FDA Executive Summary (Version 2)

Prepared for the
March 27, 2006, meeting of the
Obstetrics & Gynecology Devices Panel

P050011
Innovata plc
Adept® Adhesion Reduction Solution
(4% Icodextrin Solution)

1.) INDICATIONS FOR USE

Adept® Adhesion Reduction Solution (4% Icodextrin Solution) (Adept®) is intended for use as an adjunct to good surgical technique for the reduction of post-surgical adhesions in patients undergoing gynecological laparoscopic surgery which may include adhesiolysis. Adept® should be used as both an intra-operative irrigant and post-operative instillate as the last step of the surgical procedure.

2.) PRINCIPLE OF OPERATION

The principle of operation (P050011, Volume 1, page 71) of the device, following instillation of icodextrin solution into the peritoneal cavity after a laparoscopic procedure, is to provide a temporary physical separation of peritoneal surfaces during the early phases of the natural healing process.

In the clinical study, Adept® was used to wash the peritoneal cavity during surgery (at least 100 mL/wash; washes at least every 30 minutes) and then 1000 mL was instilled at the end of surgery. Icodextrin present in Adept® is stated to cause a fluid reservoir to be retained in the peritoneal cavity for up to 96 hours (P050011, Volume 1, page 2), which would be longer than other solutions, such as Lactated Ringers solution (LRS), saline or phosphate buffered saline. Hence, Adept® is hypothesized to provide prevent formation of adhesions by providing a physical separation of the peritoneal surfaces during the early phases of natural healing.

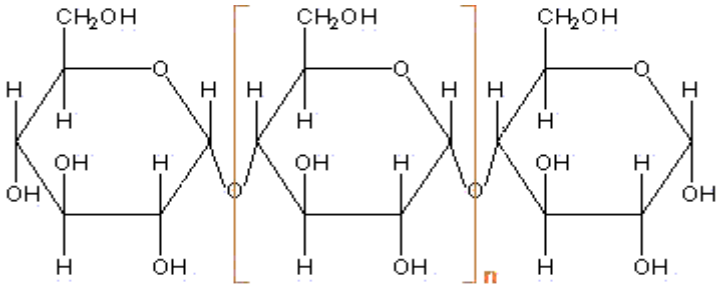
Following instillation, Adept® is expected to be cleared from the peritoneal cavity by diffusion of smaller molecular weight species (<2000 MW) across the peritoneal membrane into the systemic circulation with larger molecular weight species being cleared via the lymphatic system. In the blood, icodextrin is degraded to smaller oligosaccharides by the enzyme α-amylase, which can then be excreted in urine or undergo further enzymatic degradation to glucose by tissue-associated maltases.

3. DEVICE DESCRIPTION

Adept® is a single use, sterile, clear, and colorless to pale yellow fluid for intraperitoneal administration containing icodextrin. Icodextrin is an α-1, 4-linked glucose polymer (P050011, Volume 1, page 20), provided at a concentration of 4% w/v in an electrolyte solution.

Icodextrin (glucose polymer) used in this device is generated via hydrolysis of corn starch. This material is further purified [redacted] to produce icodextrin within a specified molecular weight distribution [redacted]. Adept® is a sterile fluid provided in flexible polyvinylchloride bags containing 1 or 1.5 liters of solution. When stored at temperatures below 30°C (86°F) Adept® 4% Icodextrin solution has a shelf life of 24 months. Adept® should not be refrigerated or frozen.

Figure 1. Glucose ($C_6H_{12}O_6$) – molecular weight = 180.15894



P050011, Volume 1, page 71

Each liter of Adept® contains the following:

1 liter of solution contains	Quantity
icodextrin	40 g
sodium chloride	5.4 g
sodium lactate	4.5 g
calcium chloride	257 mg
magnesium chloride	51 mg

Ionic composition per liter:

Ionic concentration of elements per liter	Concentration (approximate)
sodium	133 mmol
calcium	1.75 mmol
magnesium	0.25 mmol
chloride	96 mmol
lactate	40 mmol

4.) PRE-CLINICAL STUDIES

a) Biocompatibility (M040007, Module1)
A summary of the biocompatibility studies supporting the safe use of the Adept® is provided within the Innovata plc Panel Package. (See sponsor's Draft SSED Volume 1, Section 2, page 15 – 17 and P050011, Volume 1, Section 3.1.) The

biocompatibility studies conducted to support the safety of Adept® were assessed against the requirements for a medical device as recommended by ISO 10993-1:2003.

Toxicological studies:

- *In vitro* biocompatibility (cytotoxicity) tests of glucose polymer dialysis fluids to assess the effect of icodextrin on the numbers and activities of peritoneal macrophages and polymorphonuclear leukocytes were conducted *in vitro* prior to the licensing of icodextrin for use in peritoneal dialysis;
  - *In vitro* biocompatibility (cytotoxicity) of glucose polymer dialysis fluids (T. Liberek et al. Unpublished report); and,
  - Cytotoxicity of dextrin polymer (Icodextrin 10%), using THP-1 human monocytic cells [Margaret West et al. Osmotic Agents (Glucose and a Novel Dextrin Polymer) used in Peritoneal Dialysis Fluids Modify the Activity of THP-1 Human Monocytic Cells. Unpublished report.]
- Systemic toxicity using single dose intravenous (IV) and intraperitoneal (IP) administration routes;
- Systemic toxicity using repeated dose toxicity studies with intraperitoneal (IP) routes of administration;
- Genotoxicity testing, including an *in vitro* chromosomal aberration assay (Chinese hamster ovary cells *in vitro*), an Ames test (mutagenic activity with *Salmonella typhimurium*), and a mouse micronucleus test in bone marrow (CD-1 mice); and
- Haemocompatibility test direct contact method (ISO 10993-4);

Sensitization and irritation assays were not conducted because of the safe use of the 7.5% Icodextrin used for intraperitoneal dialysis. This was determined acceptable given the history of use and the other toxicity testing.

FDA has no remaining concerns – all issues resolved in PMA (P050011), March 16, 2005, (also see M040007, Module 1, Volumes 2 to 6).

b) Sterilization, Packaging and Shelf Life (M040007, Module 2)
The Adept® solution is placed in flexible polyvinylchloride bags (1 or 1.5 L) which are vacuum over-wrapped with polypropylene. This package form is then sterilized by steam in an autoclave with a cycle setting to provide a sterilizing temperature of 121°C and a sterilization time sufficient to provide a minimum lethality (F_O) of 12 minutes for a sterility assurance level (SAL) calculated to 10^{-6}. FDA has no remaining concerns regarding the sterilization of Adept® – all issues resolved in PMA (P050011), March 16, 2005.

The sponsor has proposed a 24-month shelf life for Adept® and data supporting the shelf life of Adept® was provided in M040007, Module 2. FDA has no remaining concerns regarding the shelf life of Adept® at 24-months – all issues resolved in PMA (P050011), March 16, 2005.

c) Manufacturing (Module 3)
No remaining concerns – this module was accepted and closed October 1, 2004.

d) Animal Studies (M040007, Module 1, Volumes 5, 6 and 7)
The sponsor conducted studies using animal models to verify the safety and effectiveness of Adept®. The following are the major categories of testing conducted by the sponsor:

i) Testing for delay of/or prevention of healing - The results of these studies were acceptable.
ii) Infectivity testing - The results of these studies were acceptable.
iii) Reproductive toxicity testing - The results of these studies were acceptable.
iv) Carcinogenesis/metastasis effects (Vol 6, pg 230) - The sponsor's justification for not conducting carcinogenesis studies was accepted.
v) Pharmacokinetics testing - The results of these studies were acceptable.
vi) Effectiveness studies - The results of these studies were acceptable.

A complete summary of these pre-clinical animal studies is presented in Appendix III of this FDA Executive Summary.

Each pre-clinical animal study was found to be complete. However, the results of these studies did not completely address all of our questions regarding the mode of action or pharmacokinetics of icodextrin clearance in Adept®'s intended population. Innovata plc was asked to provide additional information to support Adept®'s ability to maintain a fluid reservoir in the peritoneal cavity for a sufficient time to prevent adhesion formation. To address these issues the sponsor provided additional information from published literature. The sponsor's responses to these questions can be found in Section 3.2 of the panel package.

In addition, a summary of the pathophysiology of adhesion formation and pharmacokinetics of icodextrin clearance from the peritoneal cavity has been provided in the following section of this Executive Summary.

e) Pre-clinical Review Issues

Pathophysiology of Adhesion Formation and Pharmacokinetics of Icodextrin Clearance from the Peritoneal Cavity

Adhesions are typically formed when two injured surfaces are closely apposed. Surgical injury that reduces or eliminates blood flow (ischemia), and the presence of blood clots from the surgical procedure leads to local persistence of fibrin matrix. This adhesive fibrin matrix is capable of forming a "bridge" between closely apposed surfaces. This bridge is then infiltrated by macrophages, polymorphonuclear leukocytes (PMNs), and fibroblasts that initiate the formation of a permanent fibrous adhesion. Histological studies in animals have shown the progression of these cell types into the forming adhesion during the initial 24-96 hours after tissue injury (diZerega 2000; Ellis 1971).

