

***Lifecor Biomedical Inc., INTERGEL Adhesion Prevention Solution
Summary Clinical Review of G950025s26 and P990015.***

Intergel (IG), a.k.a. LubriCoat Gel, 0.5% Ferric Hyaluronate Gel, is a sterile, aqueous solution of sodium hyaluronate ionically cross-linked with ferric chloride. Lifecor Biomedical Inc. developed Intergel for the reduction of post-operative peritoneal adhesion formation. Initial clinical study of Intergel for this indication was a single center, 300cc Intergel or 300cc Lactated Ringers (LR: control) randomized pilot study conducted by one investigator to evaluate the method of device use and the preliminary safety of applying 300cc of Intergel in female patients undergoing laparotomy for infertility. Effect on adhesion burden was evaluated; effect on fertility was not evaluated. Pilot study outcome (G950025 supplement 9) provided the basis for Investigational Device Exemption (IDE) G950025 pivotal study design. Pivotal study outcome was presented in pre-market application (PMA) P990015 and amendment 7, during the January 11, 2000 General and Plastic Surgery Advisory Panel Meeting, and in post-panel meeting amendment 11 to P990015.

G950025 Study Designs

The G950025 pilot study was a randomized, unmasked, single investigator / single US center study of the preliminary safety and use methodology of 300cc Intergel compared to 300cc Lactated Ringers (LR: control) in female patients undergoing laparotomy for infertility. Pilot study enrolled twenty-five, consenting eighteen to forty-five year old women undergoing limited, class 1 (clean: no gastro-intestinal or genito-urinary tract breach; no infectious process), open peritoneal cavity surgery, i.e.: laparotomy. The most common procedures were adhesiolysis and myomectomy performed for infertility with expectation for “second look” laparoscopy as part of the treatment plan at 4 to 12 weeks after the initial surgery. Hence, opportunity was provided to evaluate eighteen pre-specified anatomic sites (Table 1) for adhesion incidence, extent and severity, as well as any other co-incident effects.

The G950025 pivotal study was a randomized, up to 12 US center and 200 evaluable patient study designed to evaluate the safety and effectiveness of applying 300cc of Intergel compared to 300cc of Lactated Ringers at the end of clean, laparotomy procedures for infertility, pain, and/or irregular vaginal bleeding. Pivotal study was conducted at eleven US and five European centers. Enrolled patients were otherwise healthy eighteen to forty-five year old women with limited adhesions (at less than twelve of twenty four sites), desiring to retain fertility, having no sites excised during first surgery and expecting to undergo second look laparoscopy as part of their treatment plan at 6 to 12 weeks. Hence opportunity was provided to evaluate twenty-four pre-specified anatomic sites (Table 1) for adhesion incidence, severity and extent as well as any other co-incident effects. Pivotal study masking was to be provided by the operating surgeon scrubbing out before device application and abdominal wound closure, or by the second-look procedure being conducted by a different surgeon. Second-look procedures were to be videotaped and evaluated by an independent reviewer.

Endpoints:

- Safety: rate and severity of adverse events.
- Effectiveness:
 - Pilot Study
 - Adhesion incidence, extent, severity
 - Pivotal Study
 - Primary: Modified American Fertility Society (mAFS) score
 - Secondary: Proportion of sites with adhesions.
 - Adhesion extent, severity.

Adhesion Evaluation

G950025 pilot and pivotal studies included second look laparoscopy to evaluate prospectively identified anatomic sites for incidence, extent and severity of adhesions. Evaluation details varied between studies as to number of anatomic sites: in the pivotal study, pilot study sites were divided resulting in six additional site overall. Specifically,

- Pilot study: eighteen abdomino-pelvic sites were evaluated for incidence: yes / no, severity: mild (filmy / avascular) or severe (organized / cohesive / vascular), and extent of adhesions (> or < 50% site covered). Extent was not to be determined for the anterior peritoneum, small bowel, omentum and large bowel due to anticipated difficulty in visualization and / or size. Retrospectively, a composite adhesion score was determined per patient and per cohort based on the incidence, extent and severity of adhesions at the eighteen anatomic sites evaluated per patient.
- Pivotal study: twenty-four abdomino-pelvic sites were evaluated for incidence (yes / no), severity (mild or severe) and extent of adhesions (<1/3; 1/3 to 2/3; >2/3). A composite score of 0 to 16 was determined per anatomic site based on adhesion incidence, severity and extent at each anatomic site. Scores per anatomic site (11 sites at first look; 24 sites at second look) were to be combined to determine an adhesion final score per patient.

Table 1: Anatomic Sites Evaluated

Pilot Study	Pivotal Study
Anterior peritoneum,	Caudal anterior peritoneum*
	Cephalad anterior peritoneum, right*
	Cephalad anterior peritoneum, left*
	Anterior peritoneum incision*
Small bowel,	Small bowel*
Omentum	Omentum*
Large bowel	Large bowel, right*
	Large bowel, left*
Anterior uterus,	Anterior uterus,
Posterior uterus,	Posterior uterus,
Recto-sigmoid colon,	Recto-sigmoid colon,
Posterior cul de sac,	Posterior cul de sac
Right pelvic side-wall,	Right pelvic side-wall,
Left pelvic side-wall,	Left pelvic side-wall,
Medial right ovary	Medial right ovary
Lateral right ovary	Lateral right ovary
Medial left ovary	Medial left ovary
Lateral left ovary	Lateral left ovary
Right ovarian fossa / posterior broad ligament,	Right ovarian fossa / posterior broad ligament,
Left ovarian fossa / posterior broad ligament,	Left ovarian fossa / posterior broad ligament,
Right tube and fimbria,	Right tube
	Right ampulla
Left tube and fimbria,	Left tube
	Left ampulla

*Extent of adhesion not evaluated: assigned moderate score.

The American Fertility Society (AFS) scoring system is a method of scoring adhesions at the tube and ovary described by The American Fertility Society (Fertility and Sterility, vol. 49, No. 6, June 1988). A score of 0 to 16 score is determined as per schema below (Table 2), per tube and per ovary on each side: four scores are determined per patient. The scores per anatomic side are added and the lower score per side determines the final AFS score per patient. As each anatomic site, tube / ovary, may score 0 to 16, and as the scores per side are added and only the side with the lower score is reported, the possible AFS score range is 0 –32.

American Fertility Score (AFS):

AFS Score per site	Severity	Extent
0	none	none
1	mild	localized
2	mild	moderate
4	mild	extensive
4	severe	localized
8	severe	moderate
16	severe	extensive

The G950025 composite adhesion scoring system was developed for the Intergel pivotal clinical study by applying the per site AFS score to each of twenty-four abdomino-pelvic sites. Extent of adhesion was planned to be assigned a moderate score (1/3 to 2/3) for the anterior peritoneum, small bowel, omentum and large bowel due to anticipated difficulty in visualization and / or size. A total adhesion score per patient, referred to as the modified AFS (mAFS) score, was to be determined by adding the scores of twenty four sites and normalizing (dividing) by the number of sites: the possible mAFS score range per patient being 0 – 16. Mean mAFS scores were determined for pilot study cohorts retrospectively and provided the basis for pivotal study sample size calculation.

