodenum, head of the pancreas, body of the pancreas and tail of the pancreas. Readers found improved visualization on the post dose scans compared to the pre dose scans for more than 50% of patients for each of these structures. The percentage of patients with improved visualization ranged from 78% for the stomach to 57% for the head of the pancreas.

Readers were asked to assess the effect of gas shadowing as not obscured, mildly obscured, moderately obscured, markedly obscured or completely obscured. The percentage of scans rated as not obscured or mildly obscured was 29% for the pre dose scans and 64% for the immediate post dose scans.

#### 7.5 Phase 1 Studies

There were 2 phase 1 studies, 42,440-1 and 42,440-4 with a total of 32 subjects. There were 8 normal healthy male volunteers in study 42,440-1 and 24 normal healthy adult male volunteers in study 42,440-4. The study 42,440-1 provided an indication that, in this small number of normal human subjects that SonoRx could aid in the visualization of the stomach, stomach wall and the head, body and tail of the pancreas.

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. There were 24 subjects in this study, each of whom ingested both 800 mL of SonoRx and 800 mL of water sequentially with a minimum 48 hour washout period between agents. The order of ingestion was determined by randomization.

Scans were evaluated by two blinded readers who compared pre dose and post dose images for both SonoRx and water for the overall effect of gas shadowing and for the visualization of the stomach, pylorus, duodenum, head of the pancreas, body of the pancreas and tail of the pancreas. There was no consistent

difference between found in the effect of gas shadowing for either SonoRx or water. Readers found improved visualization in post dose scans for a larger number of patients with SonoRx than with water. When the results of the two blinded readers are combined, the number of patients showing improved visualization on the post dose scans with SonoRx ranged from 46 (96%) for the stomach to 28 (58%) for both the duodenum and body of the pancreas. For water, the corresponding range is 37 (77%) for the stomach to 19 (40%) for the body of the pancreas

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## 8 Conclusions

- 8.1 The sponsor has not demonstrated substantial evidence of efficacy for the desired indication on the basis of the primary outcome variable in the pivotal studies because:
- 8.1.1 The question that the blinded readers were asked to answer "Overall, did the post dose images provide additional information over the pre dose images?" was subjective and the readers were given little or no guidance as to what properties of the image to use in forming their answer. The subjectivity of the question is evidenced by the wording of the question itself, and by the wide range in the number of patients thought to have more information in the post dose scans by the different readers in the two pivotal studies.
- 8.1.2 The sponsor claims to have demonstrated, with statistical significance, for each of the blinded readers that the percentage of patients found to have additional information in the post dose scans is greater than 1%. Since the only possible answers to the question are "yes" or "no", the percentage that would result from pure chance, or from guessing without bothering to look at the images, would be 50%. The answer would be expected to be close to 50% if the readers were very incompetent or if all of the images were of very poor quality. The study was powered, assuming a value of 70%. An upper limit on the number of "yes" answers of less than 50% would be totally meaningless. A value of 1% would mean that post dose scans would provide information that could not be obtained from the pre dose scans in one patient out of 100. An agent with such a low success rate would not be very useful in the clinic.
- 8.1.3 There was no real intent to treat analysis of the responses of the blinded readers. Blinded readers 1 and 2 in both studies were not given both the static and video images in violation of the protocol. Blinded readers 3 and 4 could not be given all of the static and video images because some of the video images were lost or unreadable (the sponsor did not specify how many were lost and how many were unreadable). Both sets of blinded readers did not receive all of the images since images deemed by a technical reviewer to be not technically acceptable were not sent to them for reading.
- 8.1.4 The pivotal trials were not placebo controlled for efficacy. The post dose images with 400 mL of SonoRx in the stomach, were compared to the pre dose images with a stomach that was empty after a minimum of 4 hours of fasting. It was not possible to really blind the blinded readers as to which was the pre dose scan and which was the post dose scan since a full stomach is easy to distinguish from an empty stomach in an ultrasound image. It is a common practice to give patients water to drink, to displace stomach gas, before performing an abdominal ultrasound study. To test the efficacy of SonoRx against what is now commonly done in clinical practice, it may have more appropriate to test SonoRx against water, as was done in the supporting phase 3 trial, instead of against an empty stomach as was done in the pivotal trials. Patients ingesting water instead of SonoRx were included in the pivotal studies for the purpose of the safety analysis. The pre and post dose water scans were read in the same manner as the corresponding SonoRx scans. The results of these readings were listed in the patient data tables but these readings were not included in the sponsor's efficacy analysis because the studies were not powered for a comparison of efficacy between SonoRx and water. Nevertheless it is interesting to note that when comparing the percentages of patients for which the post dose scans provided more information for SonoRx and for water, the confidence intervals for SonoRx and water overlapped for all 8 blinded readers in both pivotal phase 3 studies. 3 out of 4 blinded readers in study 42,440-3A and 3 out of 4 readers in study 42,440-3B, found additional information in post dose scans in a higher percentage of water patients than of SonoRx patients.
- 8.1.5 The primary efficacy variable is not directly related to either component of the proposed indication. For the primary efficacy variable the readers were asked "Overall, did the post dose images provide *additional information* over the pre dose images?", whereas the desired indication is "*the delineation of anatomy and the detection or exclusion of pathology in the upper abdomen*"