Therefore, to block adhesion formation, Innovata states that an adhesion prevention device must disrupt fibrin bridge formation in the initial 36-48 h after surgery. A study by Harris et al., 1995, assessed the kinetics of peritoneal adhesion formation in rats using different anti-adhesive agents. The results of this study showed the susceptibility of adhesion formation was decreased after the first 36-48 hours after surgery. In addition, the investigators' findings showed that agents remaining at the injury site for at least 36 hours are more effective than those with a shorter residence time.

Unlike the study above in which the most effective devices prevented adhesion formation by forming permanent barriers that blocked fibrin bridge formation, Adept®'s mode of preventing adhesion formation is hypothesized to be its ability to maintain a fluid reservoir that facilitates mobility of intraperitoneal structures and minimizes close apposition of injured surfaces.

Adept®'s ability to draw and maintain a reservoir of fluid in the peritoneal cavity is by the process of colloidal osmosis, which is achieved through the presence of molecular weight species of icodextrin that are not rapidly absorbed across the peritoneal membrane. The majority (85%) of the icodextrin in Adept® is between the molecular weights (MW) of [redacted]. Icodextrin forms <2,000 MW are rapidly absorbed across the peritoneal membrane into the blood, while forms >2,000 MW [redacted] that are too large to be directly absorbed across the peritoneal membrane are reported to be cleared via lymphatic drainage (Misty and Gokal, 1994; Davies 1994). The persistence of icodextrin forms >2,000 MW allows water and low molecular weight solutes to be drawn into the peritoneal cavity, thus maintaining a fluid reservoir that is gradually decreased as icodextrin and fluid are removed by lymphatic drainage and other clearance mechanisms.

Following clearance from the peritoneal cavity via the lymphatics, high molecular weight icodextrin molecules will be transported to the systemic circulation where they are broken down by α-amylase to smaller oligosaccharides. These oligosaccharides are then eliminated by renal excretion, or will undergo additional enzymatic degradation to glucose that can be used in cell metabolism. The supporting information presented in the articles by Bibby (1977) and Moberly (2002) provide evidence that both small and large molecular weight forms of icodextrin present in the systemic circulation can be eliminated via the renal route; however, the majority of icodextrin excreted via this route would be expected to be smaller molecular weight species due to enzymatic degradation.

The ability of a 4% icodextrin solution to maintain a fluid reservoir over an extended duration (72 to 96h) has been reported by Hosie et al., 2001. This study consisted of colorectal cancer patients undergoing intraperitoneal treatment with 5-fluorouracil in 2 liters of a 4% icodextrin solution. The treatment regime consisted of 12-hour dwell times of 2 weeks on, 2 weeks off schedule. During rest periods between treatment cycles, patients underwent additional dwells with 2 liters of 4% icodextrin, normal saline, or 1.36% glucose solution. Fluid volume remaining in the peritoneal cavity was measured at 0, 12, 24, 48 and 96 h after installation. All of the patients involved in the study had normal renal function. Results of this study showed that the 4% icodextrin was able to maintain its instilled volume for the first 24 hours, with approximately half the instilled volume remaining at 72 and 96 hours after installation. In contrast, patients receiving saline or 1.36% glucose were shown to have almost fully absorbed these solutions material within 24 hours.

The results of this study show that Adept® would be able to maintain a fluid reservoir for a longer period of time than an equal volume of a saline or glucose solution. However, the study above assessed fluid retention following placement of a 2 liter dose of a 4% icodextrin solution. It is not known whether administration of a 1 liter dose of Adept® would be capable of maintaining approximately 50% of its instilled volume for 96 hours after administration, as shown in the reference above.

Peritoneal and systemic clearance rates of Adept® have been estimated from data collected from peritoneal dialysis (PD) patients (Moberly, 2002). This study was performed to investigate the absorption and clearance of a single dose of a 7.5%

icodextrin solution in PD patients. The study consisted of 13 patients, nine of whom had residual renal function. All of these patients had been receiving PD for at least three months prior to enrollment in this study. Each patient received a single 2 liter dose of 7.5% icodextrin solution that was left in the peritoneal cavity for 12 hours. Blood, dialysate, and urine samples collected after treatment were analyzed for the presence of icodextrin and icodextrin forms. Of the total dose of icodextrin administered in 2 liters (150 g), approximately 40.1% was absorbed during the 12 hour dwell. The range of dose absorption from the peritoneum in these patients was found to be 24.2 to 63.8% of the administered icodextrin dose. The investigators also determined that urinary excretion of icodextrin and metabolites was directly related to residual renal function as shown by relative rates of creatinine clearance.

Using data from these PD patients, Innovata has estimated that the icodextrin component of Adept® will be cleared from the peritoneum between 18 and 50 hours after administration with estimated total body clearance between 31 to 63 hours. It should be noted that there are no known studies comparing lymphatic flow rates in Adept®'s intended population and PD patients. Therefore, the accuracy of this clearance estimate is not known.

In conclusion, the estimates of icodextrin clearance rates and duration of fluid retention provide reasonable evidence that Adept® may be able to maintain a sufficient fluid volume to facilitate mobility of intraperitoneal structures and minimize close apposition of injured surfaces during the time when early adhesion formation occurs (36-48 hours). However, data used to make these estimates was generated from studies performed in animals and in compromised human patient populations that are dissimilar from Adept®'s intended patient population. In addition, the volumes and/or concentrations of icodextrin solution used in these studies were greater than those intended to be used in Adept® patients. The direct applicability of this information to patients undergoing gynecologic surgery who receive one liter of a 4% icodextrin solution is not known. This information should be used only as an estimate of the devices clearance rate and is ability to be maintained in the peritoneal cavity for a sufficient time to elicit its intended effect.

4.) CLINICAL STUDIES (HUMAN TRIALS)

a) Pilot Studies

There were two pilot trials conducted with Adept®. The first study (CLASSIC) used Adept® as a lavage and as an instillate. The purpose of this study was to evaluate the safety and preliminary effectiveness of the product. In the second trial (RAPIDS) the amount of instillate was increased up to 2 liters to evaluate the safety profile of larger instillate volumes. Each study is discussed below.

Pilot Study I (CLASSIC): ***"A comparative open-label, randomized, multicenter pilot study to determine the safety and efficacy of Adept® in the reduction of post-surgical adhesions after laparoscopic surgery."*** (See Panel Package Draft SSED, Volume 1, Section 2.)

i) Objective

- The study objective was to obtain preliminary data on the safety of Adept® in comparison to Lactated Ringers Solution (LRS) during laparoscopic surgery. Safety was analyzed through the adverse events reporting.
- Preliminary effectiveness data was also obtained. The measurement of the adhesions was to provide preliminary effectiveness data. The analysis was to be descriptive in nature.

The CLASSIC Study was an open-label randomized study conducted at 5 sites with five investigators. The patients were enrolled at the screening visit if eligible. Eighty patients were enrolled to have sixty for evaluation (30 in each arm). Once enrolled the patients had a total of four visits: screening, first procedure, follow-up exam, and second look laparoscopy.

During the first surgery patients received 100 ml of solution every 30 minutes as lavage. Patients to receive Adept® would receive 1 liter. The volume of LRS was left to the discretion of the investigator.

ii) Adhesion Scoring

The incidence, extent and severity of adhesions at the following anatomical sites were recorded: anterior peritoneum (caudal, cephalad right and left), small bowel, anterior uterus, posterior uterus, omentum, large bowel (right and left), rectosigmoid portion of the large bowel, posterior cul-de-sac, right and left pelvic sidewalls, right and left ovaries (lateral, medial and fossa), right and left fallopian tubes, and right and left ampullae. At each site, the adhesion received a score as follows; the extent was graded as localized, moderate and severe; the severity was either mild (avascular) or severe (organized, vascular and dense). The scoring system, known as the modified AFS or "mAFS" system, that was used in the study is described in Johns DB, Keyport GM, Hoehler F and diZerega GS[1].

AFS scores were applied to the adnexa only as described in 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 1988; 49(6): 944-955.

iii) Patient accountability

Patient accountability data are presented in Table 1 below:

Table 1: CLASSIC study patient accountability (duplicated from V2 P15)

	Icodextrin	Control	Total
Patients screened	44	45	89
Excluded patients (screen failures)	10	17	27
Treated Patients (ITT)	34	28	62
Major Protocol Violators	7	2	9
Per Protocol (PP)	27	26	53
No adhesions at baseline	4	7	11
Adhesion reformation group (AR)- at least 1 adhesion at baseline	23	19	42

[1] Johns DB, Keyport GM, Hoehler F and diZerega GS. Reduction of postsurgical adhesions with Intergel adhesion prevention solution: a multicenter study of safety and efficacy after conservative gynecologic surgery. Fertility and Sterility 2001; 76(3): 595-604.

Table 2 shows the volume of solution used in each arm of the study.