It is notable that if the mAFS score is the sum of (# adhesions x AFS per adhesion) / 24, a patient with one adhesion may have AFS = 0.042 to 0.667, with 11 adhesions: AFS = 0.458 to 7.33, and with 24 adhesions: AFS = 1 to 16. Hence, patients with different incidence, extent and severity of adhesions can have the same mAFS score as mAFS score calculation. The clinical significance of a mAFS score or the change in a mAFS score had / has not been established. The correlation of the mAFS score to clinical outcome was / is not known.

The AFS score was not a prospectively specified parameter of adhesion evaluation and was not determined during clinical study evaluations. However, a retrospective AFS score was calculated from mAFS score data using three sites for each ovary and two sites for each tube to determine a retrospective AFS score per ovary and per tube and thereafter the retrospective AFS score per patient side, dropping the higher score of the right and left side to determine the retrospective AFS score per patient. Method of retrospective AFS score determination is attached (attachment 4).

In the original pivotal study report as well as January 12, 2000 Panel Presentation and subsequent amendments, the sponsor included analyses of

Retrospective standard AFS score

Shift tables stratifying the retrospective AFS into segments, e.g.:

Minimal: 0 – 5

Mild: 6 – 10

Moderate: 11 – 20

Severe: 21 -32

Mild / minimum: 0 –10

Moderate / severe: 11 – 32

Pivotal Study Data Combinability: US and Europe

G950025 pivotal study protocol allowed for an interim assessment of the combinability of data from the US and Europe after at least 120 patients had completed study. G950025 pivotal study combinability report was presented in G950025s26.

Combinability criteria were prospectively identified (G950025s26, p4-6):

1. There should be no significant interaction between location (US and Europe) and treatment efficacy.
2. US and European populations should be similar on demographic and pre-treatment variables and the level of medical care. Variables to be examined were to include:
 - Age
 - Race
 - Body weight

- Baseline adhesion score
 - Previous and concomitant medications
 - Presence of endometriosis
 - Surgical procedures performed
 - Estimated blood loss
 - Estimated blood loss
 - Operative time
 - Baseline clinical laboratory evaluations
 - Length of hospital stay
 - Time to second look laparoscopy
 - Number of patients lost to follow-up
3. US and European control groups should be similar on second look adhesion scores, as this variable can serve as a proxy for subtle differences in medical treatment. The 95% confidence intervals of the difference between the US and European control groups will be presented.

Data for each of the three combinability factors was to be analyzed and presented by individual center. If the US and European centers were to be found to be combinable, then study was to terminate as soon as that decision was made. If the US and European centers were to be found not combinable, then enrollment in the US protocol was to continue until 200 evaluable patients have completed study. The decision to stop or continue the study was not to be effected by the p-values of the difference between the treated and control groups: US alone or combined with Europe. In addition:

- If the data are not combinable, the US study was not to be stopped regardless of the statistical significance of the difference between the treated and control groups: either in the combined US / European study or the US study alone.
- If the data are combinable, and the difference between the treated and the control groups in the combined US/European study is not statistically significant, the study will not be continued, but will be stopped and considered to have failed.

In G950025s26, the sponsor stated (p1) that studies conducted in the US and Europe were identical except that European centers were fewer in number and smaller in patient enrollment volume, and that due to apparent differences in the baseline number of adhesions per patient in the US and Europe, combinability analysis was initiated early, i.e.: when 200 patients were entered however not all completed second look laparoscopy.

G950025s26 data demonstrated differences between US and European cohort demographics as well as mean baseline adhesions evaluation and operative parameters, as well as pre-operative medications:

- Demographics: Racial composition (G950025s26 Table 4.4.2.1)
- Baseline adhesion evaluations per patient: number of adhesions, proportion of anatomic sites with adhesions, mAFS score (G950025s26 Table 4.4.2.6)
- Operative parameters: blood loss, operative time, number of days to discharge, number of days to second look (G950025s26 Table 4.4.2.5) and procedures performed (G950025s26 Table 4.4.2.4) and
- Pre-operative medication intake e.g., herbal preparations; calcium supplementation (G950025s26 Table 4.4.2.2).

Data from these tables for race, mean baseline adhesion evaluations on per patient basis and mean operative parameters on per patient basis for the enrolled study population at the time of initial combinability assessment is presented below along with adhesion evaluation at second look for this population (G950025s26 Table 4.4.3.1). Referenced G950025s26 tables are attached (attachment 2). Pilot study data is presented for reference.

Second look adhesion data was presented adjusted and unadjusted for the number of anatomic sites with adhesions at first look which were not lysed. Adjustment was made by subtracting / not including data of the anatomic sites with adhesions at first look which were not lysed from / in the total (unadjusted) evaluation at second look. Data in this review is presented for baseline (first look) and unadjusted second look, as these data sets present the total adhesion burden per patient at the given point of evaluation. For reference, data for baseline, unadjusted second look and adjusted second look is presented in sponsor tables are provided in attachment 2 to this review.

Table 2: Pivotal Study Cohort at Time of Initial US and Europe Data Combinability Assessment

Study:	Pilot		Pivotal			
	US		US		Europe	
	Intergel	Control	Intergel	Control	Intergel	Control
N: treated	13	10	60	54	38	31
N: completed study	11	10	52	52	36	30
Demographics: Race						
Caucasian	0	0	22 (42.3%)	18 (34.6%)	29 (80.6%)	28 (93.3%)
Black	(38.5%)	(16.7%)	15 (28.8%)	13 (25.0%)	1 (2.8%)	2 (6.7%)
Oriental	(7.7%)	(8.3%)	1 (1.9%)	3 (5.8%)	3 (8.3%)	0
Hispanic	(53.8%)	(75.0%)	14 (26.9%)	17 (32.7%)	1 (2.8%)	0
Other	0	0	0	1	2 (5.6%)	0
# Anatomic sites evaluated	18	18	24	24	24	24
All patients:						
Baseline Adhesion #, mean (sd)	3.55 (4.52)	4.33 (3.93)	2.92 (3.83)	2.52 (3.71)	6.25 (4.71)	6.83 (5.04)
Second look Adhesion #, mean (sd)	6.09 (4.59)	11.0 (3.24)	6.27 (5.22)	8.15 (5.62)	5.25 (3.91)	6.87 (5.14)
Difference: Second Look minus Baseline:	2.54	6.67	3.35	5.63	- 1.00	0.04
Baseline mAFS, mean (sd)	1.76 (2.53)	2.69 (4.23)	0.94 (1.54)	0.80 (1.50)	1.71 (2.01)	2.16 (2.06)
Second look mAFS, mean (sd)	1.79 (1.61)	6.86 (4.02)	1.30 (1.50)	2.80 (2.79)	0.90 (1.14)	1.43 (1.50)
Difference: Second Look minus Baseline:	0.04	4.17	0.36	2.00	-0.81	-0.73
Blood loss (cc), mean (sd)	-	-	248 (237)	247 (280)	189 (236)	132 (112)
Operative Time (hrs), mean (sd)	-	-	2.19 (0.51)	2.06 (0.95)	1.58 (0.59)	1.52 (0.54)
Days to Discharge, mean (sd)	2.1 (1.0)	2.0 (1.0)	2.7 (1.6)	2.5 (1.0)	4.1 (1.5)	4.5 (1.9)
Days to second look, mean (sd)	42.2 (20.6)	45.7 (19.6)	57.1 (21.2)	55.1 (17.6)	66.2 (22.1)	60.8 (23.8)

