5 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

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 study 42,440-3A and the identical study,42,440-3B, 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, 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.

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. In this study all 53 patients enrolled in the study were included in the intent to treat analysis for Water. Since 2 patients dropped out before ingesting SonoRx, only those 51 patients who ingested SonoRx were included in the intent to treat analysis for SonoRx. No patients were excluded because of the technical quality of the images.

The intent to treat population was defined as patients who received any volume of either SonoRx or water and had images of acceptable technical quality for at least one of the study agents. The per protocol population was defined as patients who ingested at least 350 mL SonosRx and of water, underwent all post dose evaluations, had 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. 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 had read the protocol and therefore knew that the patients in the study were highly suspected of having upper abdominal pathology, while blinded readers 1 and 2 did not. This knowledge may have influenced the readings.

4.3 Results

Patient disposition

A total of 53 patients received one or both agents. Two patients who received water first did not receive SonoRx due to adverse events in the interim between agents. One patient developed right upper quadrant tenderness, and the other developed pancreatitis. Thus 51 patients received both sonoRx and water. Of the 53 ppatients,32 were male and 21 female. 44patients were white, and 9 patients were from other ethnic groups. The mean age was 54±15 years and the range was 27 to 86 years.

Compliance

TABLE 4.4 PATIENT COMPLIANCE IN INGESTING 400 ML SONORX OR PLACEBO

TABLE 4 Number of patients actually ingesting different doses		
Actual Dose Ingested	SonoRx n=51	water n=53
400	43	53
399-350	5	0
<350	3	0

Reviewer's Comment

Among patients who ingested both agents compliance appears somewhat better for water than for SonoRx

Safety

Adverse Events, N=53 (51 SonoRx, 53 water)

Deaths 0

Withdrawals due to adverse events 2

Serious adverse events 5 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.

31 adverse events in were reported, 24 adverse events in 13 patients (25%) after SonoRx ingestion, and 6 events in 6 patients (11%) after water ingestion. The most commonly reported adverse event was diarrhea in 12% of patients after SonoRx ingestion and in 4% of patients after water ingestion. The difference in the percentage of adverse events between SonoRx and water was not statistically significant (p=0.062)

There were 5 serious adverse events in 2 patients. Patient 712 developed abdominal pain, pelvic pain and back pain, beginning 6 hours after ingesting SonoRx. This patient had had pelvic pain after ingestion of water which was classified as moderate. An abdominal-pelvic CAT scan obtained 24 hours after ingestion showed an abnormal right psoas muscle consistent with hematoma or infection. The patient was admitted to hospital and was treated with IV antibiotics. All symptoms had resolved 2 weeks later. Pelvic pain, abdominal pain, back pain and hematoma were listed as separate serious adverse events for this patient. Patient 501 with a diagnosis of sepsis and possible pancreatic duct stone, developed pancreatitis, after water ingestion, and underwent ERCP 24 hours after ingestion of water. He was admitted to ICU due to complications (not further specified) of ERCP. For this patient ,pancreatitis was listed as a serious adverse event.

Two patients dropped out of the study due to adverse events after ingestion of water. Both patients were randomized to receive water first and did not ingest SonoRx. Patient 501 developed pancreatitis after water ingestion which required hospitalization. This was listed as a serious adverse event. Patient 415 developed abdominal pain after ingestion of water, that lasted 17 hours. This was listed as a mild adverse event. No patients dropped out of the study after ingestion of SonoRx.

TABLE 4.5 ADVERSE EVENTS

patient no.	agent	event COSTART	body system	intensity	ingested dose (mL)	drug related*	permanent sequelae
709	SonoRx	abd. pain	body as whole	mild	400	possibly	no
712	SonoRx	nausea	gastrointestinal	mild	380	possibly	no
		abd. pain	body as whole	mild			
		vomiting	gastrointestinal	mild			
		flatulence	gastrointestinal	mild			
		chills	body as whole	mild			
		dry mouth	gastrointestinal	mild			
		palpitation	cardiovascular	mild			
713	water	pelvic pain	body as whole	moderate	400	no	persistent
713	sonoRx	pelvic pain	body as whole	SERIOUS	395	no	persistent
		abd. pain	body as whole	SERIOUS		no	no
		hematoma	cardiovascular	SERIOUS		no	persistent
		back pain	body as whole	SERIOUS		no	persistent
		dysuria	urogenital	mild		no	no
102	SonoRx	diarrhea	gastrointestinal	mild	400	possibly	no
103	SonoRx	dysphagia	gastrointestinal	mild	400	possibly	no
106	SonoRx	eructation	gastrointestinal	mild	400	possibly	no
108	SonoRx	diarrhea	gastrointestinal	mild	400	possibly	no
110	SonoRx	diarrhea	gastrointestinal	mild	400	possibly	no
201	SonoRx	diarrhea	gastrointestinal	mild	400	possibly	no
401	water	headache	body as whole	mild	400	possibly	no
401	SonoRx	diarrhea	gastrointestinal	mild	400	possibly	no
401	SonoRx	headache	body as whole	mild	400	possibly	no
403	water	diarrhea	gastrointestinal	mild	400	possibly	no
407	SonoRx	diarrhea	gastrointestinal	mild	400	possibly	no
409	water	diarrhea	gastrointestinal	mild	400	possibly	no
415	water	abd. pain	body as whole	mild	400	possibly	no
501	water	pancreatitis	gastrointestinal	SERIOUS	400	no	persistent
504	SonoRx	nausea	gastrointestinal	mild	400	possibly	no
708	SonoRx	ecchymosis	body as whole	mild	400	no	no

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

TABLE 4.6 SUMMARY OF ADVERSE EVENTS BY STUDY AGENT AND BODY SYSTEM

Body System	SonoRx N=51		water N=53	
	Patients	Events	Patients	events
Body as whole	4 8%	7	2 4%	2
Lymphatic-hemic		1		0
Gastrointestinal	10 20%	13	4 8%	4
cardiovascular	2 4%	2		0
urogenital	1 2%	1		0
TOTAL	13 26%*	24*	6 12%	6

*two patients had multiple adverse events involving multiple organ systems

Reviewer's Comments.

If the 3 cases of abdominal pain, attributed to "body as a whole" by COSTART terminology, are instead considered to be of gastrointestinal origin, then of 31 adverse events, 20 (65%) would involve the GI system

Physical Examination

Six patients had changes from the pre dose exam to the post dose exam for SonoRx. Three patients had changes from abnormal to normal. The three patients who had changes from normal to abnormal had nausea, a bruise from an IM injection and upper right quadrant abdominal pain respectively. For water, one patient had a change from abnormal to normal. Two patients had a change from normal to abnormal, both involving GI complaints.

Vital signs

Vital signs taken immediately before and immediately after ingestion were compared. 9 patients experienced changes of greater than ±20% in systolic BP, 19 in diastolic BP, 10 in heart rate and 14 in respiratory rate (Table 4.7). None of these changes in vital signs were considered clinically significant by the investigators or the sponsor..

TABLE 4.7 CHANGES IN VITAL SIGNS

CHANGES IN VITAL SIGNS OF ≥ 20%			
SonoRx N=51			
	No. of pts increased	No. of pts decreased	Range of change
Systolic BP mm hg	3	2	-45% to +38%
Diastolic BP mm hg	5	7	-39% to +29%
Heart Rate bt/sec	5	0	+12% to +34%
Resp. Rate bt/sec	4	2	-6 % to +4%
water N=53			
Systolic BP mm hg	2	2	-4% to +40%
Diastolic BP mm hg	6	1	-28% to +36%
Heart Rate bt/sec	3	2	-18% to +19%
Resp. Rate bt/sec	5	3	-33% to +50%

EKG

12 lead EKGs were performed within 24 hours prior to and 1 hour ± 10 min after infusion. Tracings were evaluated by a cardiologist or a physician trained to interpret EKGs. It is not stated whether interpretations were made at each center or by a single physician at a central location. If clinically significant abnormalities were present post dose, EKGs were to be repeated until return to baseline Data for such repeat EKGs are not given for any patient, and it is not clear whether any repeat EKGs have been done.. Results are given in attachment 6 , tables 11.1 and 11.2 Readings and parameters are given for all pre dose EKGs but only for those post dose EKGs where a clinically significant change has judged to have occurred. The sponsor claims that significant changes occurred in only 3 patients but since the parameters for the post dose EKGs are not given for any other patient in the patient data tables, this can not be verified by the reviewer.. .Patient 404 had poor R wave progression across the pericardium pre dose for both SonoRx and water. Post SonoRx the patient had poor R wave progression across the pericardium. This patient is said to have a significant change pre dose to post dose although the reason is not clear. Patient 707 had an inferior MI pre dose for both water and SonoRx and developed ST elevation on leads V2 and V3 for both post dose EKGs. Patient 712 had a lead misplaced on the pre dose water EKG and a normal post dose EKG. This was called a clinically significant change. Diagnoses and parameters from post dose EKGs were not given for any other patient..