Table 2 Volume of solution used in each arm of the study

ITT population	4% Icodextrin (n= 34)	Control (n= 28)
Vol. of study sol'n used intr-op (ml)		
Mean (SD)	1785 (1037)	1802 (1398)
Min-max	0-5300	100-6500
Volume of study sol'n instilled at end of surgery (ml)		
Mean (SD)	1000 (0)	914 (182)
Min-max	N/A	400-1000
Number of patients with less than 1000ml instilled	0	6
Total time of operation (minutes)		
Mean (SD)	85 (39)	80 (30)
Min-max	45-208	34-141

iv) Safety as Measured by Adverse Events

Interpretation of adverse event data is complicated by inability to distinguish adverse events that may have been present at the screening interview from those that were reported post-operatively. Nevertheless, the following can be reported. Five events were reported in three of the Adept® patients and were considered to be possibly related to Adept®. These included two cases of moderate labial/vulvar swelling, moderate right upper quadrant tenderness, moderate abdominal cramping, and leaking from the incision.

v) Effectiveness as Measured by Adhesion Assessment

Tables 3, 4, and 5 present results for changes in adhesion incidence, extent and severity for the intent to treat (ITT), per protocol (PP) and adhesion reformation (ARG) patients. (The ARG group is the patients who had adhesions present at first look.)

Table 3: Change in incidence of adhesions

Type of population	Icodextrin or control	Patients with reduced incidence, n (%)	Patients with unchanged incidence, n(%)	Patients with increased incidence, n (%)	Total
ITT	Icodextrin	16 (47)	8 (24)	10 (29)	34
	Control	8 (29)	9 (32)	11 (39)	28
PP	Icodextrin	12 (44)	6 (22)	9 (33)	27
	Control	6 (23)	9 (35)	11 (42)	26
ARG	Icodextrin	12 (52)	4 (17)	7 (31)	23
	Control	6 (32)	6(32)	7 (34)	19

Table 4: Change in extent of adhesions

Population	Treatment group	Patients with reduced extent, n (%)	Patients with unchanged extent, n (%)	Patients with increased extent, n (%)	Total
ITT	Icodextrin	16 (47)	7 (21)	11 (32)	34
	Control	11 (39)	7 (25)	10 (36)	28
PP	Icodextrin	12 (44)	5 (19)	10 (37)	27
	Control	9 (35)	7 (27)	10 (38)	26
ARG	Icodextrin	12 (52)	3 (13)	8 (35)	23
	Control	9 (47)	4 (21)	6 (32)	19

Table 5: Change in severity of adhesions

Population	Treatment group	Patients with reduced severity, n (%)	Patients with unchanged severity, n (%)	Patients with increased severity, n (%)	Total
ITT	Icodextrin	20 (58)	7 (21)	7 (21)	34
	Control	9 (32)	9 (32)	10 (36)	28
PP	Icodextrin	15 (56)	6 (22)	6 (22)	27
	Control	7 (27)	9 (35)	10 (38)	26
ARG	Icodextrin	15 (66)	4 (17)	4 (17)	23
	Control	7 (36)	6 (32)	6 (32)	19

Adhesion reformation was also evaluated and there was essentially no difference between the two groups. Note that there were more adhesions lysed in the Adept® group when compared to the control group (mean adhesions lysed in the Icodextrin group 4.7 vs. 2.7 in the control).

vi) Conclusions of CLASSIC Study

The 4% icodextrin group and the LRS group had similar demographic variables. However, the 4% icodextrin group had higher incidence, extent and severity adhesions at the baseline. Regarding safety, the two cases of labial/vulvar edema following use of Adept® were probably related to the device. There was no evidence of other adverse events disproportionately related to either device in this study. Regarding effectiveness, this pilot study showed that the use of the 4% icodextrin solution appeared to reduce the number, extent and severity of adhesions seen at second look. There was an increase in the same parameters in the LRS group. With the small number of patients in this pilot study this difference was not statistically significant when the two groups were compared.

Pilot Trial 2 *(RAPIDS)*: "*An Open-Label, Comparative, Randomized, Multicenter Study to Determine the Safety and Efficacy of 4% Icodextrin in the Reduction of Post-Surgical Adhesions after Laparoscopic Surgery"* (See Panel Package Draft SSED, Volume 1, Section 2.)

i) The objectives of the RAPIDS study were:

- To determine the safety of a volume of up to 2 liters 4% icodextrin solution instilled postoperatively after use of the same solution during ob/gyn surgery performed by laparoscopy; and

- To determine preliminary efficacy of this volume instilled at the end of surgery. Comparisons will be made with the standard practice using LRS control at study centers (Volume 3, Page 111).

The RAPIDS Study was an open-label, randomized study conducted at 5 sites. Thirty-seven patients were enrolled and randomized of which 30 patients were evaluable, per protocol (PP) patients. The randomization was 2:1 (treatment: control). Once enrolled the patients had a total of four visits: screening, first procedure, follow-up exam and second look laparoscopy.

As with the CLASSIC Pilot Study, at least 100ml of either the treatment or control device was to be used to irrigate the cavity every 30 minutes during the surgery. At the end of the surgery additional control solution was to be placed in the cavity as is common practice at the institution. In contrast with the CLASSIC Study, however, between 1500 and 2000 ml of the treatment device was used for patients in the Adept® group. Second look laparoscopy took place 6-12 weeks after the initial surgery. The adhesions were scored via the video by a "blinded" reviewer who did not know what treatment the patient had received.

The incidence, extent, and severity were recorded using the scoring system used for the CLASSIC study.

ii) Patient Accountability

Table 6: Patient accounting for RAPIDS

	4% Icodextrin	LRS	Total
Patients screened			54
Screen failures			17
ITT	25	12	37
Major protocol violators	4	3	7
PP	21	9	30

The seven patients who were categorized as "major protocol violators" did not return for their second look.

Table 7: Volume of solution used in each arm of the study:

ITT population	4% Icodextrin (n= 25)	Control (n= 12)
Vol. of study sol'n used intr-op (ml)		
Mean (SD)	1490 (922)	1871 (2353)
Min-max	200-3200	250-9000
Volume of study sol'n instilled at end of surgery (ml)		
Mean (SD)	1972 (106)	1292 (450)
Min-max	1500-2000	1000-2000
Number of patients with less than 1500ml instilled	0	8
Total time of operation (minutes)		
Mean (SD)	70 (31)	89 (59)
Min-max	37-149	44-254

iii) Safety as Measured by Adverse Events

(1) There were more adverse events reported in the Adept® group compared to control (6.8 vs. 5.4 per patient). Every patient reported at least one adverse event. More headaches and dysmenorrhea were noted in the treatment group. Adverse events that were possibly related to Adept® included one episode of difficulty breathing, three episodes of bloating or distension, one episode of incisional oozing and one episode of labial swelling.

iv) Effectiveness as Measured by Adhesion Assessment

Tables 8, 9, and 10 provide information on the change in incidence, extent, and severity of adhesions for both the intent to treat (ITT) and PP groups for each treatment.

Table 8: Change in incidence of adhesions

Type of population	Icodextrin or control	Patients with reduced incidence, n (%)	Patients with unchanged incidence, n(%)	Patients with increased incidence, n (%)	Total
ITT	Icodextrin	10 (40)	10 (40)	5 (20)	25
	Control	3 (33)	4 (33)	4 (33)	12
PP	Icodextrin	10 (48)	6 (29)	5 (24)	21
	Control	4 (44)	1 (11)	4 (44)	9

Table 9: Change in extent of adhesions

Population	Treatment group	Patients with reduced extent, n (%)	Patients with unchanged extent, n (%)	Patients with increased extent, n (%)	Total
ITT	Icodextrin	14 (56)	7 (28)	4 (16)	25
	Control	4 (33)	5 (42)	3 (25)	12
PP	Icodextrin	14 (67)	3 (14)	4 (19)	21
	Control	4 (44)	2 (22)	3 (33)	9

Table 10: Change in severity of adhesions

Population	Treatment group	Patients with reduced severity, n (%)	Patients with unchanged severity, n (%)	Patients with increased severity, n (%)	Total
ITT	Icodextrin	13 (53)	7 (28)	5 (20)	25
	Control	5 (42)	5 (42)	2 (17)	12
PP	Icodextrin	13 (62)	3 (14)	5 (24)	21
	Control	5 (56)	2 (22)	2 (22)	9

v) Conclusions from the RAPIDS Study

The 4% icodextrin group and the LRS group had similar demographic variables. Regarding safety, one episode of difficulty breathing, three episodes of bloating or distension, one episode of incision oozing and one episode of labial swelling following use of Adept® were possibly or probably related to the device. Regarding effectiveness, this pilot study showed that the use of the 4% icodextrin solution slightly reduced the number, extent and severity of adhesions seen at second-look compared with LRS. With the small number of patients in this pilot study this difference was not statistically significant when the two groups were compared. The results are consistent with the earlier findings (CLASSIC study.)

b) Pivotal Clinical Trial

Pivotal Clinical Trial - *PAMELA*: *"A Pivotal, Double-Blind, Comparative, Multicentre Study to Determine the Efficacy and Safety of Adept® in the Reduction of Post-Surgical Adhesions after Laparoscopic Surgery"* (See P050011 Volume 1, Section 4, Protocol and Panel Package Volume 2 and 3, Sections 5.1 – 5.3, Clinical Study Results)

i) Objectives

The objectives of the PAMELA study were to determine the effectiveness and safety of Adept® when used as an intraoperative washing solution with a postoperative instillate in the reduction of post-surgical adhesions after laparoscopic surgery for adhesiolysis, compared with LRS in a double-blind, comparative, randomized, multi-centre study in the USA.