Review concluded that US and European data is not combinable due to study patient characteristics: difference in baseline evaluation of adhesion incidence and mAFS score. Differences in racial composition are understood to be due to inherent population distribution per continent: propensity for scar formation is acknowledged to vary amongst races; relation of race and peritoneal adhesion formation is not known. Differences in blood loss, hospital stay and operative time are related to standard of care and most prevalent procedure type: myomectomy in the US; adhesiolysis in Europe. Comparing baseline and second look mAFS score and adhesion incidence per treatment group differences are noted in the direction of change from baseline to second look between continents. In the US, mAFS score and adhesion incidence increase from baseline to second look in US Intergel and control treated cohorts. In Europe, mAFS score and adhesion incidence decrease from baseline to second look for the Intergel treated cohort and are essentially unchanged for the control treated cohort. The direction of change in adhesion incidence and mAFS from baseline to second-look in the US pivotal study, although different in magnitude, parallels the direction of change in these parameters in the US pilot study.

The sponsor was advised of concerns as to data combinability. Thereafter P990015 was submitted: Clinical evaluation of LubriCoat 5% Ferric Hyaluronate Gel for the reduction of adhesions following peritoneal cavity surgery, a multi-center study of safety and efficacy.

P990015 Study Outcomes

Pivotal study protocol required investigators to complete drawings related to adhesions and surgical procedures within 24hours of the operation. After the second - look laparoscopy procedures, data were to be reviewed by the monitor, then forwarded with the videotape of the second look procedure and a copy of the operative dictation notes to an independent masked Medical Review Officer, who reviewed the videotape and drawings to ensure the data had been accurately represented and transcribed on the key case report forms (P990015 p44-45). The pilot study investigator served as the Medical Review Officer as well as unmasked monitor.

Pivotal study protocol planned presentation of monitored data based on the intent to treated population (ITT); P990015 study outcomes presented effectiveness data based on evaluable (EVL) population data without reconciliation with masked evaluator review. ITT analysis was requested. Differences among the four data sets (ITT monitored; ITT unmonitored; EVL monitored; EVL unmonitored) are clinically unremarkable. The unmonitored ITT data sets are presented, as this data set is considered to be to statistically appropriate data set.

Brief P990015 Data Summary and Discussion

Table 3: Patient Accounting

Cohorts:	US		Europe	
	Intergel	Control	Intergel	Control
#Enrolled (ITT)	102	98	41	40
# at 2nd look (EVL)	93	95	38	39
Lost to Follow-up	9	3	3	1
% at 2 nd look	91.1%	96.9%	92.7%	97.5%

Table 4: Surgical Procedures*

	US		Europe	
	Intergel	Control	Intergel	Control
ITT	102	98	41	40
Adhesiolysis	39	39	32	28
Non-Adhesiolysis	63	59	9	12

*included myomectomy, endometrial ablation and / or tubal and ovarian procedures.

Table 5: Demographics (Race)

	US		Europe	
	Intergel	Control	Intergel	Control
ITT	102	98	41	40
%Caucasian	46.3	47.9	81.6	94.9
%Black	29.0	22.1	2.6	5.1
%Oriental	1.1	4.2	7.9	0
%Hispanic	20.4	23.2	2.6	0
%Other	3.2	3.2	5.3	0

Table 6: Baseline Adhesion Evaluation at 24 sites

	US		Europe	
	Intergel	Control	Intergel	Control
ITT	102	98	41	40
Incidence (N), mean Possible score: 0 - 11 of 24*	2.49	2.27	6.00	6.40
Patients with N = 0	60 (58.8%)	54 (55.1%)	8 (19.5%)	11 (27.5%)
Extent Possible score: 0, 1, 2, 3	0.20	0.19	0.58	0.65
Severity Possible score: 0, 1, 3	0.28	0.21	0.58	0.65
mAFS Possible score: 0 - 7.33	0.78	0.68	1.57	1.95
Retrospective AFS Possible score: 0 - 32	1.55	1.80	4.27	5.20

*Patients with adhesions at more than 11 sites excluded.

Differences between the US and Europe noted in the partial study cohort presented for initial combinability assessment (Table 2) were also found in the complete pivotal study cohort (P990015p70). For a given baseline adherence characteristic: the difference between continents per characteristic is greater than the difference between cohorts within a continent (Table 6). In view of these differences combinability as presented in P990015 remained questionable.

Effectiveness

The primary effectiveness variable was mAFS score. Pivotal study design was based on pilot study outcome: mean retrospective mAFS at second look 5.68 (control) and 1.70 (Intergel). Assuming a mean adherence score of 4.6 (standard deviation: 5.9) for the treated group and 6.7 (standard deviation: 4.1) for the control, a sample size of 180 patients was determined to detect a difference of 2.1 in mAFS score between control and Intergel treated cohorts given an expected standard deviation of 5.0 for both groups with 80% power at a 0.05 significance level. This sample size included patients for an expected 20% loss to follow-up for the Intergel cohort and a 10% loss to follow-up for the control treated cohort. The US cohort consisted of 102 Intergel treated patients and 98 control treated patients: sufficient sample size to demonstrate the expected effect with statistical significance and 80% power. Table 7 presents the mean mAFS score at second look for the pilot and pivotal study cohorts. The difference in mAFS score between control and Intergel treated cohorts observed in the pilot study was: $1.70 - 5.68 = -3.98$. The difference in mAFS score between Intergel and control treated cohorts observed in the 200 patient US pivotal study cohort was: $mAFS = 2.63 - 2.76 = -0.13$. Differences in mAFS score between Intergel and control treated cohorts are similar for European cohort of 81 patients, as well as the overall cohort.

Table 7: Mean mAFS at Second Look

ITT	Pilot*	Pivotal		
	US	US	Europe	All
Intergel (I)	1.70 (n=11)	2.63 (n=102)	2.01 (n=41)	2.45 (n=143)
Control (C),	5.68 (n=11)	2.76 (n=98)	2.12 (n=40)	2.58 (n=138)
I - C**	-3.98	-0.13	-0.11	-0.13
P - value		0.082	0.149	0.023

*Only in US **Intergel minus Control

Effectiveness may also be evaluated on the basis of mean change from baseline to second look: considering adherence burden at the beginning of first surgery and at second look. Table 8 presents comparison of the mean change from baseline at first surgery to second look for mAFS score, for the pilot and pivotal study cohorts. Difference between Intergel and control in mean change in mAFS from baseline at first surgery to second look was -4.12 in the pilot study and -0.09 in the overall pivotal study cohort: neither US nor European nor the overall study cohort demonstrated the level of change from baseline as the pilot study. The difference in the retrospective standard AFS score from baseline to second look demonstrated for the overall study cohort, a difference of -0.83: AFS score range of 0 to 16. For the 200 patient US cohort difference between treatment arms was -0.43 and did not reach statistical significance. For the 81 patient European cohort difference between treatment arms was -1.49 and reached statistical significance.

