

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20773

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Date: AUG 5 1998

NDA: 20-773 Amendment
Drug Class: Class 3S
Drug name: SonoRx (simethicone coated cellulose suspension)
Applicant: Bracco Diagnostics Inc.
Indication: An oral contrast agent for use in the delineation of abdominal anatomy and to assist in the detection or exclusion of pathology in patient undergoing ultrasound
Documents Reviewed: One volume (# 3.1) dated April 29, 1998
Medical Officer: Robert Yaes, M.D. HFD-160
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Key Words and Phrases: Ultrasound, delineation of anatomy, gas shadowing, Sign test, Wilcoxon signed rank test

I. Introduction/ Background

SonoRx (simethicone coated cellulose suspension) is an oral contrast agent which the sponsor, in their NDA # 20-773 of September 30, 1996, indicated for use in the delineation of abdominal anatomy and for the detection or exclusion of pathology in patient undergoing ultrasound. Following review of the sponsor's application, the agency issued a non approvable letter, dated September 30, 1997, citing insufficient evidence for the broad claimed indication, in addition to deficiencies in the chemistry section. Specifically, the letter indicated that the sponsor's data support use of SonoRx for decreasing gas shadowing and, marginally, for delineating abdominal anatomy but not for the detection or the exclusion of pathology.

The letter summarized deficiencies in the conduct and assessment of the clinical trials. Detailed discussion of these deficiencies can be found in the statistical and clinical reviews, dated 7/18/97 and 9/12/97, respectively, and in the Deputy Director's Memorandum to the File dated 9/30/97. Among the issues that were raised concerning SonoRx efficacy evaluation were: (i) relevance of the questions about the image evaluation in the case report form to the claimed efficacy and appropriateness of the response scale measurements, (ii) lack of an adequate 'standard of truth' for interpretation of the pathological findings and inconsistency of the findings across studies or readers within the same study when the investigator's diagnostic assessments were used as the truth, and (iii) exclusion of a substantial number of patients from the analyses and the high variability of the analysis results across readers.

The letter requested the sponsor, if a resubmission for the SonoRx application were to be made, to include a revised indication that would focus on the reduction of gas shadowing artifact in the upper abdomen, and on the results of delineation of anatomy in comparison to water or vehicle. It was requested also that these efficacy results be based on worst case analysis for images that were excluded from the intent-to-treat (ITT) population. Finally, it was requested that the sponsor submit updated safety information for all subjects who received SonoRx in any clinical trial (not just for phase II and III trials).

The sponsor in the present application addresses some of the issues raised in the non approvable letter. These issues were also the subject of two telecommunication discussions between the sponsor and the agency on 11/6/98 and 11/20/98. This reviewer requested during these discussions that the analysis be carried out on a simplified 3 point scale, which he believes is more appropriate for interpretation of the data at hand. The remainder of this review is organized into 4 sections. Section 2 summarizes the sponsor's approach for defining the patient population analyzed and the way of handling missing data as well as the statistical methodology for carrying out the efficacy evaluation. Section 3 presents the sponsor's efficacy and safety results along with this reviewer's comments about their comparison with the results in the original submission. Section 4 concludes with an overall summary and conclusion. Finally, recommendations from a statistical perspectives are given in Section 5.

II. Sponsor's Results:

The sponsor's re-analyses of the efficacy data of the of the two pivotal studies (Study #: 42,440-3A and Study # 42,440-3B) in this submission addresses the following endpoints: (i) the impact of SonoRx on gas shadowing artifacts and (ii) the additional information in pre-dose versus post-dose images. The sponsor's efficacy results, as indicated above, were to address the exclusion of patients from the analysis by imputing data for missing reading, and to use a simplified scale of measurements. Below we summarize the sponsor's approach to each of these issues.

II.A. Population For Analysis:

The sponsor carried out their analysis for two patient populations: (i) the all-patients-as-dosed efficacy population and (ii) intent-to-treat (ITT) population.

The all-patients-as-dosed population was defined as all enrolled patients who had received any dose of study agent. For patients who received study agent and whose images were not evaluated (due to unacceptable technical quality, miscoding of images, unreadable/missing video images, or protocol violations) the sponsor imputed, what they called, 'worst case' results. These imputed data, as will be discussed later, vary by the endpoint analyzed and by the measurements scale. The number of patients with imputed data varies from reader to reader in each study.

The number of patients included with imputed 'worst case' data among the 93 SonoRx-dosed patients and 24 control agent-dosed patients in Study 42440-3A, were as follows: investigators, 1 SonoRx patient; blinded readers 1 and 2, 8 SonoRx and 4 control agent patients; blinded readers 3 and 4, 29 SonoRx and 7 control agent patients. The corresponding numbers among the 94 SonoRx-dosed and 28 control agent dosed patients in Study 42440-3B were as follows: investigators, 1 SonoRx patient; blinded readers 1 and 2, 10 SonoRx and 5 control agent patients; blinded readers 3 and 4, 13 SonoRx and 7 control agent patients.

The ITT population, as was defined in the original submission, included all patients who received any volume of study agent and had images of acceptable technical quality. As was discussed in the Statistical Review (Sections III.B and IV.A.I) , dated 7/18/98, this patient population is not well-specified since each of the readers as well as the technical reviewer have their own individual judgement about acceptability of the technical quality of the images. This reviewer views the sponsor's 'all-patients-dosed population' as the usual ITT population. However, for maintaining consistency in terminology with the sponsor's submission and the previous reviews we will use the sponsor's terminology when presenting their results.

The sponsor analyzed the all-patients-as-dosed population for the impact of gas shadowing artifacts and for the additional information in pre-dose versus post-dose images. Data from the ITT population were re-analyzed with respect to the impact of SonoRx on gas shadowing using a 3 point scale which was based on collapsing the 5-point scale originally used to collect pre-dose and post-dose assessment from the investigators and blinded readers.

For the supportive study (Study 42,440-7) the sponsor re-analyzed the impact of gas shadowing data for the ITT and the per-protocol populations using the 3 point scale.

II.B. Methodology:

II.B.I. Impact of gas shadowing:

The pre-dose and post-dose impact of gas shadowing artifact was assessed by each reader (investigators, blinded readers 1, 2, 3 and 4) using a 5 point scale (not obscured, mildly obscured, moderately obscured, markedly obscured and completely obscured). The sponsor re-analysis of impact of gas shadowing artifact using the 5 point scale consisted of comparing post-dose ratings with the pre-dose ratings (post- minus pre-) using the Wilcoxon signed rank test after imputing data for images without evaluation. For SonoRx and the control agent patients without image evaluation, the sponsor imputed data by assuming that pre-dose images were not obscured and post-dose images were completely obscured. The imputed data could be viewed as, according to the sponsor, 'worst case' for SonoRx patients but not so for the control agent patients. The 'worst case' comparison occurs by assuming for the control agent that pre-dose images are completely obscured and post-dose images are not obscured.

The sponsor also reanalysed the impact of gas shadowing artifact using a 3 point scale (pre-dose image more obscured than post-dose image, no change, and post-dose image more obscured than pre-dose image) which they obtained by collapsing the original 5 point scale. For this analysis the sponsor used the Sign test on the 3 point scale results after excluding the cases for which no change between pre- and post-dose image assessment. In addition, following the agency request, the sponsor compared SonoRx efficacy results with those of the control agent using the Wilcoxon Rank Sum test. The study, however, was designed as a baseline control and the inclusion of the control agent was for safety assessment. Efficacy results for the gas shadowing artifact for all-patients-as-dosed population and the intent-to-treat population are presented in Section III.

Efficacy results for the supportive study (Study 42,440-7), which was designed as a cross over study to support comparison between SonoRx and the control agent, water, were based on each reader assessment of the impact of gas shadowing artifact on specified abdominal anatomy (stomach, gastric wall, pylorus, duodenum, pancreatic head, pancreatic body, pancreatic tail, pancreatic duct) for the SonoRx and water images. The images were assessed as: not obscured, mildly obscured, moderately obscured, markedly obscured, completely obscured. The sponsor's re-analysis of the impact of gas shadowing artifact consisted of collapsing the original 5 point scale into a 3 point rating scale (water image more obscured than SonoRx images, no difference,

and SonoRx images more obscured than water image). Then the Sign test was used for the efficacy evaluation for the per-protocol and the ITT analyses. Unlike the pivotal studies no efficacy results for all-patients-as-dosed population was presented for this study. The difference between the number of patients enrolled in this study (53 patients) and those of the ITT population is relatively small (0 for the investigators, 3 for blinded readers 1 and 2 and 6 for blinded readers 3 and 4). Efficacy results, as will be discussed in the following section, for all-patients-as-dosed population are not expected to be much different from those of the ITT population. For the ITT analysis the sponsor imputed what they called 'worst case' data, defined as follows: water images more obscured than SonoRx images for missing water image data; SonoRx images more obscured than water images for missing SonoRx image data, no difference if both water and SonoRx image data were missing. As discussed above, for imputing 'true' worst case data one should assume that missing water images are unobscured and missing SonoRx images are obscured.