APPEARS THIS WAY
ON ORIGINAL

Laboratory

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

Hemoglobin, Hematocrit, RBC, Albumin, Calcium ±25%
Bilirubin, SGOT, SGPT, ASAT, ALAT ±150%
Potassium, Chloride ±20%
Uric Acid +75%
Glucose +100%, -25%
Sodium, ±10%

WBC, Platelet Count ±50%
Potassium, Chloride ±20%
BUN, GGT, LDH +100%
Creatinine + 50%
Phosphorus +100%, -40%
Total Protein, ±30%

. Serum chemistry guidelines outside of the sponsor's guidelines are given in table 4.8

. TABLE 4.8 SERUM CHEMISTRY CHANGES

TABLE 9 LABORATORY CHANGES OUTSIDE OF SPONSOR'S GUIDELINES			
SonoRx N=51			
Test	number of increases	number of decreases	% change
WBC	0	1*	-76%
GGT	1	0	+112%
Glucose	1	2	-65% to +319%
water N=53			
Glucose	2	5	-76% to+145%
WBC	1*	0	+99%

* same patient

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, to the timing of the test in relation to the subject's mealtimes. The sponsor claims that laboratory values were fasting values, but patients were required to fast only for 4 hours before ingestion. The decrease in glucose in 2 patients after ingesting SonoRx is attributed by the sponsor to underlying diabetes, and the increase in one patient receiving SonoRx to Glucose in IV fluid. The fact that changes were seen in GGT in 1 patients is consistent with the fact that most of these patients have abdominal pathology which may involve the liver or biliary system.

APPEARS THIS WAY
ON ORIGINAL

Urinalysis

No changes in urinalysis parameters that are outside of sponsor's guidelines are listed.

Efficacy

Patient disposition

TABLE 4.9 PATIENT DEPOSITION	
Total Number of patients planned	48
SAFETY ANALYSIS	
Dropped Out Before Ingestion of SonoRx	2
Patients Available For Safety Analysis (SonoRx)	53-2=51
Patients Available For Safety Analysis (water)	53
EFFICACY ANALYSIS: INTENT TO TREAT	
Patients available for intent to treat analysis by investigators	53
Dropped Out Before Ingestion of SonoRx	2
Technically inadequate (by technical reviewer)	1
Patients available for intent to treat analysis by blinded readers 1 and 2	53-2-1=50
Missing video images (blinded readers 3 and 4 only)	3
Patients available for efficacy analysis blinded readers 3 and 4	50-3=47
EFFICACY ANALYSIS: PER PROTOCOL	
Dropped Out Before Ingestion of SonoRx	2
Ingested less than 350 mL study agent	3
Patients available for per protocol analysis by investigators	53-2-3=48*
Ingested <350 mL SonoRx	3
Technically inadequate (by blinded reader 1 only)	4
Patients available for per protocol analysis by blinded reader 2	50-3=47
Patients available for per protocol analysis by blinded reader 1	50-3-4=43
Patients available for per protocol analysis by blinded readers 3 and 4	47-3=44

*The one patient whose scans were found technically inadequate by the technical reviewer, must be among the
3 patients who ingested less than 350 mL agent, although this is not explicitly stated by the sponsor.

Both an intent to treat analysis and a per protocol analysis were performed for the primary efficacy endpoint only. For all other endpoints, a per protocol analysis only was performed.

Primary Efficacy Endpoint

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

TABLE 4.10 SPONSOR'S PRIMARY EFFICACY VARIABLE

TABLE 4.10 ADDITIONAL INFORMATION: SonoRx IMAGE vs. water IMAGE									
Per Protocol									
Response			blinded readers						
	investigators N=48		reader #1 N=43		reader #2 N=47		reader #3 N=44		reader #4 N=44	
SonoRx	31	65%	23	54%	18	38%	24	55%	18	41%
water	12	25%	13	30%	17	36%	7	16%	6	14%
equal	5	10%	7	16%	12	26%	13	30%	20	46%
Intent To Treat										
	investigators N=53		reader #1 N=50		reader #2 N=50		reader #3 N=47		reader #4 N=47	
SonoRx	33	62%	25	50%	19	38%	24	51%	18	38%
water	12	23%	17	34%	19	38%	10	21%	9	19%
equal	6	11%	8	16%	12	24%	13	28%	20	43%
not done*	2	4%								

*Patients who did not ingest SonoRx were assigned the "worst case" response "water is better" for the investigator's analysis, but were not included in the blinded readers' analysis.

The sponsor's primary endpoint is the number of patients for which the readers find that SonoRx images provide more information than the water images. The sponsor's null hypothesis is that this number is less than or equal to 50%. The study was powered assuming a value of 70% The sponsor used 3 different statistical tests to analyze this data, the binomial test, the equal split test and the Sign test. In the sponsor's per protocol analysis the null hypothesis was rejected with statistical significance only for reader 3 using the equal split test, p=.0226 and for the investigators and readers 3 and 4 using the sign test, p=.0029, p=.0033 and p=.0227 respectively. For the intent to treat analysis, the null hypothesis was rejected with statistical significance only for blinded reader 3, for the sign test, p=.023, and for the investigators for the equal split test and the sign test, p=.0127,and p=.0079, respectively.

Reviewer's Comment

Using the sponsor's primary efficacy variable and statistical analysis, efficacy has not been conclusively demonstrated. Using the binomial test, which would be most appropriate, the number of "SonoRx is better" answers is not significantly different from 50% for the investigators or for any of the blinded readers for either the intent to treat analysis or for the per protocol analysis. It is not clear why the sponsor took the difference between SonoRx and 50% instead of the difference between SonoRx and water as their primary outcome variable. The differences in results between the different readers is most likely due to the subjective nature of the question asked.

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

TABLE 4.11 TYPE OF ADDITIONAL INFORMATION GIVEN BY POST DOSE SCAN

TABLE 4.11 NATURE OF ADDITIONAL INFORMATION					
Information		Blinded Readers			
	Invest. N=27*	Reader#1 N=25*	Reader#2 N=17*	Reader#3 N=27*	Reader#4 N=24*
Improved delineation of abdominal anatomy	23	22	17	27	24
Improved confidence in exclusion of pathology	14	7	17	10	4
Improved delineation of pathology	13	10	3	5	0
Improved evaluation of extent of disease pathology seen	8	7	2	1	1
Other	1	0	0	0	0

*N=number of patients with additional information (SonoRx over water) according to each individual reader

Readers were asked to estimate their confidence in the diagnosis (from 0% to100%) 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±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%±15%, p=0.0001, N=81. The increase in confidence for readers #1 and #4 was not statistically significant (per protocol analysis)

Delineation 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 4.12

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TABLE 4.12 DELINEATION OF ABDOMINAL ANATOMY (per protocol)										
Structure	Investigators		Blinded Readers							
	N=48		Reader #1 N=43		Reader #2 N=47		Reader #3 N=44		Reader #4 N=44	
	sonorx	water	sonorx	water	sonorx	water	sonorx	water	sonorx	water
Stomach	29	18	28	28	41	42	5	4	17	9
Gastric Wall	28	17*	15	14	38	36	16	10	21	15
Pylorus	21	20	26	30	37	37	27	22	20	14
Duodenum	21	15	14	13	27	22	23	21	9	4
Pancreatic Head	37	35	18	15	33	32	27	24	27	26
Pancreatic Body	40	37	23	18	39	39	28	25	27	26
Pancreatic Tail	26	17	6	2	24	26	21	17	12	8
Pancreatic Duct	27	24	9	7	37	33	24	22	10	9