Table 8: Mean Change from Baseline at First Surgery to Second Look **

ITT	Mean Change mAFS				Mean Change rAFS		
	Pilot*	Pivotal			Pivotal		
	US	US	Europe	All	US	Europe	All
Intergel (I)	0.06 (n=11)	2.59 (n=102)	1.93 (n=41)	2.40 (n=143)	4.40 (n=102)	3.17 (n=41)	4.05 (n=143)
Control (C)	4.18 (n=11)	2.71 (n=98)	1.95 (n=40)	2.49 (n=138)	4.97 (n=98)	4.68 (n=40)	4.88 (n=138)
I - C	-4.12	-0.12	-0.02	-0.09	-0.43	-1.49	-0.83
P - value		0.080	0.187	0.028	0.535	0.035	0.102

*Only in US. **P990015A7 Tables (attachment 2): 2nd look - baseline.

Effectiveness variables: mAFS score, adhesion incidence, severity and extent, as well as retrospective AFS score, evaluated at baseline and at second look for Intergel and control cohorts per continent as well as combined are presented in Table 8. “I-C” presents the difference between Intergel and control at a given point of evaluation: baseline or second look. Data is presented for all patients as well as for patients who underwent adhesiolysis and those who did not, as patients who underwent adhesiolysis had a higher baseline incidence of adhesions and mAFS score than patient who had non-adhesiolysis procedure. Comparison of baseline and second look data per parameter in the US cohort demonstrates that for each parameter for all patients as well as for adhesiolysis and non-adhesiolysis patients demonstrates increase in each evaluated parameter for all cohorts: Intergel and control, all patients combined, as well as adhesiolysis and non-adhesiolysis patients. A similar trend occurs for the overall cohort. Comparison of baseline and second look data per parameter in the European adhesiolysis cohorts, however, demonstrates decrease in all parameters from baseline to second look: opposite in direction of outcomes in the US adhesiolysis cohorts. Differences between Intergel and control per parameter are otherwise small compared to the range per parameter: mAFS: 0 to 16; incidence: 0–24; extent: 0–3; severity: 0–3; retrospective AFS: 0–32. Outcomes for the unmonitored evaluable population are comparable (Table 9).

Table 8: Adhesion Evaluation Data, mean (standard deviation)

ITT	US				Europe				ALL			
	Intergel	Control	I-C	p	Intergel	Control	I-C	p	Intergel	Control	I-C	p
All, n	102	98			41	40			143	138		
Baseline mAFS	0.78 (1.46)	0.68 (1.40)	0.10	0.956	1.57 (1.87)	1.95 (1.96)	-0.38	0.506	1.01 (1.62)	1.05 (1.68)	-0.04	0.976
2 nd look mAFS	2.74 (4.45)	2.83 (3.60)	-0.09	0.128	2.21 (4.18)	2.42 (3.15)	-0.21	0.181	2.59 (4.36)	2.71 (3.47)	-0.12	0.044
Baseline Incidence	2.49 (3.57)	2.27 (3.50)	0.22	0.929	6.00 (4.59)	6.40 (5.01)	-0.40	0.845	3.50 (4.19)	3.46 (4.40)	0.04	0.931
2 nd look Incidence	8.29 (6.93)	8.07 (5.81)	0.22	0.813	7.37 (6.40)	8.20 (5.87)	-0.83	0.351	8.03 (6.77)	8.11 (5.81)	-0.08	0.469
Baseline Extent	0.20 (0.32)	0.19 (0.33)	0.01	0.886	0.47 (0.44)	0.54 (0.45)	-0.07	0.559	0.28 (0.38)	0.29 (0.40)	-0.01	0.840
2 nd look Extent	0.72 (0.85)	0.70 (0.69)	0.02	0.417	0.58 (0.77)	0.67 (0.65)	-0.09	0.260	0.68 (0.83)	0.70 (0.67)	-0.02	0.179
Baseline Severity	0.28 (0.43)	0.21 (0.37)	0.07	0.774	0.58 (0.51)	0.65 (0.54)	-0.07	0.686	0.37 (0.47)	0.34 (0.47)	0.03	0.810
2 nd look Severity	0.76 (0.82)	0.81 (0.73)	-0.05	0.273	0.60 (0.78)	0.78 (0.68)	-0.12	0.217	0.73 (0.81)	0.80 (0.71)	-0.07	0.093
Baseline rAFS	1.55 (3.59)	1.80 (5.31)	-0.25	0.613	4.27 (7.52)	5.20 (6.80)	-0.93	0.430	2.33 (5.16)	2.78 (5.96)	-0.45	0.967
2 nd look rAFS*	4.48 (9.33)	4.98 (9.26)	-0.05	0.624	3.56 (8.34)	5.18 (8.06)	-1.63	0.101	4.22 (9.04)	5.04 (8.90)	-0.82	0.202
Adhesiolysis, n	39	39			32	28			71	67		
Baseline mAFS	2.01 (1.76)	1.59 (1.86)	0.42	0.062	2.01 (1.90)	2.78 (1.78)	-0.77	0.051	2.01 (1.81)	2.09 (1.91)	-0.08	0.927
2 nd look mAFS	3.52 (4.61)	4.04 (4.24)	-0.52	0.325	1.79 (3.02)	2.41 (2.10)	-0.62	0.060	2.74 (4.04)	3.36 (3.58)	-0.62	0.045
Baseline Incidence	6.33 (2.98)	5.38 (3.75)	0.95	0.092	7.63 (3.83)	9.11 (3.29)	-1.48	0.184	6.92 (3.43)	6.94 (3.99)	-0.02	0.952
2 nd look Incidence	10.00(6.61)	10.23(6.23)	-0.23	0.700	7.38 (5.37)	9.18 (4.72)	-1.80	0.090	8.82 (6.18)	9.79 (5.63)	-0.97	0.149
Baseline Extent	0.51 (0.33)	0.46 (0.38)	0.05	0.289	0.59 (0.42)	0.77 (0.34)	-0.18	0.055	0.55 (0.37)	0.59 (0.39)	-0.04	0.565
2 nd look Extent	0.90 (0.85)	0.96 (0.77)	-0.06	0.401	0.53 (0.58)	0.73 (0.50)	-0.20	0.058	0.73 (0.76)	0.86 (0.68)	-0.13	0.051
Baseline Severity	0.71 (0.43)	0.50 (0.44)	0.21	0.011	0.73 (0.47)	0.92 (0.40)	-0.19	0.111	0.72 (0.44)	0.67 (0.47)	0.05	0.495
2 nd look Severity	0.96 (0.81)	1.06 (0.81)	-0.01	0.519	0.63 (0.63)	0.84 (0.52)	-0.21	0.056	0.81 (0.75)	0.97 (0.71)	-0.16	0.062
Baseline rAFS	4.05 (4.88)	4.51 (7.71)	-0.46	0.476	5.47 (8.14)	7.43 (7.05)	-1.96	0.111	4.69 (6.54)	5.73 (7.52)	-1.04	0.632
2 nd look rAFS	5.82(10.11)	8.18(11.14)	-2.36	0.200	2.53 (5.81)	6.04 (7.55)	-3.51	0.012	4.34 (8.56)	7.28 (9.80)	-2.94	0.009
No Adhesiolysis, n	63	59			9	12			72	71		
Baseline mAFS	0.02 (0.11)	0.07 (0.28)	-0.05	0.387	0.02 (0.06)	0.03 (0.10)	-0.01	0.944	0.02 (0.10)	0.07 (0.26)	-0.05	0.465
2 nd look mAFS	2.26 (4.31)	2.03 (2.87)	0.23	0.152	3.69 (6.99)	2.45 (4.95)	1.24	0.747	2.44 (4.69)	2.11 (3.27)	0.33	0.184
Baseline Incidence	0.11 (0.51)	0.20 (0.69)	-0.09	0.410	0.22 (0.67)	0.08 (0.29)	0.14	0.834	0.13 (0.53)	0.18 (0.64)	-0.05	0.505
2 nd look Incidence	7.24 (6.96)	6.64 (5.08)	0.60	0.809	7.33 (9.66)	5.92 (7.69)	1.41	0.830	7.25 (7.27)	6.52 (5.55)	0.73	0.881
Baseline Extent	0.01 (0.03)	0.02 (0.06)	-0.01	0.387	0.02 (0.06)	0.01 (0.03)	0.01	0.834	0.01 (0.03)	0.02 (0.06)	-0.01	0.485
2 nd look Extent	0.62 (0.83)	0.53 (0.57)	0.09	0.483	0.76 (1.27)	0.55 (0.93)	0.21	1.000	0.63 (0.89)	0.54 (0.63)	0.09	0.538
Baseline Severity	0.01 (0.07)	0.03 (0.09)	-0.02	0.407	0.01 (0.03)	0.01 (0.04)	0.00	0.944	0.01 (0.06)	0.02 (0.09)	-0.01	0.488
2 nd look Severity	0.64 (0.82)	0.64 (0.61)	0.00	0.265	0.77 (1.27)	0.61 (0.96)	0.16	0.914	0.66 (0.88)	0.64 (0.68)	0.02	0.322
Baseline rAFS	0.00 (0.00)	0.00 (0.00)	0.00	1.000	0.00 (0.00)	0.00 (0.00)	0.00	1.000	0.00 (0.00)	0.00 (0.00)	0.00	1.000
2 nd look rAFS	3.65 (8.80)	2.86 (7.12)	0.79	0.718	7.22 (14.1)	3.17 (9.15)	4.05	0.899	4.10 (9.55)	2.92 (7.43)	1.18	0.662