II.B.II. Additional information provided by post-dose images

For this efficacy endpoint, which was considered the primary endpoint in the original submission, the sponsor calculated the proportion of SonoRx images for which post-dose images provided additional information over pre-dose images for all readers in the two pivotal trials using all-patients-as-dosed population. For SonoRx and control agent patients without image evaluation data the sponsor imputed what they called 'worst case' data (i.e, no additional information provided in post-dose over pre-dose). As discussed before, the sponsor's imputed data might not represent the worst scenario for comparing SonoRx and control agent. The sponsor's analysis of the proportion of patients with post-dose image providing additional information over pre-dose images consisted, as in the original submission, of constructing 95% confidence intervals around these proportion and statistical testing against 1%. Of note here, as discussed in the statistical review of 7/18/98, the study was designed (including sample size calculations) under the assumption that SonoRx enhanced images is expected to provide additional information over pre-dose images in 75% of the cases.

II.C Safety :

For the safety analysis the sponsor indicated that there were no clinical investigations conducted with SonoRx after the submission of the NDA; and thus all-patients-as-dosed population was

derived from all clinical investigations (Phase I, II and Phase III). The sponsor stated that all adverse events were coded and categorized by body systems. Also, the sponsor summarized the incidence of adverse events by patients (the number of patients who had at least one adverse event), by treatment group (SonoRx and control agent), by intensity, and by category and relationship to study agent (definite, possible, unknown, not related).

III. Sponsor's Efficacy Results:

III.A.I Impact of Gas Shadowing Artifact for the Pivotal Studies:

Table 1 summarizes the sponsor's efficacy results for the impact of gas shadowing artifact, using the 3 point scale for all-patients-as-dosed, in the pivotal studies #'s: 42,440-3A and 42,440-3B. The reported p-values in this table are based on comparing, using the sign test, the proportion of patients for whom pre-dose images are more obscured than post-dose images with that for whom post dose images are more obscured than pre-dose.

The sponsor's comparison in Table 1 excludes images for which no change in clarity between pre- and post-dose images. The response rate for the 'no change' category, as can be seen from Table 1, is large almost for every reader. Consequently, if one limits the response to two categories by combining the 'no change' category with the 'less obscured' category, the significance of the efficacy results would be diminished. A related discussion about relevance of the efficacy questions to the efficacy endpoints was raised in the Statistical Review of 7/18/98. For the present we will limit our discussion to the sponsor's analysis results as given.

The results of the comparisons for Study 42,440-3A were significantly in favor of SonoRx according to the investigators ($p=0.0001$) and blinded reader 2 (0.0019). However, the results of the comparison for blinded readers 3 and 4 show statistical significance in favor of the pre-dose unenhanced images (with p-values 0.0328 and 0.0001 , respectively). For blinded reader 1 the results were not statistically significant ($p=0.3020$). The analogous results for the ITT population show significant results in favor of SonoRx for the investigators and blinded readers 1 and 2. For blinded reader 3 the results of pre-and post dose images were comparable, and for blinded reader 4 the results were in favor of the pre-dose image

The efficacy results for the impact of gas shadowing artifact in Table 1, using the 3 point scale, for Study 42,440-3B, are similar to those based on the 5 point scale, using the Wilcoxon signed

rank test (not presented here), with the exception of blinded reader 2, for whom the results was not significant when the 5 point scale is analysed.

Table 1/ Reviewer's Table

Impact of Gas Shadowing Artifact: Post dose versus Pre-dose, 3 point scale, all-patients-as-dosed
Pivotal Studies (42,440-3A and 42,440-3B) ^{1 2}

Reader	Impact of Gas Shadowing Artifact	Study 42,440-3A		Study 42,440-3B	
		SonoRx (N=93) % (n)	Cont. Agent (N=24) % (n)	SonoRx (N=94) % (n)	Cont. Agent (N=28) % (n)
Investigators	More obscured ³	43 (40)	71 (17)	67 (63)	46 (13)
	No change	51 (47)	29 (7)	32 (30)	46 (13)
	Less obscured	6 (6)	0	1 (1)	7 (2)
	p-Value ⁴ (ITT pop.)	0.0001 (0.0001)	0.0117 (0.0139)	0.0001 (0.0001)	0.0342 (0.0249)
Blinded Reader 1	More obscured	29 (27)	33 (8)	47 (44)	39 (11)
	No change	51 (47)	38 (9)	39 (37)	39 (11)
	Less obscured	20 (19)	29 (7)	14 (13)	21 (6)
	p-Value ⁴ (ITT pop.)	0.3020 (0.0139)	0.8236 (0.6599)	0.0001 (0.0001)	0.3604 (0.6949)
Blinded Reader 2	More obscured	29 (27)	33 (8)	21 (20)	25 (7)
	No change	62 (58)	50 (12)	62 (58)	57 (16)
	Less obscured	9 (8)	17 (4)	17 (16)	18 (5)
	p-Value ⁴ (ITT pop.)	0.0019 (0.0001)	0.8798 (0.4873)	0.6177 (0.0094)	0.8260 (0.2954)
Blinded Reader 3	More obscured	18 (17)	13 (3)	57 (54)	46 (13)
	No change	46 (43)	58 (14)	29 (27)	29 (8)
	Less obscured	35 (33)	29 (7)	14 (13)	25 (7)
	p-Value ⁴ (ITT pop.)	0.0328 ⁵ (1.00)	0.9091 (0.5744)	0.0001 (0.0001)	0.2049 (0.4869)
Blinded Reader 4	More obscured	4 (4)	8 (2)	34 (32)	39 (11)
	No change	57 (53)	54 (13)	52 (49)	36 (10)
	Less obscured	39 (36)	38 (9)	14 (13)	25 (7)
	p-Value ⁴ (ITT pop.)	0.0001 ⁵ (0.0026)	0.7573 (0.3162)	0.0066 (0.0001)	0.8057 (0.5504)

¹ Source: tables #: 1.2, p. 69; A.1.2, p. 74; B.1.2, p. 79; C.1.2, p. 84 and D.1.2, p.89 for Study -3A and tables #: 1.2, p. 95; A.1.2, p. 100; B.1.2, p. 105; C.1.2, p.110; and D.1.2, p.115 fro Study -3B.

² Values were imputed based on worst case scenario (i.e for SonoRx, post-dose more obscured than pre-dose). Number of patients with imputed worst case data: Study -3A: Investigators (1 SonoRx patient), Blinded Readers 1 and 2 (8 SonoRx and 4 control agent patients); Blinded Reader 3 and 4 (29 SonoRx and 7 control agent patients). For Study -3B Investigators (1 SonoRx patient), Blinded Readers 1 and 2 (10 SonoRx and 5 control agent patients); Blinded Reader 3 and 4 (13 SonoRx and 7 control agent patients)

³ That is, pre-dose more obscured than post dose

⁴ P-value reported in SonoRx column is based on the Sign Test for comparison of pre-dose and post-dose, p-value reported in the control agent column is for treatment group comparison and is based on the Wilcoxon Rank Sum Test.

⁵ Reported p-value is significantly in favor of pre-dose.

The analogous results for Study 42,440-3B based on the 3 point scale in Table 1 show that the comparison was significantly in favor of SonoRx for investigators ($p=0.0001$) and blinded readers 1, 3 and 4 (p -values: 0.0001, 0.0001 and 0.0066 respectively). Results for blinded reader 2 were not significant. These results for the 3 point scale are similar to those based on the 5 point scale, using the Wilcoxon signed rank test (not presented here), with the exception of blinded reader 4, for whom the results were not significant when the 5 point scale analysed. The p -values for the analogue comparison based on the ITT analysis show significant results in favor of SonoRx for all readers (investigators and blinded readers 1, 2, 3 and 4).