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 4.13. NS means not statistically significant

3LE 4.13 DELINEATION OF ABDOMINAL ANATOMY STATISTICAL RESULTS (per protocol)

Structure	Investigators	Blinded Readers			
	N=48	Reader #1 N=43	Reader #2 N=47	Reader #3 N=44	Reader #4 N=44
Stomach	p=0.0018	NS	NS	p=0.0037	p=0.0072
Gastric Wall	p=0.0003 -	NS	NS	p=0.0118	p=0.0113
Pylorus	NS	NS	NS	NS	p=0.0093
Duodenum	p=0.0144	NS	NS	NS	p=0.0036
Pancreatic Head	NS	NS	NS	p=0.0486	NS
Pancreatic Body	NS	NS	NS	NS	NS
Pancreatic Tail	p=0.0006	p=0.0069	NS	p=0.0181	NS
Pancreatic Duct	NS	NS	NS	NS	NS

Reviewer's Comment

The results in tables 11, 112 and 13 regarding delineation of abdominal anatomy appear to show a trend in favor of SonoRx. 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 fairly consistent. In table 12 all readers found that better delineation of anatomy was the most common source of additional information. In table 13, 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 13 for 34 of those 40 comparisons, readers found the visualization excellent or good in a larger number of SonoRx images than water images. In the remaining 6 cases, the numbers of patients were equal in 3 cases and higher for water in 3 cases. However, In the sponsor's analysis using the Wilcoxin signed rank test using all ratings, excellent, good poor and none, The difference between water and SonoRx is statistically significant for 13 out of 40 responses. The results are less favorable to SonoRx than the results of studies 42,440-3A and 42,440-3B where post dose images were compared to pre dose images, rather than to images obtained with placebo.

Gas Shadowing

Readers were asked to evaluate each anatomical structure for the effect of gas shadowing as: 1) not obscured, 2) mildly obscured,, 3) moderately obscured, 4) markedly obscured or 5) completely obscured. For 3 readers, the impact of gas shadowing was statistically significantly reduced by SonoRx as compared to water for a number of specific anatomic sites as shown in table 4.14. Presumably, the Wilcoxin signed rank test was used, although this is not explicitly stated in the study report. It is not stated whether for any readers for any anatomic areas, water had a statistically significant advantage over SonoRx. In table 16, where a statistically significant advantage for SonoRx over water is claimed by the sponsor, the sponsor's p value will be given.. All other cases will be listed as NS

TABLE 4.14 EFFECT of GAS SHADOWING ARTIFACT (per protocol)

ucture	Investigators	Blinded Readers			
	N=48	Reader #1 N=43	Reader #2 N=47	Reader #3 N=44	Reader #4 N=44
Stomach	p=0.0003	p=0.0011	NS	p=0.0065	p=0.049
Gastric Wall	p=0.0138	p=0.0044	NS	p=0.0352	p=0.0040
Pylorus	NS	p=0.0231	NS	p=0.0009	NS
Duodenum	p=0.0149	p=0.0342	NS	p=0.0067	p=0.0134
Pancreatic Head	p=0.0486	NS	NS	p=0.0396	NS
Pancreatic Body	NS	p=0.0367	NS	p=0.0372	NS
Pancreatic Tail	p=0.0001	p=0.0437	NS	NS	p=0.0307
Pancreatic Duct	p=0.0479	NS	NS	NS	NS

Other than the wording of the question, the readers were given no guidance as to how to rate gas shadowing for each anatomical structure. The question be is subjective, but more specific than the same question when asked about the scan as a whole. 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. Because the post dose images are obtained within 10 minutes of ingestion, the SonoRx should be mostly in the stomach when the image is obtained. Thus the effect of SonoRx should be expected to be seen in the stomach itself and in organs such as the pancreas which are posterior to the stomach. The results in tables 13,14 and 15 appear to confirm that expectation 3Except for reader 2, the differences in reader response for SonoRx scans was statistically significant for three out of four readers for the stomach, gastric wall and duodenum, for 2 out of 4 readers for the pylorus, pancreatic head, pancreatic body and pancreatic tail, and for the investigators only for the pancreatic duct.

Diagnoses (Sensitivity and Specificity)

Readers were asked to make diagnoses based on the SonoRx scans and on the water scans. The scans were unpaired and viewed separately. 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 definition and method of calculation of "sensitivity" and "specificity" are the same as in studies 42,440-3A and 42,440-3B The results of the sponsor's per protocol analysis of sensitivity and specificity are shown in table 16, and table 17 is derived from the information in table 16

Reviewer's Comment

Review of the patient data listings (Listing 31.1,vol.36, pg. 28 and listing31.2, vol. 36, pg.267) have indicated that the "comparable modality" has ranged from a an upper GI series, only (pt. 401), to CT, UGI, biopsy and surgery (pt. 405). 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 using the comparison of the investigator's diagnosis to the comparable modality diagnosis, as a measure of efficacy The comparison between diagnoses was made from the data in the case report forms by the sponsor. It is not clear what individual employee of the sponsor made this determination, what the credentials of that employee are, or even whether the determination was made by a single individual or by more than one person 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. In other cases the diagnoses may be very similar, but not identical 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. For patient 106, the comparable modality diagnosis was " dilated pancreatic duct, no evidence of mass or stone, pseudocyst head of pancreas". The diagnosis for both the SonoRx scan and the water scan was "dilated pancreatic duct, no evidence of mass or stone". According to the investigator, these diagnoses did not match. For patient704, the comparable modality diagnosis was "pseudocyst of the pancreas" and the diagnosis for the water scan was "pancreatic mass, cancer vs. pseudocyst". According to the investigators, these diagnoses did not match. Listing 31.2 which gives all 3 diagnoses (SonoRx, water, and comparable modality) side by side gives data for the investigators only. Similar tables are not available for the blinded readers.

TABLE 4.14 "SENSITIVITY" AND "SPECIFICITY"

	BLINDED READERS (PER PROTOCOL)			
	Reader #1 N=43	Reader #2 N=47	Reader #3 N=44	Reader #4 N=44
SonoRx				
Sensitivity	56.4%	37.2%	65.0%	27.5%
Specificity	100%	100%	75.0%	100%
water				
Sensitivity	43.5%	30.2%	67.5%	32.5%
Specificity	75%	100%	50.0%	100%

TABLE 17 NUMBER OF READERS FINDING HIGHER VALUE		
	sensitivity	specificity
SonoRx	2	2
water	2	0
both equal	0	2

The results in table 16 are highly reader dependent. The results in table 17 show a trend in favor of SonoRx for specificity but not for sensitivity

Reviewer's comment

With the usual definition of sensitivity and specificity, 50% would be the number obtained by pure chance. To be useful, a test should have a sensitivity and a specificity substantially higher than 50%. 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. For the SonoRx scans ,the sensitivities are less than 50% for 2 out of four readers, and for the water scans the sensitivities are less than 50% for 3 out of 4 readers. Conversely, all of the specificities ,for all of the readers for both, water and SonoRx scans are greater than 50%.

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-billiary 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"

Sponsor's Conclusion:

The results of this study show that SonoRx is a safe oral contrast agent that is well tolerated by a broad group of patients highly suspected of having abdominal pathology. SonoRx is significantly more efficacious than water in providing increased visualization and delineation of abdominal anatomy, and provides significantly more diagnostic information than water.

3.4 Reviewer's Analysis

Safety

53 patients (51 Sonorx, 53 water) were evaluable for safety analysis in this crossover study. 2 patients ingested water but dropped put of the study before ingesting SonoRx.

Adverse events

There were 31 adverse events, 24 adverse events in 13 patients (25%) after SonoRx and 6 events in 6 patients after water (11%) (table 6). 18 events in 12 patients (23%), in the reviewer's opinion were possibly related to SonoRx and 4 events in 4 patients (7.5%) were possibly related to water (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 15 adverse events in 9 patients (18%) were possibly or of unknown relationship to SonoRx and 3 events in 3 patients (6%) were possibly or of unknown relationship to water. There were 5 serious adverse events in 2 patients. Two patients dropped out of the study due to adverse events after ingesting water. 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.