*rAFS = retrospectively determined AFS score

Table 9: Adhesion Evaluation Data, mean (standard deviation)

EVL	US				Europe				ALL			
	Intergel	Control	I-C	p	Intergel	Control	I-C	p	Intergel	Control	I-C	p
All, n	93	95			38	39			131	134		
Baseline mAFS	0.83 (1.51)	0.69 (1.42)	0.14	0.864	1.66 (1.91)	2.00 (1.96)	-0.34	0.580	1.07 (1.67)	1.07 (1.70)	0.00	0.870
2 nd look mAFS	1.45 (1.69)	2.42 (2.77)	-0.97	0.015	1.12 (1.49)	2.07 (2.29)	-0.95	0.065	1.36 (1.63)	2.32 (2.63)	-0.96	0.002
Baseline Incidence	2.58 (3.67)	2.19 (3.46)	0.39	0.795	6.26 (4.55)	6.56 (4.96)	-0.30	0.930	3.65 (4.27)	3.46 (4.41)	0.19	0.744
2 nd look Incidence	6.77 (5.12)	7.57 (5.15)	-0.80	0.301	6.05 (4.48)	7.79 (5.35)	-1.74	0.159	6.56 (4.94)	7.63 (5.19)	-1.07	0.096
Baseline Extent	0.21 (0.33)	0.19 (0.33)	0.02	0.968	0.49 (0.44)	0.56 (0.45)	-0.07	0.634	0.29 (0.39)	0.30 (0.40)	-0.01	0.964
2 nd look Extent	0.50 (0.48)	0.63 (0.56)	-0.13	0.096	0.39 (0.36)	0.61 (0.53)	-0.22	0.106	0.47 (0.45)	0.63 (0.55)	-0.16	0.019
Baseline Severity	0.29 (0.45)	0.21 (0.37)	0.08	0.678	0.60 (0.51)	0.67 (0.54)	-0.07	0.751	0.38 (0.49)	0.35 (0.47)	0.03	0.670
2 nd look Severity	0.54 (0.46)	0.74 (0.62)	-0.20	0.048	0.47 (0.45)	0.72 (0.58)	-0.25	0.083	0.52 (0.46)	0.73 (0.61)	-0.21	0.007
Baseline rAFS	1.65 (3.73)	1.83 (5.39)	-0.18	0.568	4.37 (7.72)	5.33 (6.84)	-0.96	0.415	2.44 (5.32)	2.85 (6.04)	-0.41	0.988
2 nd look rAFS*	1.82 (3.79)	4.13 (8.03)	-2.31	0.183	1.32 (2.11)	4.49 (6.87)	-3.17	0.028	1.67 (3.39)	4.23 (7.69)	-2.56	0.022
Adhesiolysis, n	35	37			31	28			66	65		
Baseline mAFS	2.18 (1.78)	1.66 (1.89)	0.52	0.040	2.03 (1.93)	2.78 (1.78)	-0.75	0.063	2.11 (1.84)	2.14 (1.92)	-0.03	0.809
2 nd look mAFS	2.09 (1.81)	3.39 (3.25)	-1.30	0.121	1.33 (1.57)	2.41 (2.10)	-1.08	0.032	1.73 (1.73)	2.97 (2.84)	-1.24	0.009
Baseline Incidence	6.66 (2.93)	5.30 (3.76)	1.36	0.036	7.61 (3.90)	9.11 (3.29)	-1.50	0.199	7.11 (3.42)	6.94 (4.02)	0.17	0.739
2 nd look Incidence	8.40 (4.81)	9.49 (5.47)	-1.09	0.381	6.84 (4.50)	9.18 (4.72)	-2.34	0.051	7.67 (4.70)	9.35 (5.12)	1.68	0.045
Baseline Extent	0.55 (0.33)	0.46 (0.39)	0.09	0.131	0.60 (0.42)	0.77 (0.34)	-0.17	0.065	0.57 (0.38)	0.59 (0.40)	-0.02	0.788
2 nd look Extent	0.66 (0.48)	0.85 (0.62)	-0.19	0.166	0.45 (0.37)	0.73 (0.50)	-0.28	0.031	0.56 (0.44)	0.80 (0.57)	-0.24	0.011
Baseline Severity	0.76 (0.42)	0.51 (0.45)	0.25	0.006	0.74 (0.47)	0.92 (0.40)	-0.18	0.118	0.75 (0.44)	0.69 (0.48)	0.06	0.428
2 nd look Severity	0.72 (0.43)	0.96 (0.69)	-0.24	0.243	0.55 (0.46)	0.84 (0.52)	-0.29	0.030	0.64 (0.45)	0.91 (0.62)	-0.27	0.014
Baseline rAFS	4.37 (5.03)	4.70 (7.87)	-0.33	0.447	5.35 (8.24)	7.43 (7.05)	-2.08	0.093	4.83 (6.70)	5.88 (7.59)	-1.05	0.615
2 nd look rAFS	2.83 (4.95)	6.89 (9.89)	-4.06	0.070	1.58 (2.25)	6.04 (7.55)	-4.46	0.005	2.24 (3.94)	6.52 (8.90)	-4.28	0.001
No Adhesiolysis, n	58	58			7	11			65	69		
Baseline mAFS	0.02 (0.11)	0.07 (0.28)	-0.05	0.439	0.02 (0.07)	0.03 (0.10)	-0.01	0.868	0.02 (0.11)	0.07 (0.26)	-0.05	0.538
2 nd look mAFS	1.07 (1.50)	1.79 (2.20)	-0.72	0.029	0.17 (0.24)	1.22 (2.62)	-1.05	0.272	0.97 (1.44)	1.70 (2.28)	-0.73	0.024
Baseline Incidence	0.12 (0.53)	0.21 (0.69)	-0.09	0.466	0.29 (0.76)	0.09 (0.30)	0.20	0.740	0.14 (0.56)	0.19 (0.65)	-0.05	0.584
2 nd look Incidence	5.79 (5.10)	6.34 (4.58)	-0.55	0.366	2.57 (2.30)	4.27 (5.42)	-1.70	0.748	5.45 (4.97)	6.01 (4.74)	-0.56	0.339
Baseline Extent	0.01 (0.03)	0.02 (0.06)	-0.01	0.439	0.02 (0.07)	0.01 (0.03)	0.01	0.740	0.01 (0.03)	0.02 (0.06)	-0.01	0.561
2 nd look Extent	0.41 (0.46)	0.49 (0.47)	-0.08	0.162	0.13 (0.14)	0.33 (0.54)	-0.20	0.519	0.38 (0.45)	0.46 (0.48)	-0.08	0.142
Baseline Severity	0.02 (0.07)	0.03 (0.09)	-0.01	0.462	0.01 (0.03)	0.01 (0.04)	0.00	0.868	0.02 (0.07)	0.03 (0.09)	-0.01	0.564
2 nd look Severity	0.44 (0.44)	0.60 (0.53)	-0.16	0.065	0.13 (0.15)	0.40 (0.62)	-0.27	0.409	0.40 (0.43)	0.57 (0.55)	-0.17	0.060
Baseline rAFS	0.00 (0.00)	0.00 (0.00)	0.00	1.000	0.00 (0.00)	0.00 (0.00)	0.00	1.000	0.00 (0.00)	0.00 (0.00)	0.00	1.000
2 nd look rAFS	1.21 (2.76)	2.36 (6.04)	-1.15	0.726	0.14 (0.38)	0.55 (1.21)	-0.41	0.533	1.09 (2.63)	2.07 (5.59)	-0.98	0.662