The results of the treatment group comparison in Table 1, using the Wilcoxon Rank Sum test, for all-patients-as-dosed show inconsistent significant results for the investigators. That is, the results were in favor of the control agent in Study 42,440-3A and in favor of SonoRx in Study 42,440-3B. The results of the comparisons were not significant for any of the blinded readers. The results of the analogous comparison for ITT analysis were similar to those for the all-patients-as-dosed population.

III.A.II. Impact of Gas Shadowing Artifact for the Supportive Study:

For this study, as discussed in the previous section, the sponsor presented efficacy results using the 3 point scale for the ITT and the per-protocol populations but not all-patients-as-dosed population. Efficacy results, by anatomical area, for the ITT population are given in Table I.1 of Attachment I.

It can be seen from the results of Table I.1 that for the investigators assessment, water images are significantly more obscured than SonoRx enhanced for the stomach, gastric wall, duodenum and pancreatic tail and they are marginal significant ($p=0.049$) for the pancreatic duct. The investigators evaluation for the remaining anatomical area (pylorus, pancreatic head and pancreatic body) show non significant p -values. Concerning the blinded readers' evaluation, significant results were reported for first blinded reader's assessment for images of the stomach, gastric wall and pylorus. The only other significant p -values for the blinded readers' assessment were for the pylorus (blinded reader 3) and for the gastric wall (blinded reader 4). Having overall non-significant p -values for the blinded reader evaluations, efficacy results for the all-patients-as-dosed population are expected to be similar to those of the ITT population due to the small difference in the number of patients in the two populations (see Section II.B.I).

III.B.I Additional Information for the Pivotal Studies:

Table 2 summarizes the sponsor's efficacy results for the proportion of all-patients-as-dosed whose post-dose images provided additional information over pre-dose image, using 3 point scale in the pivotal studies.

Table 2/ Reviewer's Table

Additional Information Provided Post-dose over Pre-dose, 3 point scale, all-patients-as-dosed Pivotal Studies (42,440-3A and 42,440-3B) ^{1 2}

Reader	Study 42,440-3A				Study 42,440-3B			
	SonoRx (N=93)		Cont. Agent (N=24)		SonoRx (N=94)		Cont. Agent (N=28)	
	% (95 % CI)	n	% (95 % CI)	n	% (95 % CI)	n	% (95 % CI)	n
Investigators	58 ³ (48.0, 68.1)	54	67 (47.8, 85.5)	16	76 ³ (66.8, 84.2)	71	54 (35.1, 72.0)	15
Blinded Reader 1	38 ³ (27.8, 47.5)	35	54 (34.2, 74.1)	13	62 ³ (51.9, 71.5)	58	71 (54.7, 88.2)	20
Blinded Reader 2	90 ³ (84.3, 96.3)	84	83 (68.4, 98.2)	20	38 ³ (28.5, 48.1)	36	43 (24.5, 61.2)	12
Blinded Reader 3	45 ³ (35.0, 55.3)	42	50 (30.0, 70.0)	12	65 ³ (55.2, 74.5)	61	43 (24.5, 61.2)	12
Blinded Reader 4	16 ³ (8.7, 23.6)	15	25 (7.7, 42.3)	6	52 ³ (45.3, 65.4)	52	61 (42.6, 78.8)	17

¹ Source: tables #: 3, p. 69; A.3, p. 74; B.3, p. 79; C.3, p. 84 and D.3, p.89 for Study -3A and tables # .1.2, p. 95; A.1.2, p. 100; B.1.2, p. 105; C.1.2, p.110; and D.1.2, p.115 For Study -3B.

² Values were imputed based on worst case scenario(i.e no additional information provided post-dose over pre-dose). Number of patients with imputed worst case data: Study -3A: Investigators (1 SonoRx patient), Blinded Readers 1 and 2 (8 SonoRx and 4 control agent patients); Blinded Reader 3 and 4 (29 SonoRx and 7 control agent patients) For Study -3B Investigators (1 SonoRx patient), Blinded Readers 1 and 2 (10 SonoRx and 5 control agent patients); Blinded Reader 3 and 4 (13 SonoRx and 7 control agent patients)

³P=0.0001 for testing SonoRx response against 1% using the binomial test

The sponsor claimed that the efficacy results reported in Table 2, for all-patients-as-dosed analysis, show that SonoRx enhanced images provided more information as compared with the unenhanced images in both studies. The sponsor's claim, as in the original submission, was based on testing the calculated response rates in Table 2 against 1%, using the binomial test. However, taking into account that the pivotal studies were designed (including sample size calculations) on the assumption that post-dose SonoRx enhanced images would provide additional information over the pre-dose image in 75% of the cases, the reported significant p-values for testing against 1% do not indicate SonoRx efficacy. This issue was discussed in detail in the Statistical review of July 18, 1997 (Section IV.A.II).

III.B.II Nature of Additional Information:

The sponsor classified the additional information of the post-dose SonoRx images in the clinical studies 42,440-3A and -3B, and noted that the most frequently seen on the post-dose SonoRx image was improved delineation of abdominal anatomy for the investigators and blinded readers 1 through 4.

Tables II.1 and II.2 of Attachment II present summary of the sponsor's results concerning the nature of additional information provided by the post-dose images for the per-protocol populations in studies 42,440-3A and 42,440-3B, respectively. Since the results are based on patients with additional information and not on the total number of patients as dosed, therefore no missing data imputation have been applied.

III.C. Safety:

The clinical program for SonoRx, according to the sponsor, was comprised of eight trials (Phase I: 42,440-1, -4,-5 and -6; uncontrolled Phase II: 42,440-2; and controlled Phase III: 42,440-3A, -3B and -7). Of the 448 dosed patients, a total of 385 patients received SonoRx and 138 patients received control agents or water.

The sponsor indicated that in Phase I, II and III studies combined, a total of 127 adverse events were reported in 84 patients. Out of the 385 patients who received SonoRx 68 patients (17.7%) experienced 107 adverse events and 16 of the 138 patients (11.6%) who received the control agent experienced 20 adverse events. The most frequently reported adverse events among SonoRx patients were diarrhea (6%), nausea (3%), abdominal pain (2%) and vomiting (2%).

IV. Overall Summary and Conclusion:

The sponsor in this amendment re-analyzed efficacy data related to the following endpoints: (i) the impact of gas shadowing artifact, and (ii) the presence of additional information in post-dose compared to pre-dose images. The purpose of the re-analysis was to address the exclusion of some patients from the analyses presented in the original submission and to evaluate the efficacy results using a 3 point scale instead of the 5 point scale.

Efficacy results for the impact of gas shadowing artifact for the pivotal studies, as summarized in Table 1, were evaluated for the all-patient-as-dosed populations. The sponsor's definition of this population is the same as the ITT population. For Study 42,440-3A, the efficacy results show that pre-dose images are significantly more obscured than post-dose images according to the assessment of the study investigators and only blinded reader 2. However, the results are in the opposite direction for blinded readers 3 and 4 and are not significant for blinded reader 1 evaluation. For Study 42,440-3B the results of the comparison were significantly in favor of SonoRx for all readers (investigators and blinded readers) except for blinded reader 2. The impact of gas shadowing artifact efficacy results of Table 1 are, to a large extent, invariant to the measurement scale, that is the 3 point scale versus the 5 point scale.

The results of comparing the impact of gas shadowing artifact for the SonoRx and Water images in the supportive study (Study 42,440-7) were done for the ITT population and by anatomical area. The results of this comparison, as presented in Table I.1 of Attachment I, show that according to the investigators' assessment, water images are significantly more obscured than SonoRx enhanced images for the stomach, gastric wall, duodenum and pancreatic tail and they are marginally significant ($p=0.049$) for the pancreatic duct. For the blinded reader's assessment, significant results were reported for images of the stomach, gastric wall and pylorus (blinded reader 1), pylorus (blinded reader 3) and the gastric wall (blinded reader 4). Efficacy results for the all-patients-as-dosed population are expected to be similar to their analogous for the ITT population, due to the small difference in the number of patients between the two populations (see Section II.B.I) and the overall non significant p-value for the blinded reader evaluations.

The sponsor's efficacy results for the additional information provided by SonoRx enhanced images as compared with the unenhanced images show only marginal results in favor of SonoRx enhanced images in Study 42,440-3B (Table 2). The sponsor's reported significant p-values for testing the observed response rates, SonoRx enhanced images provided additional information over the pre-dose image, against 1%. However, the results of this post-hoc testing do not indicate SonoRx efficacy since, due to chance factors alone, the response rate is expected to be near 50%. In addition, the pivotal studies were designed under the assumption that post-dose SonoRx enhanced images is expected to provide additional information over the pre-dose image in 75% of the cases.