This pattern of adverse events does not raise any clinically significant safety concerns. The 5 serious adverse events in 2 patients were not related to SonoRx or water. The 2 patients who dropped out of the study due to adverse events had both ingested water. Two events are classified as cardiovascular. One was palpitations in a patient (712) who also experienced 5 other adverse events at the same time, and the other was a hematoma in the psoas muscle in patient 713. The majority of adverse events involved the gastrointestinal system ,the most common being diarrhea, and were, temporary and mild in severity. The only moderate adverse event was pelvic pain in a patient who ingested water and which was not related to water. There was a higher percentage of adverse events after SonoRx than after water, but this difference was not statistically significant (p=0.062). Some of 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 by precaution in the labeling.

Vital signs

Vital signs immediately before ingestion and immediately after ingestion were compared. Changes in vital signs by more than ±20% are given in table 8. There were 28 such changes in 51 patients who ingested SonoRx group for an average of 0.55 changes per patient There were 24 such changes in 24 placebo patients for an average of 0.46 changes per patient. 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

Three patients had changes from normal to abnormal after SonoRx and two patients had changes from normal to abnormal after water. Except for one bruise from an IM injection after SonoRx, all changes involved minor GI complaints

Laboratory Monitoring

Laboratory changes outside the sponsor's guidelines are given in table 9.There were two such changes in WBC, one after SonoRx and one after water .Both of these changes occurred in the same patient. Changes in routine serum chemistries outside of the sponsor's guidelines included changes in glucose only. There were 3 such changes after SonoRx and 7 such changes after water. None of these changes were considered to be clinically significant. There were no clinically significant changes in urinalysis.

EKG

EKGs were obtained on all patients, 24 hours before and 1 hour after ingestion. The sponsor claims that significant changes were seen for only 3 patients. his can not be verified since readings are given in the patient data tables for pre dose EKGs only.

Efficacy

Patient deposition for the efficacy analysis is given in table 10. In the intent to treat analysis, there are 53 patients for the investigators, 50 patients for readers 1 and 2 and 47 patients for blinded readers 3 and 4. In the per protocol analysis, there are 48 patients for the investigators, 43 for reader 1, 47 for reader 2,and 44 for readers 3 and 4.

The sponsor's primary endpoint was the readers' answer to the question "Overall, which images provided more diagnostic information SonoRx, water or both equal". Images were evaluated together, rather than separately. The answer to this question calls for a subjective judgment by the reader, and readers were given little or no guidance on what criteria and what characteristics of the image to use in making their judgment..

Sponsor's Primary Endpoint

The sponsor's primary endpoint is the reader's answer to the question "Overall, which images provided more diagnostic information SonoRx, water or both equal". (table 12) The percentage of "SonoRx is better" answers to this question were highly reader dependent, ranging from 55% (Reader #3) to 38 % (reader #2) in the per protocol analysis and from 51% (Reader #3) to 38 % (readers #2 and #4) in the. intent to treat analysis. The reason for these differences between readers is probably the subjective nature of the question. The sponsor has used three statistical tests to analyze this data. The most appropriate test would be the binomial test. The sponsor's null hypothesis is that the percentage of "SonoRx is better" answers is less than or equal to 50%. Because there are 3 possible answers (SonoRx is better, water is better or both are equal), 33.3% would be expected by pure chance. The sponsor powered the study assuming the number of "SonoRx is better" answers would be 75%. Using the binomial test, the percentage of "SonoRx is better" answers is not significantly different from 50% for the investigators or for any of the blinded readers, for either the intent to treat analysis or the per protocol analysis.

Nature of Additional Information

For those patients where readers had said that the SonoRx scans provided more 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 12).

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 13. The results appear to consistently favor the SonoRx images. Most readers consistently favored the SonoRx images for most structures listed in tables 13 (stomach, stomach wall, pylorus, duodenum, and pancreatic head body tail and duct). These are the structures that would be expected to be most effected by shadowing by gas in the stomach. Using the Wilcoxin rank sign test, the differences were statistically significant, for 2 of the 4 blinded readers, for the stomach, gastric wall and the tail of the pancreas, and for 1 blinded reader each for the pylorus, duodenum and head of the pancreas (table 14). Since SonoRx is compared to water rather than to an empty stomach in this study, these results are less favorable to SonoRx than the results of studies 42,440-3A and 42,440-3B. Interpretation of these results is confounded by the subjective nature of the question and the fact that readers were given no instructions as to where to draw the lines between excellent, good poor or none.

Gas Shadowing

In contrast to studies 42,440-3A and 42,440-3-B, readers were asked to compare SonoRx to water instead of to an empty stomach, and to evaluate the effect of gas shadowing on individual anatomic structures, rather than on the image as a whole. These differences reduce the subjectivity of the question considerably. Since the effect of SonoRx is presumed to result from the reduction in gas shadowing, the reader's responses to this question can be compared directly to the responses to the previous question concerning the visualization of these same structures. The majority of readers found less gas shadowing artifact for SonoRx over water for the majority of structures. These results were statistically significant for 3 out of 4 blinded readers for the stomach, gastric wall and duodenum, and for 2 out of 4 blinded readers for the pylorus, pancreatic body and pancreatic tail and for one blinded reader for the pancreatic head (table 15)

Diagnoses (Sensitivity and Specificity)

The diagnoses for the SonoRx scan the water scan and for the comparable modality, as stated on the case report forms were compared by the sponsor (it is not clear by which person(s) employed by the sponsor) to determine whether the diagnoses "matched". There were no specific written instructions in the protocol 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 table 16. Sensitivity, as defined by the sponsor is higher for the SonoRx scans for2 out of 4 blinded readers and for water for 2 0ut of 4 blinded readers. Specificity is higher for SonoRx for 2 blinded readers, and equal for the other 2 (tables 16 and 17). The data and the analysis is flawed 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.

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 pharmacokinitics 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 53 patients, there were 4 serious adverse events in 1 patients after ingestion of SonoRx and 1 serious adverse event in one patient after ingestion of water. For both of these patients the adverse events were considered to be unrelated to the ingested agent by the investigators, by the sponsor and by this reviewer. There were a total of 24 adverse events in 13 patients (25%) after SonoRx ingestion and 6 events in 6 patients (11%) after water ingestion. The difference is not statistically significant (p=0.062) The most common adverse event was diarrhea, which was 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.

This supportive study is the only phase 3 clinical trial in which SonoRx was tested against placebo (water). The sponsor's primary endpoint is the readers' answer to the question: "Overall, which images provided more diagnostic information, SonoRx, water or both equal?" . 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. The readers' answers to this question are given in table 11, with the variable being the number of "SonoRx ", "water" and "equal" answers to this question. Although there is a clear trend in favor of SonoRx, using the binomial test, the differences between the percentage of "SonoRx" answers and 50% was not statistically significant for all blinded readers and for both the intent to treat and the per protocol analysis. It is not clear why, in the sponsor's analysis, SonoRx was compared to 50% instead of being compared directly to water.

A more clinically meaningful endpoint would be a comparison of the SonoRx scans and water 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 16 and 17) 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. The determination of whether two diagnoses "matched" was made by the sponsor, rather than by an independent radiologist. It is not clear to the reviewer which person or persons, employed by the sponsor, actually made this determination. Taking all of these problems into account the "sensitivity" and "specificity" as defined by the sponsor, still do provide a crude measure of the ability to make a "correct" diagnosis from the ultrasound scans..