PAMELA was conducted at 16 centers in the US. The goal for each center was to recruit between 20 and 75 patients. Centers with less than 5 patients would be pooled. The plan was to enroll sufficient numbers of patients so that 410 (205 in each arm) completed the second look procedure..

Each patient was expected to be in the study between 5 and 9 weeks.

ii) Eligibility Criteria:

(1) Inclusion Criteria:

- willing, able to and having freely given written consent to participate in the study and abide by its requirements;
- female patients aged eighteen and over, in good general health including ASA (American Society of Anesthesiologists) score of 2 or less;
- laparoscopic peritoneal cavity surgery is planned for a gynecologic procedure which includes adhesiolysis; and
- patient agrees to planned second-look laparoscopy for this study 4-8 weeks after the initial surgical procedure.

(2) Exclusion Criteria

(Pre-operative)

- current pregnancy including ectopic pregnancy;
- SGOT, SGPT and/or bilirubin > 20% above the upper range of normal and considered clinically significant;
- BUN and creatinine > 30% above the upper range of normal and considered clinically significant;
- concurrent use of systemic corticosteroids, antineoplastic agents and/or radiation;
- active pelvic or abdominal infection;
- known allergy to starch-based polymers; and
- additional surgical procedure (non-OB/GYN) planned to be performed during the laparoscopic procedure.

(Intra-operative)

- clinical evidence of cancer;
- clinical evidence of pregnancy including ectopic pregnancy;
- use during this procedure of any approved or unapproved product for the purpose of preventing adhesion formation;
- fewer than 3 of the available anatomical study sites contain adhesions;
- less than three of the anatomical sites are lysed;
- if the procedure needs to be performed by a laparotomy (decision made after laparoscopy has commenced);
- if any of the anatomical sites being scored for the purposes of this study are being removed during surgery;
- if all of the available anatomical sites cannot be visualized and recorded on the video tape during the surgery; and
- any unplanned surgery which involves opening of the bowel (excluding appendectomy)" (refer to P050011, Volume 5, Page 15.)

iii) Hypothesis

The overall hypothesis for the pivotal clinical study encompassed three co-primary outcome measures, each with a respective hypothesis:

(1) The first co-primary endpoint for the pivotal study is the difference (for an individual study subject) in the number of adhesion sites between baseline and second look laparoscopy (2LL). For subjects with ten or fewer adhesions lysed at surgery, an individual patient success is defined as a decrease of at least 3 sites with adhesions between baseline and 2LL. For subjects with more than ten adhesions lysed at baseline, individual patient success is defined as a decrease in adhesions sites of at least 30% between baseline and 2LL. The study hypothesis for the 1st co-primary endpoint is that the success rate for the Adept treated patients will be at least 5% greater than the success rate for subjects treated with lactated Ringer's solution (LRS).

In the study protocol (P050011, Vol. 5, p32), the sponsor stated the hypothesis as follows:
"*The lower bound of the 95.2% confidence interval for the difference in success rates between the Adept-treated patients and control patients will be greater than 5%."*

(2) The second co-primary endpoint is the difference (for an individual study subject) in the number of adhesion sites between baseline and 2LL. In the hypothesis for this endpoint, patients serve as their own control. The hypothesis is that Adept® treated subjects would have less sites with adhesions at 2LL than they had at baseline.

In the study protocol (P050011, Vol. 5, p32), the sponsor again expresses this as a confidence interval:
"The 95.2% confidence interval for the difference between the number of adhesions at the second look and the number at the first look must be less than zero in the Adept-treated patients."

(3) The third co-primary endpoint is the difference (for an individual subject) in the number of dense adhesion sites between baseline and 2LL. For the 3rd co-primary endpoint, success for a subject is defined as any reduction in dense adhesion sites between baseline and 2LL. The hypothesis for this 3rd endpoint is that the success rate for Adept-treated subjects is greater than that for LRS treated subjects.

In the study protocol (P050011, Volume 5, p32), the sponsor states the hypothesis as follows:
"A statistically significant difference between Adept-treated and control groups in the percentage of patients with fewer sites with dense adhesions at the 4.8% significance level."

iv) Secondary Endpoints

The sponsor pre-specified the following secondary endpoints in their protocol. No hypothesis tests were specified for these endpoints.

Incidence of sites with adhesions
Change from 1st to 2nd look
Percentage of patients having 4 or fewer sites with adhesions at 2LL
Shift analysis - % patients with 2nd look incidence grouped into 4 categories
% change from 1st to 2nd look per patient
Severity of sites with adhesions
% change from 1st to 2nd look per patient
Extent of sites with adhesions
% change from 1st to 2nd look per patient
AFS score
Modified AFS score
Reformed adhesions
***De novo* adhesions**
Abdominal wall adhesions
Visceral adhesions

The study also captured relief of pain symptoms, as measured by a visual analog scale (VAS) for pain, between baseline and second look laparoscopy.

v) Interim Analysis

A planned interim analysis was conducted after 221 patients were enrolled in the study with 205 patients having undergone second look laparoscopy (2LL). The purpose of interim analysis was to determine whether the study could be stopped for success. The analysis led to the conclusion that the study should continue. (P050011, Volume 5, Section 16.1.13, page 311)

- At that time the first co-primary endpoint (larger of 3 adhesion sites at second look or a decrease or 30% of the number of adhesion sites for those patients with more than 10 adhesions lysed at baseline) had not succeeded.

- The second co-primary endpoint (subjects will not have more sites with adhesions at second look laparoscopy than they had initially) had succeeded.

- The third co-primary endpoint (the percentage of patients having fewer adhesion sites with dense adhesions at second look laparoscopy will be statistically significantly greater in the Adept® treated group than in the control group) had not succeeded.

Interim analysis concluded that stopping rules had not been met and that the study should continue.

vi) Patient Accounting and Demographics

Figure 2 provides an account of all study patients.

Figure 2. Patient Accounting

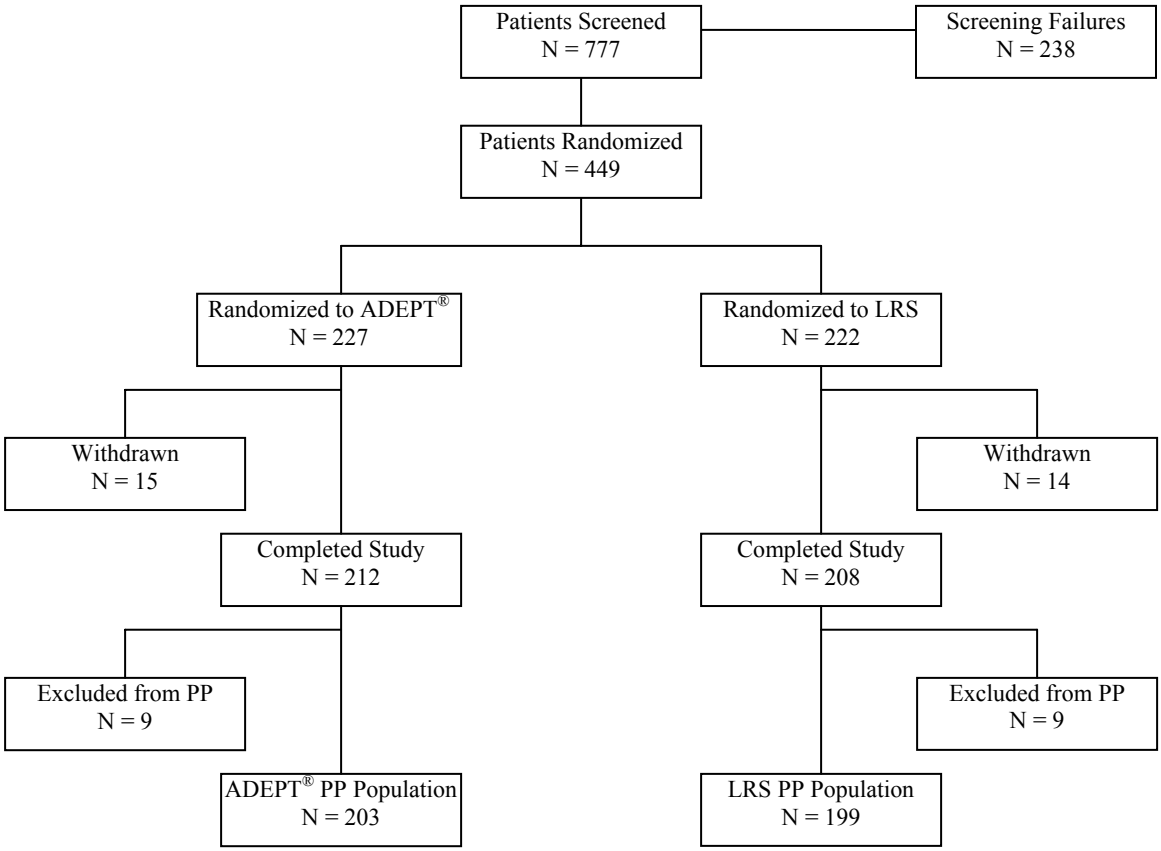


Table 11 shows the demographics and baseline characteristics of the study subjects.