- 8.2 The secondary outcome variables in the pivotal studies do not provide substantial evidence of efficacy for the “detection or exclusion of pathology” because::
- 8.2.1 A per protocol analysis only was performed for the secondary outcome variables. An intent to treat analysis was not performed.
- 8.2.2 The same deficiencies in the blinded reads were present for the primary outcome variables were also present for the secondary outcome variables; blinded readers 1 and 2 were not given the video images and blinded readers 3 and 4 were not given all of the images.
- 8.2.3 Most of the questions that were asked for the secondary outcome variables were as subjective as the question for the primary outcome variable.
- 8.2.4 Sensitivity and specificity are the secondary endpoints that would be most closely related to “the detection or exclusion of pathology” however, “sensitivity” and “specificity” as used by the sponsor did not correspond to the generally accepted definition of these terms.. The determination of whether two diagnoses listed in the case report forms “matched” was made by the sponsor rather than by an independent blinded reviewer. The actual person, employed by the sponsor, who made this determination was not specified. Even with all these deficiencies, no clear advantage in sensitivity and specificity was seen for the post dose images compared to the pre dose images. In the per protocol analysis for study 42,440-3A , 2 out of 4 blinded readers had a higher sensitivity for the pre dose images 1 blinded reader had a higher sensitivity for the post dose images and 1 blinded reader had equal sensitivities. In the same study 2 blinded readers had a higher specificity for the pre dose images 1 blinded reader had a higher sensitivity for the post dose images, and 1 blinded reader had equal specificities. In the per protocol analysis for study 42,440-3B all 4 blinded readers had a higher sensitivity for the post dose images. In the same study 1 blinded reader had a higher specificity for the pre dose images and the remaining 3 blinded readers had equal specificities
- 8.2.5 The results for the secondary variables relating to the visualization of individual anatomic structures indicate that SonoRx may be approvable with a much narrower indication. When asked what additional information was provided by the post dose scans in those cases where the post dose scans did provide additional information, the answer for the largest number of patients was “improved delineation of abdominal anatomy” for all 8 blinded readers in both pivotal studies. Readers were asked to rate the visualization of specific anatomical structures as “excellent”, “good”, “poor” or “none” In study 42,440-3A, the number of excellent or good answers were greater for the post dose images than for the pre dose images for all 4 blinded readers for the stomach, gastric wall, pylorus, duodenum; body of the pancreas and tail of the pancreas, and for 3 out of 4 blinded readers for the head of the pancreas and for the pancreatic duct. Using the Wilcoxin signed rank test, the differences between pre dose scans and post dose scans were statistically significant for all 4 blinded readers for the stomach, the pylorus and the duodenum, for 3 out of 4 blinded readers for the gastric wall, head of the pancreas and tail of the pancreas, for 2 out of 4 blinded readers for the body of the pancreas, and for 1 out of four blinded readers for the pancreatic duct. In study 42,440-3B, the number of excellent or good answers were greater for the post dose images than for the pre dose images for all 4 blinded readers for the; head of the pancreas body of the pancreas, tail of the pancreas, and pancreatic duct, and for 3 out of 4 blinded readers for the stomach gastric wall, pylorus and duodenum. Reader 2 found better visualization for an equal number of pre and post dose scans for the stomach, gastric wall, pylorus and duodenum. Using the Wilcoxin signed rank test, the differences between pre dose scans and post dose scans were statistically significant for all 4 blinded readers for the stomach, pylorus, duodenum, head of the pancreas, body of the pancreas and the tail of the pancreas, and for 3 out of 4 blinded readers for the pancreatic duct. This consistent agreement between the blinded readers, indicates that while the question may seem subjective, there is evidence for an objective improvement of the visualization of these structures.