The results of this analysis are given in tables 16 and 17. There appears to be a lack of consistency among the readers, as 2 readers find a higher sensitivity for the SonoRx scans, while the other 2 readers find a higher sensitivity for the water scans, as shown explicitly in table 17. In studies 42,440-3A and 42,440-3B, where SonoRx was compared to an empty stomach, the trend was more consistently in favor of SonoRx

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 13. There is a trend in favor of SonoRx but the differences between

SonoRx and water are statistically significant in only 13 out of 40 cases Using the Wilcoxin signed rank test these differences, in 38 out of 40 cases are statistically significant. The readers were also asked to evaluate the effect of gas shadowing on visualization of individual structures. There is a statistically significant advantage for SonoRx over water in 22 out of 40 cases (table 15)

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 trend in favor of SonoRx compared to water in the answers to the questions concerning individual anatomical structures. However the subjectivity of the question asked makes it difficult to draw any firm conclusions.

5. **Phase 3 Pivotal Trial 42,440-3A**

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

5.1 Abstract

A total of 122 patients (94 SonoRx ,28 placebo), with a high suspicion of abdominal pathology participated in the study at 8 study centers (planned, 100 patients, 75 SonoRx, 25 placebo). After fasting for a minimum of 4 hours, patients w have an abdominal ultrasound study (the pre dose study). Immediately afterwards, they ingested 400 mL of either SonoRx (93 patients) or placebo (24 patients)and a second abdominal ultrasound study was obtained All 122 patients were included in the sponsor's analysis of safety. Only the 94 patients who received SonoRx were included in the Sponsor's efficacy analysis. Placebo patients were not considered in the sponsor's efficacy analysis!

Scans were read by the investigators at each site and by 4 blinded readers. Efficacy was assessed by comparing the pre dose scans to the post dose scans. The sponsor's primary efficacy variable was the reader's answer to the question: "Overall, did the post dose images provide additional information over the pre dose images" According to the sponsor, efficacy would be demonstrated if the difference between the percentage of "yes" answers and 1% was statistically significant.

5.2 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

5.3 Study Design

Protocol 42,440-2 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 is 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 . Prior to enrollment each patient is randomized to receive either 400 mL SonoRx, or 400 mL 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 be3fore 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's clinical judgment. 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 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 5.1 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 2 of 10 sites

Adverse Events

All events involving appearance or worsening of illnesses, signs or symptoms after implementation of study procedures will be reported. An adverse event 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
Stomach Wall
Pylorus
Duodenum
Pancreas (Head, Body, Tail)
Pancreatic duct
Abdominal Aorta
Left Kidney
Left Renal Artery
Splenic Vein
Superior Mesenteric Artery
Liver
Common Bile Duct
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 independent blinded readers did not read the placebo images, 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 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 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?"

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

3) DOSAGE AND FORMULATION

SonoRx is an orally administered ultrasound contrast agent for the intended use of delineating normal anatomy and detecting pathology in the upper abdomen. The active ingredient is 22 micron fiber length cellulose fibers coated with Simethicone The cellulose is manufactured from wood and is considered safe (GRAS) Simethicone is a component of several over the counter 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 pharmacokinitics reviews). The composition of SonoRx used in this study is given in table 1 below

TABLE 5.2 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 5.3 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

Subjects

13 patients are to be recruited at each study center

Inclusion Criteria:

Age 18 years or greater

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 second inclusion criterion seems to contradict the third. 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

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

5.4 Results

5.4.1 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,42,440-3B, 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 were 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 2 of 10 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 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 SonosRx 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 12 SonoRx patients and best case data to the 1 placebo patient 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 the per protocol 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 and2 had not read the protocol, while blinded readers 3 and 4 had read the protocol

5.4.2 Patient disposition

A total of 119 patients were enrolled at 10 sites. Two dropped out before receiving any dose of either SonoRx or placebo. The remaining 117 patients were dosed (93 SonoRx ,24 placebo) and were included in the safety analysis. The demographics of these 117 patients is given in table 4

Compliance

TABLE 5.4 PATIENT COMPLIANCE IN INGESTING 400 ML SONORX OR PLACEBO

TABLE 4 Number of patients actually ingesting different doses		
Actual Dose Ingested	SonoRx n=93	Placebo n=24
400	78	22
399-350	2	0
<350	13	2

Demographics

TABLE 5.5 DEMOGRAPHICS N=117

agent	AGE (yr)		WEIGHT (kg)		HIGHT (cm)		SEX		RACE			
	mean ±SD	range	mean ±SD	range	mean ±SD	range	M	F	White	Black	Hispanic	Asian
sonorx N=93	59± 17	22-84	73± 18	43-160	168±10	145-191	43	50	64	26	3	0
placebo N=24	55± 17	29-89	77± 21	47-118	168±10	152-193	11	13	16	7	0	1

Reviewer's Comment

There appear to be no remarkable demographic differences between the SonoRx group and the placebo group

5.5 Safety

Adverse Events, N=117 (93 SonoRx, 24 placebo)

Deaths 0

Withdrawals due to adverse events 0

Serious adverse events 1

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.

27 adverse events in 20 patients (17%) were reported, 22 adverse events in 17 patients (18%) in the placebo group and 5 events in 3 patients (13%) in the placebo group. The most commonly reported adverse event was diarrhea in 5 patients (5%) in the SonoRx group and in 2 patients (8%) in the placebo group. The difference in the percentage of adverse events between SonoRx and placebo was not statistically significant (p=0.503) There were no trends observed in the incidence of adverse events by age, sex or race.

There was 1 serious adverse. event Patient 1509 , a 60 year old female who ingested 400 ml SonoRx experienced chest pain of unknown etiology that began 24 hours after ingestion and lasted 4 hours. Cardiac enzymes were normal but patient was kept in hospital for observation for 24 hours. This same patient also experienced headache and anxiety. Adverse events are tabulated in tables 6 and 7.

TABLE 5.6 ADVERSE EVENTS

patient no.	agent	event COSTART	body system	intensity	drug related*	permanent sequelae
101	SonoRx	nausea	gastrointestinal	mild	possibly	no
105	SonoRx	diarrhea	gastrointestinal	mild	possibly	no
503	SonoRx	nausea	gastrointestinal	mild	definite	no
701	SonoRx	nausea	gastrointestinal	mild	possibly	no
702	SonoRx	vomiting	gastrointestinal	mild	possibly	no
801	placebo	diarrhea	gastrointestinal	mild	definite	no
804	SonoRx	diarrhea	gastrointestinal	mild	possibly	no
"		headache	body as whole	mild	no	no
808	SonoRx	diarrhea	gastrointestinal	mild	definite	no
1001	SonoRx	diarrhea	gastrointestinal	mild	possibly	no
1002	SonoRx	nausea	gastrointestinal	moderate	possibly	no
"	SonoRx	fever (38.4° C)				
1005	SonoRx	rash	skin	mild	no	persistent
1007	SonoRx	vomiting	gastrointestinal	mild	definitely	no
"	SonoRx	pallor	cardiovascular	mild	no	no
1102	SonoRx	rash	skin	mild	unknown	persistent
"		eructation	gastrointestinal	mild	possibly	no
1201	SonoRx	ear pain	special senses	moderate	no	no
1505	SonoRx	headache	body as whole	mild	unknown	no
1506	SonoRx	pain back	body as whole	mild	no	no
"		diarrhea	gastrointestinal	mild	possibly	no
1508	SonoRx	headache	body as whole	mild	unknown	no
1509	placebo	asthenia	body as whole	mild	unknown	no
		anxiety	nervous	mild	possibly	no
		pain chest	body as whole	Serious	unknown	no
1512		vomiting	gastrointestinal	mild	possibly	no
1705	placebo	diarrhea	gastrointestinal	mild	possibly	no

* the reviewer considers all GI side effects to be possibly drug related to SonoRx or placebo

TABLE 5.7 SUMMARY OF ADVERSE EVENTS BY STUDY AGENT AND BODY SYSTEM

Body System	SonoRx N=93		Placebo N=24	
	Patients	Events	Patients	events
Serious Adverse Events				
Body as whole	0	0	1 (Pt.1509)	1 (chest pain)
Non-Serious Adverse Events				
Body as a whole	5 5.4%	5	1 4.2%	2
Cardiovascular	1 1.1%	1	0 0%	0
Gastrointestinal	13 14.0%	13	2 8.3%	2
Nervous	0 0%	0	1 4.2%	1
Skin and appendages	2 2.2%	2	0 0%	0
Special senses	1 1.1%	1	0 0%	0