The sponsor classified the additional information of the post-dose SonoRx images in the clinical studies 42,440-3A and 42,440-3B, and noted that the most frequently seen information on the post-dose SonoRx image was improved delineation of abdominal anatomy for the investigators and blinded readers 1 through 4.

V. Conclusion:

The primary goal of the sponsor's re-analyses in this amendment is to account for exclusion of some patients from the analyses of the original submission. The results of the re-analyses of the efficacy data of the two pivotal studies, support to some extent the sponsor's claim about SonoRx ability to decrease gas shadowing artifacts in one study (Study 42,440-3B). The impact of gas shadowing artifact was however a secondary endpoint in the original submission. For the primary endpoint, the rate in which SonoRx enhanced images provided additional information over that of the pre-dose (unenhanced image), the sponsor reported significant p-values in favor of SonoRx. However, the reported p-values do not support the SonoRx efficacy claim for this endpoint, since they are based on testing the response rate against 1% and not against the claimed 75% response rate which was used in the pivotal studies' design. The response rates for Study 42,440-3B, however, show some results (exceeding 50%) in favor of SonoRx for 4 out of the 5 readers. The 50% is the expected response rate due to chance factors alone. SonoRx efficacy results show wide variability in the response rates across readers within the same study and between the two pivotal studies for this endpoint.

In conclusion, from statistical perspective, the sponsor's re-analyses results provide some evidence in support of SonoRx for the impact of gas shadowing artifacts, and weak evidence for the amount of additional information in SonoRx enhanced images over pre-dose (unenhanced) images. However, the extent and utility of the additional information in the SonoRx images need to be judged by the Medical Division.

MS

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8/5/98

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Archival/ NDA 20,773

HFD-160/ Dr. Jones/ Dr. Yaes/ Ms. Jordan

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HFD-720/Dr. Welch /Dr. Sobhan /Dr. Al-Osh

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This review contains 16 pages of text and attachments.

TABLE I.1
IMPACT OF GAS SHADOWING ARTIFACT
Collapsed 3 Point Scale
Supportive Comparative Study (42,440-7): Intent-to-Treat Population

Anatomical Area	Investigators N ^a =53 ^b n ^c (%)			Blinded Reader 1 N=50 n (%)			Blinded Reader 2 N=50 n (%)			Blinded Reader 3 N=47 ^d n (%)			Blinded Reader 4 N=47 ^e n (%)		
	Water more obscured than SonoRx [®]	No Difference	SonoRx [®] more obscured than Water ^f	Water more obscured than SonoRx [®]	No Difference	SonoRx [®] more obscured than Water	Water more obscured than SonoRx [®]	No Difference	SonoRx [®] more obscured than Water	Water more obscured than SonoRx [®]	No Difference	SonoRx [®] more obscured than Water	Water more obscured than SonoRx [®]	No Difference	SonoRx [®] more obscured than Water
Stomach	24 (45)	21 (40)	8 (15)	22 (44)	20 (40)	8 (16)	12 (24)	25 (50)	13 (26)	13 (28)	29 (62)	5 (11)	16 (34)	25 (53)	6 (13)
	p=0.0070			p=0.0161			NS			NS			NS		
Gastric Wall	23 (43)	20 (38)	10 (19)	23 (46)	18 (36)	9 (18)	10 (20)	25 (50)	15 (30)	12 (26)	29 (62)	6 (13)	16 (34)	26 (55)	5 (11)
	p=0.0351			p=0.0201			NS			NS			p=0.0266		
Pylorus	14 (26)	29 (55)	10 (19)	16 (32)	29 (58)	5 (10)	11 (22)	27 (54)	12 (24)	18 (38)	22 (47)	7 (15)	13 (28)	25 (53)	9 (19)
	NS			p=0.0266			NS			p=0.0433			NS		
Duodenum	23 (43)	22 (42)	8 (15)	16 (32)	27 (54)	7 (14)	10 (20)	32 (64)	8 (16)	19 (40)	20 (43)	8 (17)	14 (30)	24 (51)	9 (19)
	p=0.0107			NS			NS			NS			NS		
Pancreatic Head	15 (28)	32 (60)	6 (11)	13 (26)	31 (62)	6 (12)	9 (18)	30 (60)	11 (22)	14 (30)	25 (53)	8 (17)	5 (11)	36 (77)	6 (13)
	NS			NS			NS			NS			NS		
Pancreatic Body	13 (25)	34 (64)	6 (11)	11 (22)	35 (70)	4 (8)	12 (24)	27 (54)	11 (22)	11 (23)	29 (62)	7 (15)	6 (13)	36 (77)	5 (11)
	NS			NS			NS			NS			NS		
Pancreatic Tail	20 (38)	31 (58)	2 (4)	10 (20)	36 (72)	4 (8)	10 (20)	34 (68)	6 (12)	14 (30)	26 (55)	7 (15)	16 (34)	22 (47)	9 (19)
	p=0.0001			NS			NS			NS			NS		
Pancreatic Duct	13 (25)	36 ^g (68)	4 (8)	9 (18)	36 (72)	5 (10)	10 (20)	32 (64)	8 (16)	12 (26)	28 (60)	7 (15)	13 (28)	26 (55)	8 (17)
	p=0.0490			NS			NS			NS			NS		

Table data derived from Tables I, A.1, B.1, C.1, D.1 (Appendix III).
Refer to Table P in the original clinical study report (NDA Volume 1.34 [Item 8], or Volume 1.55 [Item 10]) for patient evaluability information.

^a Number of Intent-to-treat patients.
^b Number of patients with Images rated as indicated.
^c 2 patients were included with worst case data for SonoRx[®] images as defined in Section 2.1.2.1.
^d 3 patients were included with worst case data for both SonoRx[®] and water images as defined in Section 2.1.2.1.
^e Water enhanced images were more obscured from gas shadowing than were SonoRx[®] images.
^f SonoRx[®] enhanced images were more obscured from gas shadowing than were water images.
^g 8 patients were included with worst case data for both SonoRx[®] and water as defined in Section 2.1.2.1.
^h p<0.05 denotes statistical significance in the difference in the proportion of water images more obscured from gas shadowing than SonoRx[®] images and vice versa (Sign test)
(NS denotes not significant p>0.05).

Attachment II:

TABLE II.1								
NATURE OF ADDITIONAL INFORMATION PROVIDED POST-DOSE OVER PRE-DOSE SonoRx® and Control Agent Patients in Pivotal Controlled Study 42,440-3A Per-Protocol Population ^a								
Reader	SonoRx®				Control Agent			
	Improved delineation of abdominal anatomy n/N ^b (%) ^c	Improved confidence in exclusion of pathology n/N ^b (%) ^c	Improved delineation of pathology n/N ^b (%) ^c	Improved evaluation of extent of disease or pathology n/N ^b (%) ^c	Improved delineation of abdominal anatomy n/N ^b (%) ^c	Improved confidence in exclusion of pathology n/N ^b (%) ^c	Improved delineation of pathology n/N ^b (%) ^c	Improved evaluation of extent of disease or pathology n/N ^b (%) ^c
Investigators	32/46 (70)	17/46 (37)	19/46 (41)	5/46 (11)	11/14 (79)	4/14 (29)	7/14 (50)	5/14 (36)
Blinded Reader 1	23/32 (72)	15/32 (47)	9/32 (28)	1/32 (3)	12/13 (92)	6/13 (46)	2/13 (15)	1/13 (8)
Blinded Reader 2	72/72 (100)	72/72 (100)	0/72	0/72	19/19 (100)	19/19 (100)	2/19 (11)	2/19 (11)
Blinded Reader 3	40/42 (95)	15/42 (36)	5/42 (12)	0/42	11/12 (92)	4/12 (33)	1/12 (8)	0
Blinded Reader 4	15/15 (100)	0/15	0/15	0/15	6/6 (100)	0	0	0

Table data derived from 42,440-3A clinical report.

^a No data was imputed due to the type of data collected for this analysis.
^b n=number of patients with respective nature of additional information.
N=Number of per-protocol patients with additional information.
^c Percentages are relative to the total number of patients with additional information as identified by each reader.

Investigators/blinded readers may have indicated more than one response per patient.