*rAFS = retrospectively determined AFS score

Table 10: Wound Inflammation, Opening, and Infection

	Pilot		Pivotal		Europe		All	
	US	Control	US	Control	IG	Control	IG	Control
Enrolled	13	12	102	98	41	40	143	138
Incision inflammation			8 (7.8%)	7 (7.1%)	0 (0.0%)	1 (2.5%)	8 (5.6%)	8 (5.8%)
Incision opening			6 (5.9%)	5 (5.1%)	1 (2.4%)	0 (0.0%)	7 (4.9%)	5 (3.6%)
Infection P990015a6	1	0	4 (3.9%)	1 (1%)	2 (4.9%)	1 (2.5%)	6 (4.2%)	2 (1.4%)
Infection P990015a11*	na	na	8 (7.8%)	2 (2.0%)	2 (4.9%)	2 (4.9%)	10(7.0%)	4 (2.9%)
• Total reported								
Possibly device related:	na	na	5 (4.9%)	2 (2.0%)	1 (2.5%)	1 (2.5%)	6 (4.2%)	3 (2.2%)
• Sum of Investigator & Independent assessment								

*Presented after 1/12/01 Panel Meeting (attachment 2)

Table 10 presents a summary of wound inflammation, opening and infection data as presented in P990015a6 as well as a re-presentation of infection data in P009915a11. Sponsor presented data tables are included in attachment 2. P990015a11 included a detailed listing of patients with infection and suspected relation to device use as per the investigator and an independent evaluator. This list identifies 10 Intergel (8US) patients with infection and 4 (2US) Control patients with infection. Infection occurred in one Intergel patient in the small pilot study compared to none in the control cohort. In pivotal study P990015a6 report, increase in the incidence of infection in Intergel treated patients compared to control was notable, specifically as to the nearly fourfold increase in incidence of infection for otherwise healthy patients undergoing clean procedures. P990015a11 report also identifies several fold increase incidence of infection, which investigators and the sponsor's independent assessment noted as possibly device related. The increased trend presents for the overall cohort (US and Europe), driven by an increase in incidence of infection reported for the US cohort.

It is recognized that neither pilot nor pivotal study design was sized to evaluate statistical equivalence for safety, e.g. infection. Nevertheless, a trend toward increased incidence of infection is observed in Intergel treated patients compared to control in all cohorts, which consisted of clean cases in otherwise healthy 18 to 45 year old women undergoing clean (class 1) procedures.

Brief Summary

- Device use was studied in clean class, non-cancer and relatively low baseline adhesion burden 18 to 45 year old female patients who were otherwise in good health.
- A 180 patient sample size was calculated to demonstrate device effectiveness by mAFS score with 80% power and 0.05 statistical significance (alpha), assuming a minimal clinically significant difference of 2.1 in mean mAFS score between Intergel and control treated patients. Clinical study enrolled 281 patients: 200 US; 81 European.
- Differences between continents are not consistent with prospective criteria for combinability: baseline adhesions incidence and mAFS score, as well as demographics (race) and operative parameters (combinability criteria 2), and second look adhesion evaluation (combinability criteria 3).
- Differences between continents per treatment group for baseline adhesion evaluation (mAFS; adhesion incidence, extent, severity) are greater than differences within a continent per treatment group.
- Safety data analysis for infection, including assessment by investigators and the sponsor's independent assessors, indicates a trend toward increase in infection, which is possibly related to device (Intergel) use. This trend is driven by increased incidence of infection in the US Intergel treated cohort.
- Effectiveness on the basis of difference between Intergel and control in the US is on the order of one adhesion (possible range 0 –24), and less than one unit in change in the mean adhesion extent (possible range: 0-3), severity (possible range: 0-3) and mAFS (possible range: 0 –16), and on the order of less than 1 for the retrospective AFS score (possible range: 0-32).
- Effectiveness outcomes per treatment are not clinically consistent between continents in magnitude or direction when considering patients who underwent adhesiolysis and patients who did not.