Table 11: Pivotal Study Demographics and Baseline Data, ITT

		Adept®	Control
# patients randomized (ITT)		227	222
Demographics ± s.d.			
Age, yr		32.6 ± 5.9	32.3 ± 5.7
Height, in(n)		64.7 ± 2.7 (225)	64.2 ± 2.8 (221)
Weight, lb (n)		153.2 ± 36.9 (225)	152.0 ± 35.0 (220)
Race	Caucasian	160 (70.5%)	144 (64.9%)
n(%):	East Asian	3 (1.3%)	7 (3.2%)
	Afro-Caribbean	32 (14.1%)	32 (14.4%)
	Hispanic	24 (10.6%)	35 (15.8%)
	Oriental	3 (1.3%)	1 (0.5%)
	Other	5 (2.2%)	3 (1.4%)
Base vital signs			
Systolic blood pressure, mmHg(n)		114.9 ± 12.1 (224)	114.5 ± 11.8 (221)
Diastolic blood pressure, mmHg(n)		71.5 ± 8.8 (224)	71.4 ± 8.8 (221)
Heart rate, bpm(n)		73.1 ± 8.8 (224)	73.2 ± 8.3 (218)
Primary diagnosis n(%)			
Pelvic pain		152 (67.0%)	134 (60.4%)
Endometriosis		94 (41.4%)	93 (41.9%)
Infertility		115 (50.7%)	127 (57.2%)
Adhesions		126 (55.5%)	127 (57.2%)
Others		36 (15.9%)	43 (19.4%)
Medical history n(%)			
# of patients with resolved medical conditions		192 (84.6%)	191 (86.0%)
# of patients with ongoing medical conditions		224 (98.7%)	219 (98.6%)
No. of patients with surgical history		205 (90.3%)	196 (88.3%)
Baseline assessment of adhesions			
Number of Sites with Adhesions		10.27 ± 4.26	10.34 ± 4.39
Number of Sites with lysed Adhesions		8.69 ± 4.15	8.46 ± 4.02
Number of Sites with dense Adhesions		6.17 ± 4.74	6.23 ± 5.26
Number of Sites with lysed dense Adhesions		5.35 ± 4.56	5.15 ± 4.46
Baseline AFS score for infertility subgroup (PP)*		8.98 ± 9.86	8.20 ± 9.88
Baseline mAFS score (PP)*		2.71 ± 2.47	2.81 ± 2.93
Endometriosis n(%)			
Present at baseline		140 (61.7%)	135 (60.8%)
Treated		138 (60.8%)	135 (60.8%)
Others			
Operative Time (mins) (median) (ITT)		85.0	88.0
Days between first and second look surgery (ITT)		39.9 ± 10.3	39.9 ± 10.7
Average volume of solution lavaged and instilled, ml (min-max)		2,502 (1,300-12,000)	2,570 (1,300-12,000)

From this table it is apparent that the study arms were well balanced. It is important to note that almost all sites with adhesions were lysed (on average 10 at baseline with 9 lysed for both groups). The mean decrease in sites with dense adhesions is just greater than one (6.2 to 5.25 overall). Also note that this population had a fairly substantial adhesion burden with an average of 10 sites per subject and 6 sites with dense adhesions per subject.

It was noted that the center effect was statistically significant for most analyses, reflecting the variations and difference in specialties among the participating centers (see Appendix II).

vii) Pivotal Study Results

(1) Primary Effectiveness Endpoints

First Co-Primary Endpoint: 45.4% of the patients in the Adept® group were defined as a "clinical success" compared to 35.6% in the control group (p=0.016, two-tailed test) (Table 12). However, the lower bound of the 95.2% CI around the difference in success rates (0.7%) is less than the pre-specified 5%.

Second Co-Primary Endpoint: Patients in the Adept® group had significantly fewer sites with adhesions at second-look compared to first look laparoscopy (p<0.001). The 95.2% confidence intervals were less than zero for both the Adept® treated patients (–2.83 to –1.62) and the LRS-treated patients (-2.24 to -0.96).

There was a significantly greater reduction in the number of sites with adhesions in the Adept® treated patients compared with the control group (p=0.047, two-tailed test). The Least Square (LS) mean for change in Table 12 (Pivotal Study Primary effectiveness endpoints) is the difference between the two groups adjusted for baseline score and center effect.

Third Co-Primary Endpoint: In the Adept® group, 50% of patients had fewer sites with dense adhesions at second look (p<0.001); in the control group, the figure was similar (49%) (Table 12). There was no statistically significant difference between treatments (p=0.73).

Table 12: Pivotal Study Primary effectiveness endpoint (ITT)

	Adept®	**Control**
Total number of patients	227	222
Success		
Number reporting	103 (45.4%)	79 (35.6%)
Difference in % of patients with success	9.8%	
95.2 CI for % of patients with success	(0.7%, 18.9%)	
Number of sites with adhesions		
First look (mean±sd)	10.27±4.26	10.34±4.39
Second look (mean±sd)	7.88±4.64	8.49±4.98
Change from first to second look (mean±sd)	-2.40±3.66	-1.86±3.35
LS mean for change (95.2% CI)	**-2.22 (-2.83, -1.62)**	-1.60 (-2.24, -0.96)
p-value for change	**<0.001**	<0.001
Difference between LS means	-0.62	
95.2% CI	(-1.24, -0.004)	
p-value for treatment	0.047	
Percentage of patients with fewer sites with dense adhesions		
Number of patients with fewer dense adhesions at second look (%)	114 (50.2%)	109 (49.1%)
p-value for difference	0.73	
First look (mean±sd)	6.17±4.74	6.23±5.26
Second look (mean±sd) (n)	5.02±4.60 (212)	5.25±5.26 (208)
Change from first to second look (mean±sd) (n)	-1.19±3.43 (212)	-1.01±3.24 (208)
p-value for change	<0.001	<0.001

*Least square mean for change, adjusted for center and baseline.

(2) Secondary effectiveness endpoints (PP population)

There were ten pre-specified secondary effectiveness endpoints. These were analyzed for the per protocol population. Table 13 provides a summary of these endpoints. The results are consistent with the analyses for the primary effectiveness endpoints. Note that several of the secondary analyses performed by the sponsor were not pre-specified. These included subgroup analyses of patients with infertility as a primary diagnosis, 50% of the total subject population.

To properly evaluate these secondary endpoints, multiplicity adjustments must be applied to account for the high correlation between these endpoints. When FDA applied multiplicity adjustments, (Appendix I), only one of these endpoints appears to be statistically significant in favor of Adept®: infertility patients with a reduction in their AFS score.

Table 13: Pivotal Study Secondary Effectiveness Endpoints (PP)

Endpoint / Variable	Adept®	Control	P-value*
Incidence of sites with adhesions			
Change from 1st to 2nd look	-2.64 ± 3.66	-2.02 ± 3.19	0.039
% patients with reduction	76.4%	69.3%	0.121
Change from 1st to 2nd look excluding non-lyzed sites	-2.64 ± 3.66	-2.02 ± 3.19	0.068
% patients with four or fewer sites with adhesions at 2nd look	32.0	28.1	0.510
Shift analysis - % patients with 2nd look incidence grouped Into 4 categories	0: 4.9 1-4 27.1 5-9 36.0 ≥10 32.0	0: 4.5 1-4 23.6 5-9 31.7 ≥10 40.2	0.173
Severity of sites with adhesions			
% change from 1st to 2nd look per patient	-24.2 ± 45.2	-21.5 ± 41.0	0.415
% patients with reduction	72.9%	69.8%	0.446
Extent of sites with adhesions			
% change from 1st to 2nd look per patient	-26.9 ± 51.4	-21.8 ± 48.5	0.240
% patients with reduction	77.3%	69.8%	0.084
AFS score			
Change from 1st to 2nd look for patients with a primary Diagnosis of infertility	(n=102) -3.46 ± 6.77	(n=112) -1.10 ± 6.36	0.011
% patients with reduction for patients with a primary diagnosis of infertility	**52.9%**	**30.4%**	**0.001**
Shift analysis - % patients with 2nd look scores grouped Into 4 categories	(n=102) minimal: 68.6 mild: 10.8 moderate: 11.8 severe: 8.8	(n=112) minimal: 59.8 mild: 13.4 moderate: 15.2 severe: 11.6	0.066
Modified AFS score			
Change from 1st to 2nd look	-0.67 ± 1.54	-0.48 ± 1.61	0.094
% patients with reduction	70.4%	69.8%	0.722
Reformed adhesions			
Number of sites with reformed adhesions	4.92 ± 3.91	5.11 ± 4.12	0.722
Number of sites without reformed adhesions	3.77 ± 2.72	3.32 ± 2.29	0.065
% patients with at least one	87.7%	86.9%	0.832
***De novo* adhesions**			
Number of sites with	1.13 ± 1.85	1.29 ± 1.61	0.036
% patients with at least one	47.3%	57.3%	0.029
Abdominal wall adhesions			
Change from 1st to 2nd look in number of sites	-1.17 ± 1.63	-0.94 ± 1.60	0.184
% patients with reduction from 1st to 2nd look in no. sites	65.5%	58.3%	0.129
Visceral adhesions			
Change from 1st to 2nd look in number of sites	-1.47 ± 2.62	-1.07 ± 2.22	0.046
% patients with reduction from 1st to 2nd look in no. sites	68.5%	63.3%	0.228
VAS score for pelvic pain			
Change from screening to 2nd look for patients with primary diagnosis of pelvic pain	(n=118) -35.8 ± 32.8	(n=108) -30.8 ± 30.2	0.995

*** not adjusted for multiplicity.**

(3) Safety

Table 14 shows the total number of adverse events for all enrolled study subjects (ITT).