Source: Sponsor's submission of April 29, 1998, Table H.1, p.43

TABLE II.2

**NATURE OF ADDITIONAL INFORMATION PROVIDED POST-DOSE OVER PRE-DOSE
SonoRx® and Control Agent Patients in Pivotal Controlled Study 42,440-3B
Per-Protocol Population***

Reader	SonoRx®				Control Agent			
	Improved delineation of abdominal anatomy n/N ^b (%) ^c	Improved confidence in exclusion of pathology n/N ^b (%) ^c	Improved delineation of pathology n/N ^b (%) ^c	Improved evaluation of extent of disease or pathology n/N ^b (%) ^c	Improved delineation of abdominal anatomy n/N ^b (%) ^c	Improved confidence in exclusion of pathology n/N ^b (%) ^c	Improved delineation of pathology n/N ^b (%) ^c	Improved evaluation of extent of disease or pathology n/N ^b (%) ^c
Investigators	57/66 (86)	39/66 (59)	32/66 (48)	17/66 (26)	12/14 (86)	10/14 (71)	7/14 (50)	4/14 (29)
Blinded Reader 1	55/55 (100)	37/55 (67)	9/55 (16)	7/55 (13)	19/19 (100)	7/19 (37)	4/19 (21)	2/19 (11)
Blinded Reader 2	30/33 (91)	10/33 (30)	5/33 (15)	2/33 (6)	10/11 (91)	5/11 (45)	1/11 (9)	0
Blinded Reader 3	56/61 (92)	45/61 (74)	17/61 (28)	12/61 (20)	11/12 (92)	6/12 (50)	7/12 (58)	5/12 (42)
Blinded Reader 4	52/52 (100)	24/52 (46)	7/52 (14)	2/52 (4)	17/17 (100)	11/17 (65)	3/17 (18)	0

Table data derived from 42,440-3B clinical report.

* No data was imputed due to the type of data collected for this analysis.

^b n=number of patients with respective nature of additional information.

N=Number of per-protocol patients with additional information.

^c Percentages are relative to the total number of patients with additional information as identified by each reader.

Investigators/blinded readers may have indicated more than one response per patient.

Source: Sponsor's submission of April 29, 1998, Table H.2, p.44

STATISTICAL REVIEW AND EVALUATION

Date JUL 18 1997

NDA: 20-773
Drug Class: Class 3S
Drug name: SonoRx® (simethicone coated cellulose suspension)
Applicant: Bracco Diagnostics Inc.
Indication: An oral contrast agent for use in the delineation of abdominal anatomy and to assist in the detection or exclusion of pathology in patient undergoing ultrasound
Documents Reviewed: Volumes 1.1 and 1.37 through 1.57 dated September 30, 1996 and one volume (no number) dated January 15, 1997
Medical Officer: Robert Yaes, M.D. HFD-160
Statistical Reviewer: Mohamed Al-Osh, Ph.D., HFD-720
45 Day Meeting Date: 11/20/1996

Key Words: Ultrasound Image Assessment, Multiple Blinded Reader, Sensitivity and Specificity, Matched Pairs, McNemar Test, Marginal Homogeneity Test, Kappa Statistics.

Major Review Issues:

- * The 'Intent-to-Treat' population was not specifically defined; consequently the sponsor's analyses did not include all eligible images.
- * The formulation of the primary efficacy question, in the Case Report Form, was not appropriate, and thus the data analyzed did not adequately address efficacy.
- * The first two blinded readers were not provided with all information as planned in the study protocol.
- * Two additional blinded readers were employed after results of the first two blinded readers were found unacceptable,
- * The sponsor's post-hoc analysis tested the response rate against 1%, whereas the study was planned on a 75% threshold.
- * Sensitivity and specificity estimates of the pre-dose and post-dose images are subject to a large bias due to the way in which different comparative modalities were used for pathology diagnosis.

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I. Introduction:

SonoRx is an orally administered ultrasound contrast agent, for use in the abdominal ultrasound imaging indicated for the delineation of anatomy and the detection or exclusion of pathology in the upper abdomen, including the upper gastrointestinal tract. The sponsor claimed that preclinical and clinical studies have shown that SonoRx has the capability to adsorb and displace stomach and bowel gas, helping to eliminate the shadowing artifacts typically present in abdominal ultrasound, thus enabling improved visualization of stomach, pancreas and duodenum, and consequently, allowing for improved detection and /or exclusion of pathology.

To support their claim of safety and efficacy of SonoRx, the sponsor submitted the results of 4 Phase I studies (42,440-1 42,440-4 through 42,440-6), one Phase II study (42,440-2) and 3 Phase III studies (42,440-3A, 42,440-3B, both pivotal, and one supportive study, 42,440-7). In addition, the sponsor summarized meetings with the agency on 4/7/93, 8/5/94 and 5/14/96.

This review mainly addresses the 3 Phase III studies (studies: 42,440 -3A /-3B and 42,440-7). Section II discusses the design of these studies. Section III presents the sponsor's efficacy results and this reviewer's comments on them. Section IV presents the reviewer's overall comments and analyses in light of the comments in the previous section. Section V considers the safety and the pediatric use. Finally, Section VI presents an overall summary and conclusion.

II. Design of Phase III Studies:

Table 1 presents an overall summary of the sponsor's Phase III studies submitted in support of their claim of efficacy. The two pivotal studies (42,440-3A, 42,440-3B) were conducted, over the periods 6/94 - 12/94 and 7/94 - 11/94, respectively, in patients highly suspected of having abdominal pathology. The two studies were identical in design (same Protocol and Case Report Forms). They were randomized, double blind, Phase III, U.S. multicenter (10 and 8 sites respectively) studies. Each site was to enroll 13 patients to be randomly assigned to SonoRx (10 patients) and to a control agent (3 patients). The sponsor claimed that the purpose of including the control agent, flavored colored water, was for safety comparison only and was not intended for statistical comparison of efficacy data.

The main criteria for inclusion in the study were: Patients of 18 years of age or more who were highly suspected of upper abdominal pathology and had been referred for abdominal ultrasound imaging after undergoing a comparative diagnostic modality (other than ultrasound).

Table 1: Summary of the Sponsor's Phase III Studies

Study # (Protocol)	No. of Centers	Design ¹	Dose a) Active b) Control	Type of Control	No. Pat's - Total - Eval. - ITT ^{2,3}	Subgroups: M/F ³
42.440-3A	10	DB, R, RI, P	a) 400 mL b) 400 mL	control agent ⁴	95:24 * 79:21 93:24	43/50: 11/13
42.440-3B	8	DB, R, RI, P	a) 400 mL b) 400 mL	control agent ⁴	95:28 88:25 94:28	56/38: 12/16
42,440-7 (Supportive Study)	6	SB, R, CO	a) 400 mL b) 400 mL	water	53:53 48:48 51:53	32/21

¹ DB: Double Blind, SB: Single Blind (Investigator Blinded), R: Randomized Administration, RI: Images Randomized for Blinded Reader, P: parallel Design, CO: Cross-over design

² ITT: Intent to Treat

³ Numbers before the ':' sign are for SonoRx and after ':' sign for the control agent

⁴ The control agent was used for safety only: its formulation was identical to SonoRx excluding: simethicone-coated cellulose, xanthan gum, medical anti-foaming agent A [simethicone U.S.P.] and sodium lauryl sulfate)

* Each study site was to study 13 patients, 10 to receive SonoRx and 3 to receive a control agent.

Upon meeting the entry criteria, patients were randomized to receive a 400 mL single dose of either SonoRx or the control agent. Selection of this dose was based on the results of Phase I and Phase II data. Patients were to fast for a minimum of 4 hours prior to the pre-dose ultrasound evaluation. Each patient was to ingest the study dose (SonoRx or the control agent) within 15 minutes. Post-dose imaging was to start within 10 minutes of administration of the entire dose. The pre-dose and post-dose ultrasound procedures associated with each administration were to be completed in approximately 90 minutes. Patients were to be monitored for safety through 24 hours post-dosing.

Study 42,440-7 was conducted as a supportive Phase III, multi-center (6 sites), randomized, single-blind (investigator blinded), comparative, placebo control, crossover study in patients highly suspected of having abdominal pathology. This study was conducted over the period 10/94 through 2/95 with inclusion criteria similar to those of the pivotal studies.