P990015amendment(a)11

P990015a11 was submitted to complete response to FDA 12/7/99 deficiency letter to the sponsor as well as to address unresolved issues regarding safety and effectiveness raised during the FDA review and the 1/12/00. P990015a11 included:

- Change in Indication for Use:

Original Indication for Use: Intergel Solution is indicated for use as a single use, intraperitoneal instillate for reduction of adhesions following gynecological pelvic surgery. It has been shown to reduce the incidence, extent and severity of post-surgical adhesions throughout the abdominal cavity when used as an adjunct to good surgical technique during laparotomy procedures.

Revised Indication for Use: Intergel Solution is a single use, intra-peritoneal instillate indicated to reduce the likelihood of developing moderate or severe post-operative adnexal adhesion in patients undergoing adhesiolysis or myomectomy during conservative gynecological pelvic surgery by laparotomy, when used as an

adjunct to good surgical technique. Intergel Solution was also shown to reduce adhesion reformation to sites in addition to the adenexa, and adhesion formation at surgical sites, including the anterior abdominal incision.

- Amendment to Clinical Trial Report with
 - Statistical methods for analyses
 - Justification for use of data from all trial sites
 - Analysis of incomplete ascertainment subject data
 - Study Results: analysis of effectiveness

Justification of use of data from all clinical trial sites is presented for baseline characteristics or surgical parameters are discussed. The sponsor states that stratification by continent, showed differences in race, adhesiolysis, operation time, days to discharge, days to second-look, and blood loss, and that by definition, these variables would only be considered confounders if they were differently distributed between the treatment and control groups and were related to outcome. Comparison of pivotal study outcomes in the US and Europe, demonstrate differences in the noted variables and in direction of trend in adhesion incidence and score. While outcomes may be statistically poolable, outcomes in US and Europe do not meet prospective combinability criteria 2 and 3: are not clinically poolable.

In Study Results, the sponsor provides a stratified primary efficacy analysis (P990015a11, p14-15), and states that differences between treatment and control remained statistically significant. Table 3.1 (P990015a11, p15) provides data per continent and combined continents, per none / minimal – mild / moderate – severe adhesion score category. Statistical significance is not achieved in any category per continent. Table 3.1 (P990015a11, p15) in attachment 2.

Indications for Use maintain similar target population and expectations of device use. Data noted for support of device effectiveness is based upon shift in binary retrospective AFS score. Literature references to the clinical significance of a standard AFS score, change in score and binary scores (0-10; 1-32) are few and limited, report AFS score with variations, e.g., in the anatomic sites evaluated, score assignment, and do not present consistent correlation with specific clinical findings. Brief review of available literature is attached (attachment 3). Hence binary retrospective AFS shift interpretation should be in conjunction with other basic measures of adhesions, e.g., incidence, extent and severity.

Of the 281 patients treated (ITT cohort), 265 patients are evaluable (EVL cohort). Data noted in support of the Indication for Use is presented on the basis of the EVL cohort. P990015a11 (section 2 p 1) revised Indications for Use states that “Intergel Solution is a single use, intra-peritoneal instillate indicated to reduce the likelihood of developing moderate or severe post-operative adenexal adhesion in patients undergoing adhesiolysis or myomectomy during conservative gynecological pelvic surgery by laparotomy, when used as an adjunct to good surgical technique...” is stated to be shift tables presented in Table 5.12 (attachment 2). Data in this table was presented at the 1/12/00 Advisory Panel meeting in sponsor slides titled “Shift Table for AFS Score” and “Binary Shift Table for AFS Score.” Similar tables for mAFS score were also presented by the sponsor at the 1/12/00 Advisory Panel meeting (attachment 6). The sponsor notes (P990015a11 section 2 p2) that “overall, 3 (of 131) patients in the Intergel Solution group (2.3%) had moderate or severe adhesion scores at second-look compared to 17 (of 134; 12.7%) patients in the control group. Based on these data, the relative risk of treatment failure in the control group is 5 times that of the Intergel Solution group.”

It is notable, however, that at baseline, there were 9 (of 131) patients in the Intergel Solution group with moderate to severe (retrospective AFS score = 11 to 32) adhesion scores and 17 (of 134) patients in the control group: at baseline 8 more control patients than Intergel treated patients had retrospective AFS scores in the moderate to severe range. Of these patients with moderate to severe retrospective AFS score at baseline, at second look, 7 more control patients than Intergel treated patients had retrospective AFS scores in the moderate to severe range. Relatively, for this group, both Intergel and control cohorts had a decreased number of patients with moderate to severe retrospective AFS score at second look: 9 fewer Intergel treated patients and 10 fewer control treated patients. Considering the overall evaluable study population (n= 265), at baseline, the control cohort had 8 (= 17 – 9) more patients with moderate to severe adhesions than the Intergel cohort, and at second look the control had 14 (= 17 – 3) more patients with moderate to severe adhesions than the Intergel cohort.

Stratification of the percentage of patients with moderate or severe scores at second-look per continent is presented in Table 5.13. US data indicate that 5 of 93 US Intergel and 7 of 95 US control patients had moderate to severe adhesions at baseline; and 3 of 93 Intergel Solution patients and 11 of 95 control patients had moderate to severe adhesions at second look.. Hence, of 188 US patients treated, a cohort that approximates the prospectively calculated sample size (n = 180), at baseline 2 more control patients than Intergel treated patients had moderate to severe adhesions, and at second-look, for this group 3 more control patients than Intergel treated patients had moderate or severe adhesions. Relatively, for this group, both Intergel and control cohorts had a decreased number of patients with moderate to severe retrospective AFS score at second look: 5 fewer Intergel treated patients and 4 fewer control treated patients. .Considering the overall evaluable US study population (n = 188), at baseline, the US control cohort had 2 (= 7 - 5) more patients with moderate to severe adhesions than the US Intergel cohort, and at second look the US control cohort had 8 (= 11 - 3) more patients with moderate to severe adhesions than the US Intergel cohort.

Data noted in support of Indication for Use statement "...Intergel solution was also shown to reduce adhesion reformation to sites in addition to the adnexa, and adhesion formation at surgical sites, including the anterior abdominal wall" is presented for combined continents (P990015a11, p47, attachment 2). Statistical significance is demonstrated for mean difference in surgical site adhesion of less than 1 on a scale of 0 to 24, as well as for severity (difference in means = 0.36; range 0 to 3), and extent (difference in means = 0.33; range = 0 to 3). The difference between the means of Intergel and control treated patients are on the order of magnitude less than one unit of measure. Data for reformed adhesions is presented as in pre-panel submission: with less than one unit of measure difference between treatment cohorts.