Clinical and Laboratory Monitoring

Physical Examination

There were 6 patients in the SonoRx group (6%) with post dose physical examinations with findings on the post dose physical examination that were not present on the pre dose examination. Three of these were rash, blanching and macular-popular rash which were reported as adverse events. The other three findings, new subclavian central venous line, midline abdominal scar post Whipple and midline abdominal scar were probably missed or not commented on for the first examination. No changes in physical examination were noted for any of the patients in the placebo group. The new subclavian line may have been placed between the two physical examinations. These last 3 findings are obviously not related to SonoRx

Vital signs

Vital signs taken immediately before and immediately after ingestion were compared 12 patients experienced changes of greater than ±20% in systolic BP, 16 in diastolic BP, 16 in heart rate and 29 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 5.8 CHANGES IN VITAL SIGNS

CHANGES IN VITAL SIGNS OF ≥ 20%			
SonoRx N=93			
	No. of pts increased	No. of pts decreased	Range of change
Systolic BP mm hg	5	5	-54 to +30
Diastolic BP mm hg	4	7	-28 to +30
Heart Rate bt/sec	10	4	-30 to +50
Resp. Rate bt/sec	19	5	-8 to +8
Placebo N=23*			
Systolic BP mm hg	1	1	-30 to +32
Diastolic BP mm hg	5	0	-22 to -14
Heart Rate bt/sec	1	1	-24 to +50
Resp. Rate bt/sec	4	1	-6 to +6

* one placebo patient is apparently not available for vital sign analysis

EKG

. Post dose EKGs were performed on 26 patients, 21 SonoRx and 4 placebo) at 2 study centers. 2 SonoRx patients did not have pre dose EKGs available for comparison, leaving 24 evaluable patients EKGs were read by a cardiologist and determined to be normal or abnormal. No patient had a normal pre dose EKG followed by an abnormal post dose EKG

TABLE 5.9 EKG CHANGES

EKGs N=24 (21 SonoRx, 4 placebo)		
	pre dose normal	pre dose abnormal
post dose normal	10 (42%)	2 (8%)
post dose abnormal	0 (0%)	12 (50%)

Laboratory

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

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

Two female SonoRx patients had CBC changes that exceeded the Sponsor's guidelines. One of these was considered by the investigator to be clinically significant. Patient 1505 experienced a 142% increase in WBC from 8.6 to 20.8 This patient was receiving chemotherapy with Taxol which is known to cause leukocytosis.

There were 20 serum chemistry value changes that exceeded the sponsor's guidelines, 19 changes in 15 SonoRx patients and 1 change in 1 placebo patient. These changes are given in table 10-A

TABLE 5.10-A SERUM CHEMISTRY CHANGES

TABLE 5.10-A SERUM CHEMISTRY CHANGES OUTSIDE OF SPONSOR'S GUIDELINES N=117			
		SonoRx	
Test	number of increases	number of decreases	% change
Albumin	1	0	+35%
SGPT	1	0	+632%
SGOT	1	0	+853%
GGT	1	0	+200%
BUN	1	0	+140%
Uric Acid	3	0	+78% to +129%
Glucose	1	6	-67% to +102%
Phosphorus	0	1	-43%
Potassium	2	1	-26% to +42%
		Placebo	
Potassium	1	0	+21%

None of the serum chemistry changes were considered clinically significant by the sponsor. The most common change was a decrease 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 in relation to meals. The fact that large changes were seen in LFTs in 3 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 and values are shown in table 10-B

TABLE 5.10-B URINALYSIS RESULTS

TABLE 5.10-B URINALYSIS						
Test	SonoRx			placebo		
	pre dose	post dose	change	pre dose	post dose	change
pH	6	6	0.1	5.6	5.8	0.2
specific gravity	1.0	1.0	0	1.0	1.0	0

There are no clinically significant changes in these urinalysis results A total of 14 urinalysis deviations in 9 patients (8 SonoRx, 1 placebo) were noted by the investigators. There were 5 urinalyses positive for glucose, 1 positive for ketones, 4 positive for protein, 3 positive for blood and one abnormal y high specific gravity. All of these could be possibly be explained by pre- existing diabetes or other disease, recent nephrotoxic chemotherapy or by dehydration. One investigator thought that SonoRx may have worsened the effect of diabetes.

5.6 Efficacy

5.6.1 Patient disposition

Data obtained from the 24 patients who received placebo were not included in the efficacy analysis. Scans were obtained from the placebo patients and these scans were read by the readers but these results were not included in the efficacy analysis. 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. Therefore data on the placebo patients for the primary endpoint only and for the blinded readers only will be addressed in this review. Of the 95 patients randomized to receive SonoRx, 2 were not dosed The remaining 93 patients were included in the intent to treat analysis of the investigator's readings (each of the 10 investigators read the images from his/her center only. The scans of these 93 patients were reviewed by the technical reviewers, and 8 images were excluded for technical reasons The images of the remaining 85 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 12 patients who had ingested less than 350 mL SonoRx 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 was performed for readers 3 and 4 for the primary efficacy variable only. Thus together the 10 investigators read a total of 93 scans, blinded readers 1 and 2 each read a total of 85 scans and blinded readers 3 and 4 read a total of 73 scans.

The population available for the per protocol analysis was obtained by excluding those patients with images found by the technical reviewers to be of unacceptable quality, and patients who ingested <350 ml SonoRx. There were 79 evaluable patients for the per protocol analysis for the investigators, 73 patients for blinded readers 1 and 2 and 64 for readers 3 and 4, because videotapes for 9 patients were missing or unreadable.

TABLE 5.11 PATIENT DEPOSITION FOR EFFICACY ANALYSIS	
Total Number of patients planned	100
Total Number of patients enrolled	119
Dropped Out Before Ingestion	2 (both SonoRx)
Patients Available For Safety Analysis (SonoRx 93) (Placebo 24)	119-2=117
Patients Available For Efficacy Analysis (SonoRx patients only*)	117-24=93
Intent to Treat Analysis By Investigators	93
Technically inadequate per technical reviewer	8
Intent to Treat Analysis By Blinded readers 1 and 2	93-8=85
Video Images Missing or Not Readable	9
Intent to Treat Analysis By Blinded readers 3 and 4 (primary efficacy endpoint only)	85-9=76
Intent to Treat Analysis By Blinded readers 1 and 2	85
Patients Who Ingested <350 mL	12
Per Protocol Analysis By Blinded readers 1 and 2	85-12=73
Video Images Missing or Not Readable	9
Per Protocol Analysis By Blinded readers 3 and 4	73-9=64

*placebo data used for safety analysis only

5.6.2 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 12

TABLE 5.12 SPONSOR'S PRIMARY EFFICACY VARIABLE

TABLE 5.12 ADDITIONAL INFORMATION: POST DOSE IMAGE vs. PRE DOSE IMAGE					
Per Protocol					
Response		blinded readers			
	investigators N=79	reader #1 N=73	reader #2 N=73	reader #3 N=64	reader #4 N=64
yes	46 58%	32 44%	72 99%	42 66%	15 23%
no	33 42%	41 56%	1 1%	22 34%	49 77%
confidence interval % yes	47.4-69.1	32.5-55.2	96.0-100	54.0-77.3	13.1-33.8
Binomial test yes≤1%	p=0.0001**	p=0.0001**	p=0.0001**	p=0.0001**	p=0.0001**
Intent To Treat					
	investigators N=93*	reader #1 N=85	reader #2 N=85	reader #3 N=76***	reader #4 N=76***
yes	54* 58%	35 41%	84 99%	42 55%	15 20%
no	38* 41%	50 59%	1 1%	34 45%	61 80%
confidence interval % yes	48%-68%	30.7%-51.5%	96.5%-100%	44.1%-66.4%	10.8%-28.7%
Binomial test yes≤1%	p=0.0001**	p=0.0001**	p=0.0001**	p=0.0001**	p=0.0001**

* 54+38=92 One patient was not imaged post dose and was not available for this analysis. This patient was not included in the per protocol analyses

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

*** "worst case" data has been imputed to the 12 patients whose images were not sent to blinded readers 3 and 4. In reality the results of the intent to treat analysis for readers 3 and4 conveys no additional information over the per protocol analysis

Reviewer's Comment

The entries in table 12 were taken directly from the sponsor's tables S, T, AA and AB, (pgs.70, 71, 83 and 85, vol.24). 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 reviewers 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% , a glance at the confidence intervals would demonstrate that the null hypothesis would be rejected for neither the investigators nor for any of the blinded readers. The null hypothesis would be rejected for all readers for a choice of 10% (a yes answer for 1 patient out of every 10) with a p of 0.05, but this choice of 10% would have been made arbitrarily, after the fact to fit the data.