Patients were randomly assigned to receive both SonoRx and water in a crossover fashion, with the order of administration randomized. The time between administration of the two study agents was 1 to 4 days. Other aspects of the trial such as dose, drug administration and imaging were similar to those of the pivotal studies.

II.A. Study Objectives and Evaluation Parameters:

The objectives of the two pivotal studies (42,440-3A, 42,440-3B) were:

- 1) to determine the efficacy of SonoRx in the delineation of abdominal anatomy and to assist in the detection or exclusion of pathology in patients undergoing abdominal ultrasound; and
- 2) to expand the initial safety profile established in Phase I and Phase II studies.

The primary efficacy parameter was whether the post-SonoRx dose images provided additional information over the pre-dose images (with two possible answers: 'Yes' or 'No' as indicated in Question # 13 of the Case Report Form). The secondary efficacy parameters include: (i) change in the delineation of abdominal anatomy post-dose vs. pre-dose, (ii) change in the investigator's degree of confidence in the post-dose vs. pre-dose diagnosis/pathologic process, (iii) impact of gas shadowing artifact, and (iv) comparison of the pathology diagnostic information provided by the results of pre-dose and post-dose SonoRx images with those of other modalities currently in use. The sponsor stated, in the inclusion criteria, that these modalities included, but were not limited to, computed tomography (CT), magnetic resonance imaging (MRI), nuclear medicine imaging, endoscopy, laparoscopy, standard abdominal x-ray, biopsy and/or surgery. This diagnostic comparisons were to be made on the basis of the sensitivity /specificity estimates for pre- and post-dose images.

The objectives of the supportive study (42,440-7) were the evaluation of the safety and efficacy of SonoRx vs. water, instead of vs. pre-dose as in the pivotal studies, in patients highly suspected of having abdominal pathology. For this study, the primary efficacy parameter was whether the post-SonoRx images provided more information over the post-water images. The sponsor claimed that pre-dose images were obtained for all patients for the purpose of patient management and were not part of this clinical trial and that only post-dose images were evaluated in this study.

SonoRx efficacy evaluations were to be conducted, as the sponsor claimed, based on data collected from the investigators at their sites as well as from two independent blinded readers, in each study, unaffiliated with any of the study centers. The blinded readers were to assess both static and video images. The sponsor, however, claimed that they were advised, as a result of consultation with some investigators, that looking at video images during ultrasound interpretation was not typically done and that the static images alone should be sufficient. Consequently, the sponsor provided Blinded Readers 1 and 2 of each study with static images only.

Following analyses of the data of the two studies in June 1995, the sponsor found that the results of these studies were not consistent with those of the Phase II which did not employ blinded readers, Study # 42,440-2. Based on this, the sponsor decided, after seeking experts' opinions for possible explanations for the inconsistency in the efficacy results, to have two additional blinded readings for each of the pivotal studies as well as the supportive study. The new readers, Blinded Readers 3 and 4, were provided with both the static and video images, were given standardized training prior to image evaluation, and were instructed to limit the reading time to 8 hours in a 24 hour period, with a break after 4 hours.

For safety evaluation, the protocols called for patient monitoring through evaluation of medical history, physical examination, vital signs and clinical laboratory tests (blood and urine samples). These evaluations were to be conducted prior and after the administration of the study drug.

II.B. Imaging Procedure:

Each study site was to use the same ultrasound unit, transducer, and imaging parameters for each patient's pre- and post-dose scans. All abdominal ultrasound scanning were to be performed by sonographer(s) at their sites. The transducer providing the best resolution for each patient's body habitus was to be utilized by the sonographer for both pre- and post-dose scans. The parameters used for all imaging acquisitions were to be recorded on the appropriate Case Report Form.

Each patient was to be imaged in the: supine, left and right posterior oblique views to obtain optimal images of the anatomy listed below. The sonographer used his/her clinical judgment to determine the best position to obtain optimal images. The sponsor stated that investigators were instructed to obtain both static and video images for each patient.

Pre-dose and post-dose ultrasound images were to be obtained for the following abdominal anatomy: stomach, left kidney, gastric wall, left renal artery, pylorus, splenic vein, duodenum, superior mesenteric artery, pancreas (head, body, tail, duct), common bile duct (CBD), abdominal aorta, para-aortic lymph nodes, liver, and gallbladder. In addition, images for the gallbladder were to be taken in order to evaluate the effect of both SonoRx and the control agent on gallbladder contraction.

II.C. Image Evaluation:

Pre- and post- dose ultrasound images were evaluated by the individual site investigators and were also reviewed by the blinded readers. The evaluation was based on the following criteria: •Technical quality •Delineation of specified abdominal anatomy •Ultrasound diagnosis •Level of confidence in making ultrasound diagnosis •Overall effect of gas shadowing artifacts •Potential change in patient's future management/therapy •Potential change in patient diagnosis (investigators only) •Additional post-dose information provided over pre-dose (and/or vice-versa) •Information provided by pre-dose image not seen post-dose •Gallbladder contraction (investigators only).

II.C.I. Investigators' Evaluation

Both pre- and post-dose images (static and video) for each patient were evaluated by the investigator for all patients at his/her site. Images for each patient were placed side by side and reviewed. Each investigator was blinded only to the agent administered and had knowledge of patient identity, medical history, clinical profile and presumptive diagnosis. The investigators' image evaluations comprise the investigators' readings for the efficacy analysis.

II.C.II. Blinded Readers' Evaluation

The sponsor's approach for this evaluation was first to have all images be evaluated by a radiologist (technical reviewer) to ensure their technical adequacy and adherence to the protocol specifications. Then images deemed technically adequate were to be sent to the blinded readers for evaluation. The sponsor stated that throughout the evaluation process, the blinded readers had no knowledge of the study agent administered or patient's clinical information. Blinded readers were to perform both unpaired and paired readings on the pre-dose and post-dose images for each patient and by using identical Case Report Forms which included an Individual Image Evaluation section (unpaired readings) and a Comparison Image Evaluation section (paired readings). Note that the primary endpoint (whether the post-dose images provided additional information over the pre-dose images) was based on the paired readings. The secondary endpoints (delineation of abdominal anatomy, pre-dose and post-dose) were based on the unpaired readings.

Blinded Readers 1 and 2 read all static images they assessed as technically acceptable. For the Individual Image Evaluation, the unpaired, unlabeled pre- and post-dose images were combined into one group and the blinded readers were instructed to evaluate each film by randomization number.

After completion of this stage, a reader's assistant matched the pre-dose and post-dose images for the paired readings. Then the sponsor instructed the blinded readers to complete the Comparison Image Evaluation for the paired comparison.

Blinded Readers 3 and 4 reviewed both static and video images which were technically acceptable from patients considered evaluable for the per-protocol efficacy analysis. The image evaluation process for these readers, aside from having additional video images, were similar to those of Blinded Readers 1 and 2.

III. Sponsor's Statistical Methods and Data Analyses with Reviewer's Comments:

III.A. Sample Size Determination:

The sponsor based their sample size calculations in the pivotal studies on requiring that the 95% confidence intervals to be within 10% of the observed percentages of interest, that is the rate for which SonoRx post-dose images provide additional information over the pre-dose images. By assuming the actual rate is greater than 75%, the sponsor concluded that a minimum of 75 SonoRx patients were needed to result in appropriate confidence intervals.

In addition, 25 patients (approximately 20%) were to be administered the control agent. The sponsor claimed that this assignment was intended for purposes of safety comparison only and the study was not powered for efficacy comparisons between the two treatment groups.

For the supportive Study, the sample size calculation was based on testing the null hypothesis that the proportion of SonoRx images providing additional diagnostic information was the same as that of water images against the alternative hypothesis that the SonoRx images provide additional information in at least 70% of the cases. The sponsor concluded that a sample size of at least 36 evaluable patients was needed to demonstrate efficacy that 70% is significantly different from the null hypothesis of no difference (50%) for a one-sided test of hypothesis, $\alpha = 0.05$ and power = 80%. The sponsor commented that although the sample size was based on a one-sided test of hypothesis, the sample size in this study provided at least 80% power for a two-sided test (at least 42 evaluable patients were needed). Therefore, p-values based on two-sided tests are presented.

III.B. Populations Analyzed:

An Intent-To-Treat (ITT) population was defined as patients who received any volume of either SonoRx or control agent and had images of acceptable technical quality. An ITT analysis was performed for the primary and secondary efficacy parameters based on data collected from the investigators and Blinded Readers 1 and 2.