Table 14: Adverse Events (ITT), PMA Vol 4, p156

	Adept®		LRS	
	Number of patients reporting	Number of reports	Number of patients reporting	Number of reports
	227	1065	222	1047
Overall	221	1065	218	1047
Prior to first surgery	17	22	16	20
Between first and second surgery	221	1009	217	985
Related to study device	55	84	38	48
Starting ≤8 days post first surgery	217	635	214	636
After second surgery	30	34	35	42
Serious adverse events	8	25	11	19

Table 15 shows the adverse events with an incidence of 5% or greater.

Table 15: Adverse Events, ≥ 5% incidence

	Adept®		LRS	
	Number of patients reporting	Number of reports	Number of patients reporting	Number of reports
Total number of patients at risk	227		222	
Adverse Events n(%)				
POST PROCEDURAL PAIN	**192 (84.6%)**	**223**	**194 (87.4%)**	**233**
HEADACHE*	***81 (35.7%)***	***131***	***72 (32.4%)***	***127***
Nausea	39 (17.2%)	41	37 (16.7%)	41
Post procedural discharge	31 (13.7%)	31	30 (13.5%)	30
Dysmenorrhea	30 (13.2%)	32	26 (11.7%)	34
Constipation	24 (10.6%)	26	23 (10.4%)	24
Pelvic pain	23 (10.1%)	32	21 (9.5%)	21
Arthralgia	20 (8.8%)	22	19 (8.6%)	19
Flatulence	19 (8.4%)	19	17 (7.7%)	19
Urinary tract infection	16 (7.0%)	17	12 (5.4%)	13
ABDOMINAL PAIN	**15 (6.6%)**	**26**	**19 (8.6%)**	**23**
DYSURIA*	***15 (6.6%)***	***16***	***8 (3.6%)***	***9***
Nasopharyngitis	15 (6.6%)	15	18 (8.1%)	18
VAGINAL BLEEDING*	***14 (6.2%)***	***15***	***5 (2.3%)***	***5***
Abdominal distension	13 (5.7%)	13	10 (4.5%)	10
POST PROCEDURAL NAUSEA	**13 (5.7%)**	**13**	**20 (9.0%)**	**20**
PYREXIA*	***13 (5.7%)***	***13***	***7 (3.2%)***	***7***
VOMITING	**13 (5.7%)**	**13**	**22 (9.9%)**	**22**
VULVAR & VAGINAL SWELLING*	**13 (5.7%)**	**13**	**1 (0.45%)**	**1**
Back pain	12 (5.3%)	15	12 (5.4%)	13
Insomnia	12 (5.3%)	14	8 (3.6%)	8
Cough	10 (4.4%)	10	12 (5.4%)	13
DIARRHEA	**3 (1.3%)**	**3**	**13 (5.9%)**	**15**

AEs in ***ITALICS/BOLDED**** are higher (≥ 2%) for the Adept® subjects.
AEs **CAPITAL/BOLDED** are higher (≥ 2%) for the LRS subjects.

Note that several of these are imbalanced (bolded) with a ≥ 2% difference between groups. There is more pain and more abdominal pain in the LRS group (which had less pain as primary diagnoses) but not more pelvic pain. There is also more nausea, vomiting and diarrhea in the LRS group. There are more headaches, fever, vaginal bleeding and dysuria in the Adept® group.

Table 16 provides the differences in the AEs identified (bolded) that occurred ≤ 7 days post first surgery.

Table 16: AEs with ≥ 2% difference between the two groups that occurred ≤ 7 days post first surgery.

	Number of patients reporting Adept®	Number of reports	Number of patients reporting LRS	Number of reports
Total number of patients at risk	227		222	
Adverse Events n(%)				
Post procedural pain	188 (84.6%)	194	192 (86.5%)	233
Headache	28 (12.3%)	30	31 (14%)	37
Abdominal pain	14 (6.1%)	19	18 (8.1%)	20
Dysuria	11 (4.8%)	11	7 (3.2%)	8
VAGINAL BLEEDING*	***13 (5.7%)***	***13***	***7 (3.3%)***	***7***
VULVAR & VAGINAL SWELLING*	**13 (5.7%)**	**13**	**1 (0.45%)**	**1**
Post procedural nausea	31 (13.7%)	32	31 (14.0%)	34
Pyrexia	11 (4.8%)	11	7 (3.2%)	7
VOMITING	**12 (5.3%)**	**12**	**21 (9.5%)**	**21**
DIARRHEA	**2 (0.9%)**	**2**	**6 (2.7%)**	**6**

AEs in ***ITALICS/BOLDED**** are higher (≥ 2%) for the Adept® subjects.
AEs **CAPITAL/BOLDED** are higher (≥ 2%) for the LRS subjects.

Vaginal hemorrhage, uterine hemorrhage and vaginal discharge were combined as vaginal bleeding. Abdominal pain and lower abdominal pain were combined as abdominal pain. In the immediate post operative period all discrepancies between the two groups disappear (<2%) except for vomiting, diarrhea and vaginal bleeding.

Labial, vaginal, and vulvar swelling and vaginal fullness are adverse events associated with this product. According to the sponsor it occurs in 0.03 - 0.04% of the patients receiving this product in Europe. In this study the event occurred in 14 (6%) of the patients. The same adverse event occurred in 1 (0.5%) of the LRS patients. Eight Adept® patients reported the swelling as mild. The other 5 reported moderate and 1 severe. All of these reports occurred within the first seven days post-instillation of the device. Most occurrences resolved on average within 7 days without sequelae. This is a true adverse event for the product. This must be weighed against a potential adhesion improvement.

There were a total of 45 serious adverse events, no deaths. The following could be related to the treatment; 2 Adept® and 2 LRS.

Table 17: Serious Adverse Events possibly related to the treatment

Center #/Patient #/treatment	Days post op	Age	SAE	Duration and severity	Details
13/637[a] **Adept®** Vol. 2 Page 372-4	Same day	42	Inability to void, labial swelling, ecchymoses at port site, nausea, vomiting	All lasted 1-2 days except ecchymoses which lasted 12 days. Urinary was severe, all else moderate	Admitted day of surgery for inability to void, observed overnight with intermittent catheterization and developed ecchymoses, nausea and vomiting. Discharged on second day of hospitalization
14/485 **Adept®** Vol. 4 Pages 375-8	Same day	25	Pain in pelvis, chest, shoulder, abdomen, nausea, dysuria, urinary frequency	1-7 days, All severe	Pt with h/o chronic pelvic pain. Admitted two days after surgery, only finding noted was pneumoperitoneum, nausea from sound of fluid moving around in her stomach, urinary frequency developed in hospital
14/555 **LRS** Vol. 4 Pages 420-2	4	23	Severe abdominal pain, nausea, vomiting, lower back pain	1-2 days, all severe except back pain which was moderate	Initial ER visit was Day of surgery, followed up with office visit with acute abdominal pain followed by nausea and vomiting and hosp for observation, (-) CT scan. Symptoms resolved spontaneously,
13/073 **LRS** Vol. 4 Page 183	2	43	Decreased urinary output, elevated creatinine	Both events 2 days	Admitted for 2-days, catheterized, given IV fluids, discharged

[a] This event was considered by the investigator as unrelated to Adept®.

(4) Laboratory Values

The sponsor identified three patients treated with Adept® who developed elevated liver functions between surgeries that resolved by visit four (the second surgery). They provided no explanation for these evaluations. There could be variety of causes for these abnormalities such as the treatment itself, the anesthetic medications or sources unrelated to the surgery.

Hyperkalemia was noted in eight patients and hypokalemia was noted in one patient in the Adept® group. Of the 8 patients with hyperkalemia, the value was slightly above the upper limit of the normal range (5.3) and ranged from 5.4 – 5.8. Only one patient in the LRS group had potassium abnormalities.

(5) Conclusions from PAMELA

Safety

To date, no serious adverse events have been associated with Adept® in this clinical trial. Vaginal/vulvar edema is a side effect associated with the use of Adept®, but has not resulted in serious morbidity.

Effectiveness: Primary Endpoints

The study was designed with three co-primary endpoints and respective hypotheses. Therefore, study success in biostatistical terms requires that all three hypotheses be met. Since only one of the three objectives was met, the results from this clinical study did not achieve statistical significance.

The results for the co-primary endpoints:

- The first co-primary effectiveness objective was not met. The study showed a 9.8% improvement (95.2% CI: 0.7 - 18.9) in the success rate for Adept-treated subjects compared to the patients in the control arm. Although the Adept group had a significantly higher success rate than the LRS group (p=0.016), the study did not meet the hypothesis for this endpoint since the lower bound (of 0.7%) of the 95.2% confidence interval was less than pre-specified 5%.

  By way of explanation, the sponsor notes that the 35.6% success rate in the control group was much higher than expected and undermined the ability of the study to achieve its objective with the designated sample size.