- 8.3 The conclusions that can be drawn from supporting study 42,440-7 are very similar to the conclusions that can be drawn from the pivotal studies. The comparisons in this supporting study are between water and SonoRx so differences might be expected to be smaller than when SonoRx is compared to an empty stomach. Readers were asked: "Overall, which images provide more diagnostic information, SonoRx, water or both equal?" The percentage of patients for which the readers answered "SonoRx" was greater than or equal to the percentage for which they answered "water", for all 4 blinded readers, in both the intent to treat analysis and the per protocol analysis but the difference between the percentage answering "SonoRx" and 50% was not statistically significant, using the binomial test, for any of the blinded readers in either of the analyses. Thus while there is a suggestion of an advantage for SonoRx, the differences were not statistically significant. When readers were asked the nature of the additional information in those patients who had additional information in the SonoRx scan, the most common answer was "improved visualization of abdominal anatomy" When readers were asked to rate the visualization of specific structures, the number of "excellent" and "good" answers was greater for SonoRx than for water for all 4 blinded readers for the gastric wall, duodenum, pancreatic head pancreatic tail and pancreatic duct, for 3 out of 4 blinded readers for the pylorus and pancreatic body and for 2 out of 4 blinded readers for the stomach. The differences between SonoRx and water was statistically significant for 2 out of 4 blinded readers for the stomach, gastric wall and pancreatic tail, and for 1 out of 4 blinded readers for the pylorus, duodenum and pancreatic head
- 8.4 The phase 2 dose escalation study, 42,440-2 has established 400 mL as an optimal dose on the basis that there is no substantial increase in efficacy for doses above 400 mL and that compliance (ability of the patient to ingest the total amount of SonoRx) decreases with increasing dose. There does not seem to be consistent increase in the number or percentage of adverse events with increasing dose.

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## 9 Recommendations

- 9.1 This NDA is non approvable for the sponsor's desired indication.. The sponsor has not provided substantial evidence of efficacy for the desired indication in the phase 3 clinical trials
- 9.2 These studies may be salvageable with a narrower indication and another blinded read. The data on the visualization of the individual anatomical structures indicates that SonoRx may be efficacious in aiding in the visualization of these structures. The evidence presented however is deficient because of the subjective nature of the question asked of the readers and the fact that neither of the blinded reads were performed according to protocol. Assuming that all of the scans used in this study are still available, additional blinded reads of these scans may produce substantial evidence of efficacy for a narrower indication. Ways in which these new reads should be performed include Reads should be focused on the visualization of the stomach, gastric wall, pylorus, duodenum, head of the pancreas, body of the pancreas and tail of the pancreas. These are the structures that would seem most promising on the basis of the present data, and are also the structures that would be most likely effected by shadowing by gas in the stomach. Specific objective questions should be asked about these structures, such as " Is the entire structure visualized?, Is visualization impaired by gas shadowing? , Are the borders well demarcated?, Is the echogenicity uniform? etc.. The actual wording of the questions should be arrived in consultation with experts in ultrasound imaging of the abdomen, to insure that they reflect properties of the images that are useful to radiologists in making a diagnosis. There should be at least 2 blinded readers for each study, who have not been previously involved, in any capacity in any SonoRx study. Blinded readers should be given all images obtained in the study including those that may be considered technically inadequate or where the video images may be lost or unreadable. These images must be included in the intent to treat analysis although they may be excluded from the intent to treat analysis. If diagnoses are to be compared to eachother or to a "comparable modality" comparisons should be made by an independent radiologist, using clearly stated criteria, not by the sponsor. For the studies to be considered independent, a different radiologist for each study. Comments to this effect should be sent to the sponsor with the action letter.
- 9.3 This reviewer recommends 3 possible options
- 1) Non-Approvable
  - 2) Approvable with the narrower indication "SonoRx is an orally administered ultrasound contrast agent that is indicated for improvement of visualization of the stomach, duodenum and pancreas in ultrasound studies of the upper abdomen."
  - 3) Approvable with this narrower indication after another blinded read that would address the deficiencies noted above, if the results of that additional reading confirms the results of the previous readings supporting the narrower indication
  - 4) If the NDA is approvable with the narrow indication, the labeling should include a disclaimer. "In clinical studies scans obtained after ingestion of SonoRx demonstrated a statistically significant improvement in visualization of the stomach, duodenum and pancreas, when compared to scans obtained on an empty stomach immediately before SonoRx ingestion. In studies comparing scans obtained after ingestion of SonoRx to those obtained after ingestion of an equal volume of water, a statistically significant improvement in visualization has not been demonstrated".

### cc. File

Dr. Love  
 Dr. Raczkowski  
 Dr. Jones  
 Dr. Yaes  
 DR. Al Osh

SEE DEPUTY DIRECTOR'S REVIEW FOR  
 ADDITIONAL COMMENTS

V. D. L. 9/12/97

20-773 (SonoRx)

**SAFETY UPDATE**

October 29, 1998

There have been no new clinical studies conducted since the first review cycle.

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