The sponsor stated that only images of patients who fulfilled the per-protocol analysis criteria (defined below) were inadvertently sent for Blinded Readers 3 and 4. The sponsor's ITT analysis for these blinded readers was carried out by imputing for patients with missing data the following 'worse case' outcomes: (i) no additional information provided by post-dose compared to pre-dose for SonoRx patients, and (ii) additional information provided by post-dose compared to pre-dose for control agent patients. The sponsor stated that there were total of 19 patients in the two studies (16 SonoRx, 3 control agent) whose images were not sent to Blinded Readers 3 and 4. For these readers the sponsor carried out analysis on ITT population only for the primary endpoint.

The per-protocol population was defined as patients who underwent pre-dose and post-dose evaluations, had images of acceptable technical quality, received a comparative diagnosis by an accepted modality (specified in study protocol), ingested at least 350 mL of SonoRx or control agent, and had no significant protocol violations. A per-protocol analysis was performed for the primary and secondary efficacy parameters based on data collected from the investigators and all four blinded readers.

The statistical plan for the per-protocol analysis originally included only those patients who ingested exactly 400 mL of the study agent. However, the sponsor decided, to maintain consistency with Protocol No. 42,440-7, to include patients who had ingested equal to or greater than 350 mL. This criterion added 3 patients (2 in Study 42,440-3A and 1 in Study 42,440-3B) to the per-protocol analysis as compared with the original statistical plan.

For the supportive study the sponsor remarked that 2 patients did not receive SonoRx. Image evaluation for these 2 patients were categorized as "not done" for the ITT analysis because the water images of these patients were not sent to the readers for evaluation. As in the pivotal studies, instead of sending all available technically acceptable images to Blinded Readers 3 and 4, only images of patients who fulfilled the per-protocol population criteria as defined before were sent. There were five patients (3 ingested <350 mL and 2 did not receive both agents) whose images were not sent. The

sponsor's claimed that their intent-to-treat analysis for the primary efficacy parameter was done with the "worst case" result imputed (i.e., water provided more diagnostic information as compared with SonoRx) for the three patients who ingested <350 mL. An intent-to-treat analysis was not performed on the secondary efficacy data collected from Blinded Readers 3 and 4. A per-protocol analysis was performed for the primary and secondary efficacy parameters based on the data collected for the investigators and all four blinded readers.

Table 2 presents the patients' disposition in Phase III studies, classified by the intent-to-treat and per-protocol populations. The sponsor indicated that there were 3 patients (1 SonoRx and 2 control agent) at one site (Site # 9115) in Study 42,440-3A who did not receive the appropriate study agent according to the randomization schedule. These patients were included in the analyses based on the agent they received rather than the randomization schedule assignment.

Reviewer's Comments on the Number of Patients Analyzed:

Table 2 shows great variability in the numbers of patients available for analyses whether one considers the intent-to-treat or the per-protocol populations. Study 42,440-3A, in particular, shows that whereas the number of patients included in the ITT analysis was 93 for the investigators, it was 85 for Blinded Readers 1 and 2 and 76 for Blinded Readers 3 and 4. Considering the per-protocol analysis, the corresponding numbers of patients were 79, 73 and 64, respectively. Variability in the number of patients in the other two studies (42,440-3A and 42,440-7) was not as large as that of the first study.

This variability in the number of patients available for analyses can be attributed, as can be seen from Table 2, to having videotapes not readable or missing or having images of unacceptable technical quality. As discussed previously, the sponsor set various stages for evaluating the images for technical acceptability. According to the sponsor, all images were first evaluated for technical acceptability by the investigators. Then, prior to blinded readings, all images were evaluated for technical acceptability by a technical reviewer. Thereafter, each blinded reader evaluated the technical quality of those images deemed acceptable by the technical reviewer. These different image evaluation stages, in addition to not sending the videotape images to the first two blinded readers, made it difficult to check for data consistency concerning the number of patients available for analyses.

Reviewer's Table 2/ Sponsor's Results
Numbers of Intent-to-treat and Evaluable Patients for Efficacy

	Pivotal studies				Supportive study 42.440-7 SonoRx and Water
	42.440-3A		42.440-3B		
	SonoRx	Control	SonoRx	Control	
Patients Disposition					
Patients enrolled	95	24	95	28	53
Patients dosed	93	24	94	28	53 ^l
Efficacy Analyses					
Intent-to-Treat Population					
-Investigators Readings ^a					
# pat.s evaluable for analysis	93	24	94	24	53
-Blinded Readers 1-4 ^b					
Patients excluded:					
Unacceptable technical quality	8		9 ^g		1
Miscoding of images			1		2 ^m
Patients included in the analysis					
Blinded Readers 1 and 2	85	24	84	24	50
Videotapes not readable/ missing	9				3
Blinded Readers 3 and 4	76	24	85	24	47
Per-protocol Population					
Patients dosed	93	24	94	28	53
- Investigators Readings ^a					
Patients excluded due to:					
Ingested <350 mL of SonoRx ^{g, b}	13 ^c	3 ^e	3 ^h	3 ^k	5 ^k
Post-dose imaging not performed	1 ^d		3 ⁱ		
# Pat.s evaluable for analysis	79	21	88	25	48
-Blinded Readers					
Unacceptable technical quality (see footnotes d,e)	8	2	9 ^g	3 ^k	1
Blinded Readers 1 and 2 (Exc. 4 unaccep. In -7)	73	19	80 (78) ^j	22	43 (47) ^l
Blinded Readers 3 and 4 (excl. 9 in - 3A and 3 in -7 whose videotapes not readable/ missing)	64	17 ^f	81	21 ^k	44

Source: Sponsor Table Q, pp. 97-98 . Table AH, p.125 and Table AJ. p. 133 , Table AK, p. 134, Vol. 1.37 with some modifications and footnotes by the reviewer.

^a All images were evaluated for technical acceptability by the investigators

^b All images were evaluated for technical acceptability by a technical reviewer prior to the blinded readings, thereafter blinded readers evaluated technical quality which deemed acceptable by the technical reviewer

^c This number was reported 12 , instead of 13, when counting number of patients analyzed for the blinded readers.

^d This patient was not reported when counting the number of patients analyzed for the blinded readers

^e the investigator was not blinded for one patient

^f videos were not readable for two patients.

^g Includes 2 patients with pre-dose images rated not acceptable by Blinded Reader 2 . These patients included in the ITT analysis but excluded from the per protocol analysis

^h This number was reported 2, instead of 3, when counting number of patients analyzed for the blinded readers.

ⁱ Post-dose image not performed for one patient and 2 patients were excluded for other reasons (1 drug left standing < 2 minutes and 1 for NBO <4 hours).

^j Second number for Blinded Reader 2.

^k patients were excluded for different reasons which the sponsor explained.

^l Two patients received only water (first administration).

^m Water images not provided to reader.

Having the images evaluated at different stages for technical acceptability is, in light of the imprecise definition of the ITT population, the source for the variability observed in the numbers of patients. For example, in accounting for the number of patients in the ITT population in Study 42,440-3A, out of the 93 patients with acceptable quality according to the investigators, 8 were excluded from the blinded readers evaluation due to unacceptable technical quality. The sponsor listed these patients but did not give details about who excluded them. Thereafter, out of the remaining 85 patients, 9 patients (#'s : 109, 110, 111, 114, 1005, 1701, 1702, 1703 and 1707) were excluded from Blinded Readers 3 and 4's assessments because their videotapes were not readable or missing, the sponsor did not give details about the numbers of not readable and missing. The per-protocol population in this study was reduced further by 13 patients (12 SonoRx and one control) whose images the sponsor did not send to the blinded readers for evaluations.

Furthermore, there are a few unexplained cases of patient disposition in Study 42,440-3A. The sponsor mentioned that post-dose image was not performed for patient # 1512 when accounting for investigators' readings, but this patient was also listed among the patients with unacceptable technical quality. Similarly, patient # 1704 was listed among patients of unacceptable technical quality when accounting for the blinded readers (ITT analysis) but listed among the patients excluded because they ingested <350 in investigators' readings (per protocol analysis). Similarly, for Study 42,440-3B, the sponsor did not explain the difference in the number of patients included in the analyses for Blinded Readers 1&2 (84) vs those for blinded reader 3&4 (85). Also, when considering the number of patients per protocol analysis, the sponsor listed 3 patients who ingested <350 mL of SonoRx when considering the investigator readings, but listed only 2 such patients for the blinded reader readings. However, these are minor deviations and might be attributable to having multiple reasons for exclusion from the analysis, and the sponsor might have listed them under different causes in different places.