- The second co-primary effectiveness objective was met. With subjects serving as their own controls, the study showed that Adept-treated patients did not have more adhesions at second look laparoscopy compared to the number of adhesion sites at baseline surgery (p=0.001).

- The third co-primary effectiveness objective was not met. The study showed no difference between the two arms in the percentage of patients with fewer dense adhesions at second look laparoscopy. Approximately 50% of subjects in both arms had fewer dense adhesions at second look laparoscopy.

During its March 27, 2006 meeting, the Obstetrics-Gynecology Devices Panel will be asked to weigh the relative merits of these three findings towards the overall risk-benefit profile of the Adept 4% icodextrin solution when used as intended.

Effectiveness: Secondary Endpoints

After applying multiplicity adjustments (Appendix I), one secondary effectiveness endpoint appears to be statistically significant in favor of Adept®: infertility patients with a reduction in their AFS scores.

It was noted that the center effect was statistically significant for most analyses, reflecting the variations and difference in specialties among the participating centers (see Appendix II).

6.) OUTSIDE U.S. MARKET EXPERIENCE – ARIEL REGISTRY

Since Adept® was first marketed in the UK in 2002, the sponsor has obtained information on postmarket experience in use of this device through two different sources: the Adept® Registry for Clinical Evaluation (ARIEL) and spontaneous reports. The sponsor has also provided FDA with published literature on postmarket experience of Adept®.

Registry (ARIEL)

The Adept® Registry for Clinical Evaluation (ARIEL) commenced in the United Kingdom (UK) in 2000 following the initial regulatory approval of Adept® and its subsequent launch in the UK.

The objective of ARIEL was to capture the clinical experiences of surgeons during routine use of Adept® in a systematic way during general (General Surgery Registry) and gynecological surgery (Gynecology Registry). A Registry Form was used to collect information on use of Adept®. The major outcome data that ARIEL collected include overall satisfaction of using Adept® (surgeon's perspective), leakage of peritoneal fluid/Adept® at closure, complications during surgery, postoperative complications, mortality, length of hospital stay, abdominal discomfort reported by patients, and post discharge adverse events. ARIEL also collected data on patients' date of birth, date of surgery, reason for admission, history of endometriosis and adhesion, other relevant medical history, and type of surgery (laparotomy vs. laparoscopy). ARIEL did not collect information on race/ethnicity or other demographic characteristics.

Between February 2000 and December 2003, ARIEL captured data from the routine surgical use of Adept® by surgeons in six European countries. A total of 4,620 patients were enrolled in the registry, which include 2882 patients who underwent gynecologic surgeries (2069 laparoscopies and 813 laparotomies) and 1738 patients who underwent general surgeries (269 laparoscopies and 1469 laparotomies). Table 1 shows the number and percentage of patients with selected adverse events in patients treated with Adept® in the ARIEL Gynecology Registry.

Table 18. Top five adverse events in 2,069 ARIEL gynecological laparoscopy patients

Adverse Event	ARIEL
	Number (%)
Pyrexia	10 (0.5)
Device failure	9 (0.4)
Abdominal pain	5 (0.2)
Abdominal distension	5 (0.2)
Urinary retention	5 (0.2)

Postmarket Experience Outside of US

Since Adept® was first marketed in the UK, this device has been launched in 29 EU countries. Based on the assumption of 2 x 1L bags or 1 x 1.5L bags (accounting for irrigation and instillation), the number of patients treated with Adept® was 113,114 as of June 2005. Of the 29 countries where Adept® was marketed, 16 countries require reporting adverse events while 13 countries do not have such a requirement. Of the total number of patients treated, the number undergoing gynecologic laparoscopy cannot

be estimated, and therefore, the prevalence and incidence of any individual adverse event cannot be estimated.

The most frequently reported adverse events in gynecologic patients were vulval oedema (n = 3) and peritonitis (n = 2).

Published Literature

The sponsor provided two articles on Adept® that have been accepted for publication in peer-reviewed journals. A brief summary of these two articles is as follows:

Article 1: Sutton C, Minelli L, Garcia E, et al.,[2] reported that the incidence of overall adverse events was 7.5% in laparoscopy group and 13.9% in laparotomy group. The most common adverse events in patients who underwent laparotomy surgeries with Adept® were septic/infective events (2.7%), surgical/technical events (2.0%), and pain (1.7%). In the laparoscopy cohort, the most common adverse events were irrigation/instillation events (1.9%), hematological events (1.0%), and pain (1.0%). Postoperative ileus and vulval oedema were also reported, but at a much lower incidence (0.1% and 0.5%, respectively, in laparoscopic surgery; 1.0% and 0.3%, respectively, in laparotomy).

Article 2: Menzies D, Hidalgo M`, Walz MD, et al.,[3] reported that adverse events occurred in 30.6% of laparotomy patients and 16.7% of laparoscopy patients. The most common adverse events were septic/infective events (4.2% and 3.4% in the laparotomy and laparoscopy groups respectively).

[2] Sutton C, Minelli L, Garcia E, et al. Use of icodextrin 4% solution in the reduction of adhesion formation after gynecological surgery. Gynecological Endoscopy (in press).

[3] Menzies D, Hidalgo M, Walz MD, et al. Use of icodextrin 4% solution in the prevention of adhesion formation following general surgery: experience from the multicentre ARIEL Registry. Ann R Coll Surg Engl 2006 (in press).

Appendix I: Multiplicity Adjustment for Secondary Endpoints

There are ten secondary effectiveness endpoints (24 tests (subsections)) in this PMA. The statistical reviewer raised the multiplicity problem in the July 1, 2005, deficiency letter. The sponsor responded that it is not necessary to adjust the multiplicity because the secondary endpoints were exploratory and intended to provide supporting/confirmatory evidence for the primary endpoints. Furthermore, the sponsor said that there is no easy way to adjust the multiplicity because the secondary endpoints are correlated. The statistical reviewer believes that the sponsor's response that the secondary endpoints are only intended to provide confirmatory evidence for the primary endpoints if successful is acceptable.

However, if the sponsor wants to use the secondary endpoints to show the effectiveness of its device in the panel meeting, then it is necessary to explore the multiplicity adjustment to evaluate the degree of evidence that can be drawn from the secondary endpoints.

A widely used method for multiplicity adjustment is the Bonferroni correction. This method is appropriate when all endpoints are independent. When endpoints are correlated, this method is conservative.

The Bonferroni correction changes the threshold of the significance level alpha (usually 0.05) according to the degree of correlation among endpoints. For example, with 10 independent hypothesis tests, the alpha for each hypothesis to be significant would be 0.01/10=0.005. If two of the hypotheses are perfectly correlated (if one is rejected then the other one is also rejected), the alpha would be 0.05/9=0.006. If half the 10 are perfectly correlated, the alpha would be 0.05/2=0.025.

Generally, we do not know the correlations among these endpoints. The following Table 19 shows which endpoints are significant when different correlations are assumed (from 1 in which all are perfectly correlated to 24 in which all are independent). The column 1 means that there is no multiplicity adjustment. The column 24 means that the most conservative multiplicity adjustment is used. For this PMA, the two extremes are obviously inappropriate.

In addition, this table shows that with a very non-conservative adjustment (assuming there are only two independent secondary endpoints; only a small adjustment), none of the endpoints are statistically significant except for the two endpoints under the "AFS score". On the other hand, with the most conservative Bonferroni correction, the endpoint "% patients with reduction for patients with a primary diagnosis of infertility" is still statistically significant. Hence, we can safely say that the endpoint "% patients with reduction for patients with a primary diagnosis of infertility" is statistically significant after multiplicity adjustment.

Table 19: Multiplicity Adjustment for Secondary Endpoints

("√" means that the corresponding endpoint is statistically significant after multiplicity adjustment.)

Endpoint / Variable Adjusted Threshold for p-value	p-value	1 *0.05*	2 *0.025*	3 *0.017*	4 *0.013*	5 *0.01*	7 *0.007*	10 *0.005*	24 *0.002*
Incidence of sites with adhesions									
Change from 1st to 2nd look	0.039	√							
% patients with reduction	0.121								
Change from 1st to 2nd look excluding non-lyzed sites	0.068								
% patients with four oe fewer sites with adhesions at 2nd look	0.510								
Shift analysis - % patients with 2nd look incidence grouped into 4 categories	0.173								
Severity of sites with adhesions									
% change from 1st to 2nd look per patient	0.415								
% patients with reduction	0.446								
Extent of sites with adhesions									
% change from 1st to 2nd look per patient	0.240								
% patients with reduction	0.084								
AFS score									
Change from 1st to 2nd look for patients with a primary diagnosis of infertility	0.011	√	√	√	√				
% patients with reduction for patients with a primary diagnosis of infertility	0.001	√	√	√	√	√	√	√	√
Shift analysis - % patients with 2nd look scores grouped into 4 categories	0.066								
Modified AFS score									
Change from 1st to 2nd look	0.094								
% patients with reduction	0.722								
Reformed adhesions									
Number of sites with reformed adhesions	0.722								
Number of sites without reformed adhesions	0.065								
% patients with at least one	0.832								
De novo adhesions									
Number of sites with	0.036	√							
% patients with at least one	0.029	√							
Abdominal wall adhesions									
Change from 1st to 2nd look in number of sites	0.184								
% patients with reduction from 1st to 2nd look in no. sites	0.129								
Visceral adhesions									
Change from 1st to 2nd look in number of sites	0.046	√							
% patients with reduction from 1st to 2nd look in no. sites	0.228								
VAS score for pelvic pain									
Change from screening to 2nd look for patients with primary diagnosis of pelvic pain	0.995								

Appendix II: Center Effect

Table 20 shows that the center effect was predominantly statistically significant, reflecting the variations and difference in specialties among the participating centers. The advantage of Adept® varies from variable to variable and no one particular center has a consistently better treatment effect with Adept®. The sponsor provided explanations for these variations and differences among centers. The center effect was always adjusted when doing analyses for both primary and secondary effectiveness endpoints. Therefore, the statistical reviewer believes that the center effect does not affect the conclusions drawn from this study.