Brief summary:

- Device use was studied in clean class, non-cancer and relatively low baseline adhesion burden patients in otherwise good health.
- Baseline evaluation differences between continents, per treatment group, are greater than differences within a continent, per treatment group are not consistent between continents.
- Safety data analysis for infection, including assessment by investigators and the sponsor's independent assessors, indicates a trend toward increase in infection, which is possibly related to device (Intergel) use per investigators and independent assessment.
- Differences in effectiveness of prospective outcome measures between US Intergel and control cohorts were generally less than one unit of measure group. Effectiveness outcomes per treatment are not consistent between continents.
- Validity and reliability of the clinical significance of changes in the retrospective endpoint: stratified retrospective AFS, is limited.
- Differences in effectiveness on the basis of retrospectively calculated and stratified AFS score represent a number of patients that are on the order of magnitude as the differences at baseline, and therefore do not provide a reasonable assurance of effectiveness for the overall study population.
- Pivotal study outcomes for combined continents, as well as for the US only cohort do not approximate the order of magnitude of outcome demonstrated in pilot study.

Comment on P990015a11 from the Ob-Gyn perspective is provided by consult from the DRAERD Ob-Gyn clinician. (attachment 1)

Attachments

1. P990015a11 Ob Gyn consult review
2. Tables: G950025s26, P990015a7; P990015a11
3. Brief literature reference review
4. Method of determining retrospective AFS score.

Attachment 1: P990015a11 Ob Gyn consult review

Attachment 2: Tables: G950025s26, P990015a7; P990015a11

Attachment 3: Brief literature reference review

Literature to support AFS score use was presented and is briefly summarized:

1. “The American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Mullerian anomalies and intrauterine adhesions.” (Fertility and Sterility, Vol. 49, No. 6, June 1988). The American Fertility Society the non-linear 0 – 16 point classification scheme for the tube and ovary. The authors describe a 0 – 16 point adhesion score evaluating adhesions as filmy or dense adhesions in 33% increments of the surface of the ovary and 33% increments of the surface of the tube. Discussion is provided as to adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, Mullerian anomalies and intrauterine adhesions. No data is presented to support the classification scheme. Authors state that modification is likely in the future, that broader application may cause flaws to become evident resulting in additions, deletions, and / or modifications, that the scores applied to differentiate between minimal, mild, moderate and severe adhesion are arbitrary but considered appropriate until prospective studies are performed.
2. “Pre-operative classification to predict the intrauterine and ectopic pregnancy rates after distal tubal microsurgery.” Mage, G. et al (Fertility and Sterility, Vol. 46, No. 5, November 1986). The authors describe a study of 34 patients in whom tubal and tubal adhesion scores were determined. Tubal scores were determined by hysterosalpingogram and pre-operative laparoscopy. Tubal adhesions scores were determined per a 0 – 20 point adhesion score evaluating adhesions as filmy or vascular or dense adhesions in 33% increments of the surface of the tube. Statistical analysis of combinations of tubal and adhesion grade is stated to have shown no correlation between tubal grade and adhesion grade: adhesions of each grade are about equally divided between each grade of tube. Except in the case of severe adhesions, pregnancy rate was better correlated to tubal grade than adhesion grade. Specifically, intra-uterine pregnancy occurred at 58.3%, 36.6%, 9.5% and 0% in patients with tube grades 1 to 4 respectively, and in 38.8%, 32.0%, 26.6% and 5.5% in patients with no, mild, moderate and severe adhesions, respectively.

The scoring system used by Mage et al differs from the AFS scoring system as to anatomic sites evaluated and points assigned, and study does not clearly support clinical inference from retrospective AFS of mAFS scores or ranges as presented in P990015.

3. “Peri-ovarian adhesions interfere with the diffusion of gonadotrophin into the follicular fluid.” Nagata, Y. et al (Human Reproduction, vol.13 no.8 pp2072-2076. 1998). The authors report study of 26 patients with laparoscopic scoring of peri-ovarian adhesions, using the AFS score adapted so that a score of 32 represents bilateral expanded dense adhesions on the ovaries; tubes were not evaluated. Significant negative correlations were found between the peri-ovarian adhesion score and both the follicular HCG concentration and the HCG ratio.

The scoring system used by Nagata et al differs from the AFS scoring system as to the anatomic sites evaluated and the method of final score determination: sum of both ovarian scores (Nagata et al) compared to lower of the sum of tube and ovary scores per side, as well as the method of score evaluation: correlation to score range (0-32; Nagata et al) compared to discrete value or range (retrospective AFS, mAFS).

4. “The prognostic value of salpingoscopy.” DeBruyne, F. et al (Human Reproduction, vol. 12 no 2 pp 266-271. 1997). The authors report study of 226 women with pelvic inflammatory disease undergoing salpingoscopy and microsurgery, as well as tube evaluation by AFS score. Each tube was classified according to the AFS classification. Comparison of salpingoscopy findings with the AFS classification found only weak to moderate correlation between these systems. In the multivariate analysis the salpingoscopic classification was statistically significant at the 0.5% level, whereas the AFS classification was not (p=0.67).
5. “Resolution of laparoscopic findings to self-report of pelvic pain.” Stout, AL et al (Am J Ob Gyn 1991 Jan; 164(1 Pt 1): 73-9. The authors evaluated 102 women scheduled for laparoscopic surgery for chronic pain. Surgeons masked to patient self-report of pain completed the AFS classification for endometriosis and adhesions on the basis of observed physical disease. The Authors State that although AFS classification

scores were significantly related to self-assignment into pain or no-pain groups, the extent of disease evaluated by this procedure was not significantly correlated with ratings of pain levels or a number of indexes of impairment.

6. "Improvement of inter-observer reproducibility of adhesion scoring systems," by The Adhesion Scoring Group, was published in *Fertility and Sterility*, 62, 984-988 (1994). This article compared the interobserver reproducibility of two adhesion scoring methods: the AFS adhesion scoring method (the non-linear 0-16 score, applied to the tube and ovary on each side) and a more comprehensive adhesion scoring method specifically demonstrating locations (23 sites), severity (0-3), and extent (0-3) of adhesions with scores determined by the addition of the severity plus the extent score at each location or the multiplication of the severity times the extent score at each location, before summing all locations to achieve the final score. The study concluded that using the more comprehensive adhesion scoring method, a marked improvement in reproducibility between physician pairs was noted regardless of whether the additive or multiplicative method was utilized: positive correlation, $r \geq 0.7$ using AFS was 64%, 32% of pairings respectively; additive 89%, 75%; multiplicative, 96%, 67%.

Study by Gomel et al *Fertility Sterility* 64:P097, 1990 referenced in P990015a5 (p8) is not published.

Literature studies present study of small cohorts of patients and different methods of adhesion assessment, various degrees of correlation with different scores ranging from minimal to substantial. Extrapolation of the clinical significance of an AFS (or retrospective AFS or mAFS) score or range of scores is limited.

Attachment 4: Method of determining retrospective AFS score.

Attachment 5: FDA Clinical presentation slides

Attachment 6: Sponsor Panel slides