III.C. Statistical Methods for Efficacy and Safety Evaluation:

III.C.I. Primary Efficacy Parameters:

For each pivotal study, the sponsor's analysis of the primary endpoint, the proportion of SonoRx patients for which the post-dose images provided additional information over pre-dose images, which I will denote as 'the proportion of success' consisted of:

- (i) a 95% binomial confidence interval, using the normal approximation, for the proportion of success.
- (ii) binomial tests for the proportion of success against 1% and against 50%. The sponsor considered

the testing as a supplementary analysis and claimed that testing against the 50% was used simply for consistency with the supportive study (Study 42,440-7) and was not used as an indication for efficacy.

The primary efficacy parameter was also summarized by sex, race, age groups, body surface area and by study site. In addition, a chi-square test was performed to assess site differences for the primary endpoint.

The sponsor also performed a pairwise agreement analysis for the blinded readers' assessments of the primary efficacy parameter by calculating the Kappa statistic (Kappa correlation) for each pair of blinded readers' assessments for the number of patients in common with non-missing results.

III.C.II. Secondary Efficacy Analyses:

The sponsor analyses for the secondary endpoints in each study consisted of the following:

- The Wilcoxon signed rank test was used for testing if there is statistically significant improvement in the delineation of abdominal anatomy as well as for testing for reduction of gas shadowing artifact (post-dose minus pre-dose).
- The paired t-test was used to test change in the investigator's degree of confidence (0-100%) in the post-dose diagnosis/pathologic process versus the pre-dose diagnosis/pathologic process. A 95% confidence interval around the difference was also constructed.

The sponsor also calculated the sensitivity and specificity rates for both the unenhanced (pre-dose) images and SonoRx-enhanced images (post-dose) with respect to other modalities currently (see Section II.A for partial listing). The sponsor's estimates of the sensitivity and specificity were based on the investigators' response to whether or not pathology was identified from the comparative procedure conducted prior to the start of the study and, if identified, whether the same pathology was found upon examination of pre-dose and post-dose images. The sensitivity and specificity estimates for the blinded readers were based on the sponsor's evaluation of Case Report Form data rather than the blinded readers' actual assessment of diagnostic information obtained from comparative modalities.

III.C.III. Safety :

The sponsor considered for safety analysis all patients who enrolled in the study and ingested any volume of SonoRx or the control agent. Safety analyses consisted of : (1) comparison of post-dose

physical exams and pre-dose exams to determine if changes had occurred, (2) comparison of pre-dose versus post-dose electrocardiogram (ECG) results from two investigational sites, (No. 9115 and 9367 in Study 42,440-A) which performed ECGs, to determine if there was any treatment effect, (3) comparison of adverse events by treatment groups (i.e. SonoRx and control agent) using Pearson's chi-squared test, and (4)-comparison of pre-dose and post-dose vital signs via graphical methods.

In addition to the above mentioned analyses the sponsor summarized the demographics data (age, weight, height, sex, race, body surface area) for all dosed patients by treatment group (SonoRx and control agent) and included the mean, standard deviation and range. Also, medical history results for all patients who ingested SonoRx or the control agent were tabulated and summarized using simple descriptive statistics.

III.D. Sponsor's Efficacy Results for Phase III Studies and Reviewer's Comments:

III.D.I. Pivotal Studies:

Subsection III.D.I.A presents the sponsor's primary and secondary efficacy results for the SonoRx patients in the two pivotal studies for the ITT and the per-protocol populations. Assessment of the blinded readers' agreement concerning these results is presented in Subsection III.D.I.B. Subsection III.D.I.C discusses the SonoRx secondary efficacy results in the pivotal studies and finally Subsection III.D.I.D presents the primary efficacy results for control patients in these studies. Reviewer's comments follow the sponsor's results in each subsection.

III.D.I.A. SonoRx Primary Efficacy Results: Additional Post-dose Information Provided Over Pre-dose

Tables 3 and 4 present, respectively, the sponsor's efficacy results for the primary endpoint, the percentage of patients with post-dose image providing additional information over pre-dose image, for the ITT and the per-protocol populations.

Reviewer's Table 3/ Sponsor's Results
Primary Efficacy Results: Percentage of Patients with Post-dose Image Providing Additional Information Over Pre-dose Image/ (Pivotal Studies, SonoRx Patients, ITT Population)

Reader	Study 42.440-3A		Study 42.440-3B	
	n/Na (%)	(95% CI) p-value: testing vs 1% (vs 50%) ^b	n/N (%)	(95% CI) p-value: testing vs 1% (vs 50%) ^b
Investigators	54 / 93 (58)	(48.0, 68.1) p=0.0001 (0.1462)	71 / 94 (76)	(66.8, 84.2) p=0.0001 (0.0001)
Blinded Reader 1	35 / 85 (41)	(30.7, 51.6) p=0.0001 (0.1284)	58 / 84 (69)	(59.2, 78.9) p=0.0001 (0.0006)
Blinded Reader 2	84 / 85 (99)	(96.5, 100.0) p=0.0001 (0.0001) ✓	36 / 84 (43)	(32.3, 53.4) p=0.0001 (0.2299)
Blinded Reader 3	42 / 76 ^c (55)	(44.1, 66.4) p=0.0001 (0.4422)	61 / 85 ^d (72)	(62.2, 81.3) p=0.0001 (0.0001)
Blinded Reader 4	15 / 76 ^c (20)	(10.8, 28.7) p=0.0001 (0.0001)* ✓	52 / 85 ^d (61)	(50.8, 71.5) p=0.0001 (0.050)

Source: Sponsor Table V, p. 107, Vol. 1.37, with some modifications; tables 10.1, A.2.1, B.2.1, C.2.1, D.2.1 Vol.1.46 and tables 10.1, A.2.1, B.2.1, C.2.1, D.2.1 Vol. 1.51.

- a n=number of patients with additional information provided post-dose over pre-dose and N=number of intent-to-treat patients.
 - b Normal approximation was used for constructing the 95% confidence interval and the binomial test was used for the p-values.
 - c Includes 12 patients from 42,440-3A study not evaluated by Blinded Readers 3 and 4 whose images were assigned "worst case" scenario responses for the primary efficacy parameter (i.e.. post-dose did not provide additional information over pre-dose).
 - d Includes 4 patients from 42,440-3B study not evaluated by Blinded Readers 3 and 4 whose images were assigned "worst case" scenario responses for the primary efficacy parameter (i.e..post-dose did not provide additional information over pre-dose).
- * Significantly less than 50%.

Reviewer's Table 4/ Sponsor's Results
Primary Efficacy Results: Percentage of Patients with Post-dose Image Providing Additional Information Over Pre-dose Image (Pivotal Studies, SonoRx Patients, Per-protocol Population)

Reader	Study 42,440-3A		Study 42.440-3B	
	n/Na (%)	(95% CI) p-value: testing vs 1% (vs 50%) ^b	n/N (%)	(95% CI) p-value: testing vs 1% (vs 50%) ^b
Investigators	46 / 79 (58)	(47.4, 69.1) p=0.0001 (0.1766)	66 / 88 (75)	(66.0, 84.0) p=0.0001 (0.0001)
Blinded Reader 1	32 / 73 (44)	(32.5, 55.2) p=0.0001 (0.3492)	55 / 80 (69)	(58.6, 78.9) p=0.0001 (0.0011)
Blinded Reader 2	72 / 79 (99)	(96.0, 100.0) p=0.0001 (0.0001)	33 / 78 (42)	(31.3, 53.3) p=0.0001 (0.2127)
Blinded Reader 3	42 / 64 (66)	(54.0, 77.3) p=0.0001 (0.0169) ✓	61 / 81 (75)	(65.9, 84.7) p=0.0001 (0.0001)
Blinded Reader 4	15 / 64 (23)	(13.1, 33.8) p=0.0001 (0.0001) ✓	52 / 81 (64)	(53.8, 74.6) p=0.0001 (0.014) ✓

Source: Sponsor Table R, p. 99, Vol. 1.37; Tables 10.1, A.2.1, B.2.1, Vol. 1.45 and Tables C.2.1, D.2.1 Vol. 1.46.

- a n=number of patients with additional information provided post-dose over pre-dose and N=number of per-protocol patients
- b Normal approximation was used for constructing the 95% confidence interval and the binomial test was used for the p-values.