Although not used in the 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?"

TABLE 5. 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	32	44	13	68	72	99	19	100	42	34	5	29	15	23	6	35
no	41	56	6	32	1	1	0	0	22	66	12	71	49	77	11	65
total	73	100	19	100	73	100	19	100	64	100	117	100	73	100	19	100
Confidence interval-yes	32.5%-55.2%		47.5%-89.3%		96.0%-100.0%		100.0%-100.0%		54.0%-77.3%		48.9%-93.2%		13.1%-33.8%		12.6%-58.0%	

The SonoRx entries in table 12Bare 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 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.

Reviewers 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 13-A TYPE OF ADDITIONAL INFORMATION GIVEN BY POST DOSE SCAN

TABLE 5.13 NATURE OF ADDITIONAL INFORMATION					
		Blinded Readers			
	Investigators N=46*	Reader#1 N=32*	Reader#2 N=72*	Reader#3 N=42*	Reader#4 N=15*
Improved delineation of abdominal anatomy	32	23	72	40	15
Improved confidence in exclusion of pathology	19	15	72	15	0
Improved delineation of pathology	17	9	0	5	0
Improved evaluation of extent of disease pathology seen	5	1	0	0	0
Other	2	1	0	0	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% to100%) for pre dose and post dose scans. There was a statistically significant increase in confidence from pre dose to post dose for reader #2, with a change of +2.8±4%, p=0.0001, N=73 and a statistically significant decrease in confidence from pre dose to post dose for reader #3, with a change of -5.7%±21%, p=0.0295, N=64. There were no significant differences for readers #1 and #4 (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

TABLE 5.14 DELINEATION OF ABDOMINAL ANATOMY

ucture	Investigators		Blinded Readers							
	N=79		Reader #1 N=73		Reader #2 N=73		Reader #3 N=64		Reader #4 N=64	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Stomach	3	30	3	22	28	64	7	38	4	20
Gastric Wall	12	42	16	19	30	63	8	40	6	20
Pylorus	13	38	18	29	34	66	5	33	13	21
Duodenum	6	20	2	4	17	44	1	23	5	10
Pancreatic Head	29	48	38	38	47	56	41	48	21	27
Pancreatic Body	46	62	48	52	65	71	50	54	36	39
Pancreatic Tail	11	30	20	23	37	53	17	31	17	18
Pancreatic Duct	17	27	8	12	58	66	54	55	8	7

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

TABLE 5.15 DELINEATION OF ABDOMINAL ANATOMY STATISTICAL RESULTS (per protocol)

Structure	Investigators*	Blinded Readers			
	N=79	Reader #1 N=73	Reader #2 N=73	Reader #3 N=64	Reader #4 N=64
Stomach	p=0.0001	p= 0.0001	p=0.0001	p=0.0001	p=0.0001
Gastric Wall	p=0.0001	NS	p=0.0001	p=0.0001	p=0.0001
Pylorus	p=0.0001	p=0.0015	p=0.0001	p=0.0001	p=0.0021
ıodenum	p=0.0001	p=0.0109	p=0.0001	p=0.0001	p=0.0001
ıcreatic Head	p=0.0001	NS	p=0.0001	p=0.0054	0.0075
ancreatic Body	p=0.0001	NS	p=0.0002	p=0.0273	NS
Pancreatic Tail	p=0.0001	p=0.0126	p=0.0001	p=0.0001	NS
Pancreatic Duct	p=0.0001	NS	p=0.0001	NS	NS

*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, with out further guidance for assigning the rating can be considered subjective. However the responses of the readers are remarkably consistent. In table 13 all readers found that better delineation of anatomy was the most common source of additional information. In tables 14 and 15 , 4 blinded readers and the investigators were asked to rate the visualization of 8 different anatomical structures, in the upper abdomen, 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 one case the numbers were equal, and reader #4 found one more pre dose image of the pancreatic duct to be good or excellent than for the post dose images. In table 15 it is shown that in 33 out of 40 cases the difference in ranking between post and pre dose images is highly statistically significant, using the Wilcoxin signed rank test..

5.6.3 Gas Shadowing

The overall image was evaluated with respect to gas shadowing as:1) not obscured 2) mildly obscured, 3) moderately obscured, 4) markedly obscured or 5) completely obscured. The

number of scans rated mildly obscured or not obscured, by dose and scan is given in table 9 for the pre dose scan and the 4 post dose scans

TABLE 5.16 EFFECT of GAS SHADOWING ARTIFACT

Gas Shadowing	Investigators		Blinded Readers							
	N=79		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	1	1	0	0	0	0	3	2	0	0
Markedly Obscured	14	4	7	4	1	0	15	15	3	3
Moderately Obscured	42	30	19	19	18	3	29	20	10	14
Mildly Obscured	20	39	38	32	52	60	14	17	50	46
Not Obscured	2	5	9	18	2	10	3	10	1	1

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 blinded readers 1, 2 and 3, using the Wilcoxin signed rank test..

5.6.4 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 scan 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 plain film of the abdomen only, to a CT scan of the abdomen and pelvis, upper GI series 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. 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

TABLE 5.17 "SENSITIVITY" AND "SPECIFICITY" (PER PROTOCOL PATIENTS)				
	BLINDED READERS (PER PROTOCOL)			
	Reader #1	Reader #2	Reader #3	Reader #4
Pre SonoRx				
Sensitivity	51.6%	37.5%	54.5%	34.5%
Specificity	33.3%	55.6%	55.6%	55.6%
Post SonoRx				
Sensitivity	51.6%	28.1%	45.5%	36.4%
Specificity	22.2%	44.4%	100%	55.6%
	BLINDED READERS (INTENT TO TREAT)*			
Pre SonoRx				
Sensitivity	55.3%	38.2%	*	*
Specificity	33.3%	55.6%	*	*
Post SonoRx				
Sensitivity	53.9%	28.9%	*	*
Specificity	22.2%	44.4%	*	*

- 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 pre dose scans for readers 2 and 3,greater in the post dose scans for reader 4,and equal for reader 1. The specificity is greater for the pre dose scans for readers 1 and 2, greater in the post dose scans for reader 3 and equal for reader 4. For the intent to treat analysis sensitivity is greater in the pre dose scans for readers 1 and 2. The specificity is greater for the pre dose scans for readers 1 and 2. For the sensitivity and specificity the way that the sponsor defined it, there is no clear advantage for the post dose scans, in fact, at first glance the pre dose scans seem better. However these results are not statistically significant (see statistical review).

TABLE 5.18 NUMBER OF READERS FINDING HIGHER VALUE				
	Per protocol		intent to treat*	
	sensitivity	specificity	sensitivity	specificity
Pre dose	2	2	2	2
post dose	1	1	0	0
both equal	1	1	0	0

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

Table 19 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 5.19 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:

Sensitivity = TP/(TP+FN), Specificity = TN/(TN+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, only apply 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 and 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")

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 5.20 COMPARISON OF DIAGNOSES READER # 1 N=85 INTENT TO TREAT			
Ultrasound Diagnosis	Comparative Modality Diagnosis		
Pre Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	42	6	48
Same Pathology Not Found	34	3	37
Total	76	9	85
Sensitivity 55.3%	Specificity=33.3%		
Post Dose Scan			
	Pathology Found	Pathology Not Found	
Same Pathology Found	41	7	48
Same Pathology Not Found	35	2	37
Total	76	9	85
Sensitivity 53.9%	Specificity=22.2%		

TABLE 5.21 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	33	6	39
Same Pathology Not Found	31	3	37
Total	64	9	73
Sensitivity 51.6%	Specificity=33.3%		
Post Dose Scan			
	Pathology Found	Pathology Not Found	
Same Pathology Found	41	7	48
Same Pathology Not Found	35	2	37
Total	76	9	85
Sensitivity 53.9%	Specificity=22.2%		

TABLE 5.22 COMPARISON OF DIAGNOSES READER # 2 N=85 INTENT TO TREAT			
Ultrasound Diagnosis	Comparative Modality Diagnosis		
Pre Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	29	4	33
Same Pathology Not Found	47	5	52
Total	76	9	85
Sensitivity 38.2%	Specificity=55.6%		
Post Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	22	5	27
Same Pathology Not Found	54	4	58
Total	76	9	85
Sensitivity 28.9%	Specificity=44.4%		

TABLE 5.23 COMPARISON OF DIAGNOSES READER # 2 N=73 PER PROTOCOL			
Ultrasound Diagnosis	Comparative Modality Diagnosis		
Pre Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	24	4	28
Same Pathology Not Found	40	5	45
Total	64	9	73
Sensitivity 37.5%		Specificity=55.6%	
Post Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	18	5	23
Same Pathology Not Found	46	4	50
Total	64	9	73
Sensitivity 28.1%		Specificity=44.4%	

TABLE 5. 24 COMPARISON OF DIAGNOSES READER # 3 N= 64 PER PROTOCOL			
Ultrasound Diagnosis	Comparative Modality Diagnosis		
Pre Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	30	4	34
Same Pathology Not Found	25	5	20
Total	55	9	64
Sensitivity =54.5%		Specificity =55.6%	
Post Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	25	0	25
Same Pathology Not Found	30	9	39
Total	55	9	64
Sensitivity 45.5 %		Specificity100 %	

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TABLE 5.25 COMPARISON OF DIAGNOSES PER PROTOCOL	READER # 4 N= 64		
Ultrasound Diagnosis	Comparative Modality Diagnosis		
Pre Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	19	4	23
Same Pathology Not Found	36	5	41
Total	55	9	64
Sensitivity =34.5%		Specificity =55.6%	
Post Dose Scan			
	Pathology Found	Pathology Not Found	Total
Same Pathology Found	20	4	24
Same Pathology Not Found	35	5	40
Total	55	9	64
Sensitivity 55.6%		Specificity 55.6%	

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. Of all the values for all of the readers the only one that can be said to be substantially higher than 50% is the 100% specificity found by reader #3 for the post dose scans (table 16) Reader #1 had specificities less than 50% for both pre and post dose scans in both the per protocol and the intent to treat analyses. Similarly, blinded reader #2 had sensitivities less than 50% for all 4 cases and specificities less than 50% in 2 out of 4. Readers 3 and 4 had per protocol analyses only .Reader #4 had sensitivities less than 50% for both pre and post dose scans. Reader #3 had a sensitivity less than 50% for the post dose scans.

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 teach particular patient happened to have. This workup ranged from CAT scan of the abdomen and pelvis, upper GI series and endoscopy with biopsy, to nothing more than a plain film of the abdomen. 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. Could be a result of the small number of true positives. The low values for the specificities could be the result of the relatively small number of true negatives (9 out of 85 [10.6%] in the intent to treat analysis), 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"

5.6.5Sponsor'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.

5.7) Reviewer's Analysis

5.7.1Safety

117 patients (93 Sonorx,24 placebo) were evaluable for safety analysis

5.7.2 Adverse events

There were 27 adverse events in 20 patients out of 117 patients (17%), 22 adverse events in 17 patients (18%) in the SonoRx group and 5 events in 3 patients in the placebo group (12.5%) (table 6). 25 events in 18 patients (15%), 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 18 adverse events in 17 patients were definitely possibly or of unknown relationship to the agent There was one serious adverse event, One female patient in the placebo group developed headache, anxiety, vomiting and chest pain. Because this patient was hospitalized for 24 hours to rule out a cardiac etiology for the chest pain, this event was classified as serious. Since cardiac enzymes were normal (and presumably there was an EKG that was taken during this period of observation and was normal, although this is not specifically mentioned in the study report.), this event was considered to not be of cardiac origin but of unknown etiology. It was also therefore classified as "body as a whole rather than cardiovascular system. It was considered serious because of the 24 hour hospital admission for observation. 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 2 events classified as moderate by the investigators. One patient in the SonoRx group developed nausea which was classified as moderate and another patient in the SonoRx group developed ear pain that was classified as moderate but which was probably not related to SonoRx The difference in the number of adverse events between SonoRx and placebo was not statistically significant (p=0.503) The most common adverse events were diarrhea (7 patients, 5 SonoRx and 2 placebo) and nausea or vomiting (7paients, all SonoRx)

This pattern of adverse events does not raise any clinically significant safety concerns The only serious adverse event occurred in the placebo group. The this event was chest pain which required hospitalization for 24 hours for observation, but the chest pain turned out not to be of cardiac origin. The majority of the other adverse events involved the gastrointestinal system ,the most common being diarrhea or nausea and vomiting , 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.

5.7.3 Vital signs

Vital signs immediately before ingestion and immediately after ingestion were compared. Changes in vital signs by more than ±20% are given in table 8. There were 59 such changes in the 93 patients in the SonoRx group for an average of 0.63 change s per patient There were 14 such changes among the 24 placebo patients for an average of 0.61 changes per patient. More increases in heart rate, 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

5.7.4 Physical Examination

Six changes were noted on physical examination. Three have already been discussed as adverse events. The other three involving surgical scars and a subclavian line were probably missed or not commented on during the first physical examination

5.7.5 Laboratory Monitoring

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

5.7.6 Efficacy

Efficacy was evaluated for the SonoRx group only. The scans of the patients who ingested placebo were not read and were not reported in the efficacy analysis in this study. 93 Sonorx patients were available for the intent to treat analysis by the investigators, 8 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 were excluded, there were 73 patients remaining for the per protocol analysis by blinded readers 1 and 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 . However since video images were lost or unreadable for 9 patients, these patients were excluded from the reading by blinded readers 3 and 4 In addition due to an error, only the images for the per protocol patients were sent to blinded readers 3 and 4. An intent to treat analysis was not possible for these last 2 readers, so a per protocol analysis only was reported for 64 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 immediate post dose images provide additional information over the post dose image" In order to answer this question, the readers would have had to evaluate 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 any 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 word 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 scans 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 same "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, that was actually done. This ranged from a CAT scan, UGI series, and endoscopy with biopsy, for one patient ,to a plain film of the abdomen 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 was an extensive workup.

The readers were asked whether in their opinion the additional information 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"

5.7.7 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 99% (Reader #2) to 23 % (reader #4) in the per protocol analysis and from 99%(Reader #2) to 20 % (reader #4) 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%. Except for reader #2 the 95% confidence interval would either have included or be below 50%. 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.

5.7.8 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 13).

5.7.9 Visualization of Individual Organs

Readers were asked whether to rate the visualization of individual anatomic 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. The investigators and the blinded readers consistently found better visualization for the stomach, gastric wall, pylorus, duodenum, pancreatic body and pancreatic tail. Four out of five readers found better visualization in the post dose image for the pancreatic head and pancreatic duct. Using the Wilcoxin signed rank test, the were statistically significant for all readers for the stomach, pylorus, and duodenum, for four out of five readers for the gastric wall, pancreatic head, body and tail, and for two out of five readers for the pancreatic duct (table 15).

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. If SonoRx had been tested against placebo, this would not have been a problem. 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.

5.7.10 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 table16. Except for reader #4, 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 for blinded readers 1, 2 and 3, 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.

6.7.11 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 deter mine 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) was higher for the pre dose images for readers 2 and 3 and equal for reader #1 in the per protocol analysis and for both readers 1 and 2 in the intent to treat analysis. Sensitivity was higher for the post dose images only for reader 4 in the per protocol analysis. Sensitivity is higher for the pre dose images for readers 1 and 2 for both the per protocol analysis and the intent to treat analysis. Sensitivity is equal for both images for blinded reader 4 and greater for the post dose image for reader 2, for the per protocol analysis (see