Table 20: Center Effect on Primary Effectiveness Endpoints (ITT)

Center Number	Randomized		1st Primary Endpoint		2nd Primary Endpoint		3rd Primary Endpoint	
	Adept®	LRS	Adept®	LRS	Adept®	LRS	Adept®	LRS
1	37	38	48.6%	52.6%	-2.19	-1.97	37.8%	31.6%
2	38	37	42.1%	29.7%	-3.26	-2.22	68.4%	62.2%
3	11	14	72.7%	57.1%	-4.82	-3.43	54.5%	50.0%
4	11	10	63.6%	50.0%	-3.36	-2.70	45.5%	40.0%
5	6	3	16.7%	0.0%	1.83	0.67	50.0%	66.7%
6	30	30	36.7%	23.3%	-1.73	-0.50	63.3%	46.7%
7	18	17	38.9%	5.9%	-1.00	-0.06	38.9%	29.4%
8	1	0	0.0%	-	-0.01	-	0.0%	-
9	5	8	40.0%	50.0%	-1.80	-3.00	60.0%	87.5%
10	10	9	30.0%	11.1%	-3.40	-1.22	50.0%	55.6%
11	17	15	70.6%	46.7%	-3.59	-2.87	23.5%	33.3%
12	8	10	62.5%	40.0%	-1.88	-1.90	62.5%	70.0%
13	8	5	12.5%	20.0%	-1.25	0.00	37.5%	60.0%
14	9	9	44.4%	44.4%	-2.33	-2.45	44.4%	22.2%
16	10	12	40.0%	8.3%	-2.10	-1.75	40.0%	66.7%
18	8	5	45.4%	100.0%	-2.38	-5.20	75.0%	100.0%
Total	227	222	45.4%	35.6%	-2.40	-1.86	50.2%	49.1%

Appendix III: Pre-Clinical Animal Studies

i) **Testing for delay of/or prevention of healing**

Effect of administration of 4% icodextrin on anastomotic and incisional healing (Vol 5/pg133)

This study was conducted to evaluate the effects of 4% icodextrin on colonic anastomosis and incisional wound healing. Rats (n=32) in this study underwent colon transection 2.5 cm aboral (away from mouth) to the ileocecal junction. The transected ends were then sutured back together. Test or control solutions (20 ml/kg) were applied to the abdomen just prior to closure of the abdominal wall. During the course of this study three 4% icodextrin rats and 2 control rats died of complications associated with the surgical procedure.

Rats from each group were euthanized at 7, 10, and 21 days after surgery and tissue was collected for bursting (colon segment) or breakage (skin at incision site). It should be noted that at necropsy two of the 21 day 4% icodextrin rats had necrotic tissue (bowel distal to the site of anastomosis) and foul smelling liquid in the abdominal cavity. The test report indicates that these findings were not reported at other time points, and that the significance of this observation is uncertain.

Results of this study showed that on days 7 and 10 there were no difference in the force promoting bursting (pressure) at the site of anastomosis between control and treated rats, however on day 21 the force promoting bursting (pressure) in treated rats was significantly higher than control rats. There were no differences between groups in regards to incisional tear strength.

Conclusion: 4% icodextrin does not affect tissue healing in rats

The sponsor states that this *rat* study was conducted as a feasibility study and not as a GLP study (i.e., conducted under 21 CFR Part 58, Good Laboratory practices), and that the limited number of animals tested and the lack of a surgical control group were limitations to the study design. The sponsor also stated that the most likely cause of necrotic tissue/foul smelling liquid observed would be due to trauma/inadvertant enterotomy during the surgical procedure. Further, the sponsor stated that the *rabbit* is the usual model for evaluation of anastomotic and incisional healing. The sponsor has conducted a GLP study in this model. None of the rabbits in this test showed the presence of necrotic tissue as noted in the rat feasibility test.
The sponsor's response/justification was deemed acceptable.

Effect of administration of 4% icodextrin solution on anastomotic and incisional healing in rabbits (Vol 5/pg140)

This randomized blinded study was designed to evaluate the effect of 4% icodextrin on the healing of bowel anastomoses and laparotomy incisions in rabbits. Forty-eight rabbits were randomly assigned to one of three treatment groups (surgical control, 4% icodextrin solution, or lactated Ringer's solution [LRSin
]) and one of two sacrifice groups (post-operative day 7 or 21) for a total of 6 groups with 8 animals per group. In the treated groups, test and control materials were used intraoperatively and left postoperatively after re-anastomosis. The surgical control underwent surgical treatment only. At the time of euthanasia, adhesion and abscess formation were evaluated. Mechanical

testing (bursting and tear strength) were evaluated in 6 animals per group. The remaining two animals were selected for histology and were used to assess anastomotic and incisional healing.

On rabbit in the control group died during the course of this study and was replaced with an additional rabbit. Results from this study showed that there were no statistical differences noted between groups for tissues evaluated for adhesions, abscesses, bursting or tear strengths. Histological assessment of the bowel and abdominal muscle repair sites for inflammation, fibroblast growth, blood vessel formation and collagen maturity were similar between the groups.

Conclusion: 4% icodextrin has no effect on the healing of bowel anastomoses and laparotomy incisions in rabbits.

The results of this study were acceptable.

ii) **Infectivity testing**

Effect of administration of 4% icodextrin in abscess formation after intraperitoneal infection in rats (Vol 5, pg 229).

Rats (n=15 per treatment) were placed in three treatment groups (surgical control, 4% icodedxtrin (4 ml), or LRS) in two treatment arms (bacterial inoculum LD_{10} or LD_{50}). All of the rats were surgically implanted with a single gelatin capsule containing rat cecal contents and barium sulfate at a concentration previously shown to cause 10% or 50% mortality in rats. Four milliliters of 4% icodextrin solution or LRS were administered to rats in these groups prior to closing surgical incisions. Rats euthanized on day 11 of the study were necropsied and examined for the presence of adhesions. Rats that died before day 11 were necropsied to confirm the presence of an acute bacterial infection. Results of this study showed that treatment with either 4% icodextrin or LRS did not affect survival of rats at either level of bacterial inoculum, and neither treatment showed an increased incidence of abscess formation. The investigators concluded that 4% icodextrin administration should not potentiate a peritoneal infection.

Conclusion: 4% icodextrin administration should not potentiate a peritoneal infection.

The results of this study were acceptable.

Effect of intraperitoneal anti-adhesive fluids in a rat peritonitis model (Vol 5/pg 229)

In addition to the infectivity testing the sponsor conducted on Adept® (Vol 5/pg 220), the sponsor has also provided a copy of a journal article (Vol 5/pg 229; Müller et al. Arch Surg. 2003; 138:286-290) that examines the effects of 4% icodextrin solution on adhesion and abscess formation in rats. In this study, experimental peritonitis was induced using a cecal ligation and puncture model. One-day after cecal ligation and puncture the abdominal cavity was rinsed with saline and the cecum resected. Animals were randomly placed in three treatment groups (LRS [control], 4% icodextrin, and phospholipids). Before closing the abdomen, control or test solutions (5 ml/kg) were placed in the peritoneal cavity. In each group, 50% of the rats were euthanized at day 11 with the remaining rats euthanized on day 21. Rats were assessed for the areas of adhesions and number of abscesses formed.

Results from this study for the control and icodextrin groups showed a greater occurrence of adhesions in the icodextrin group than the LRS group. The abscess score was also higher in the icodextrin group than in the LRS group at both days 11 and 21 (icodextrin, day 11 = 0.81± 0.30,

day 21 = 0.14±0.14; LRS, day 11 = 0.15±0.08, day 21 = 0). The data from this study shows that icodextrin treatment resulted in significantly more adhesions and promoted the formation of abscesses.

Conclusions: Results from this study are different from those in the infection potentiation study performed by the sponsor (Vol 5/pg 220), which showed that icodextrin did not increase the incidence or severity of abscesses as compared to control rats.

The sponsor was asked to provide a discussion describing the problems with the infection potentiation model presented in this journal article, and provide a justification as to why the results of this study should not influence FDA's safety assessment of Adept®. In their response to this question, they state that the model used in the journal article was in the past the standard method to assess intraperitoneal abscess formation. In the mid-1990's this protocol was replaced by an intraperitoneal inoculation model, which was used to assess Adept®. The cecal ligation and puncture model is problematic in that increased variability exists in the relative inoculation size and subsequent trauma animals undergo at the time of ligation. In addition, this model requires 2 surgical interventions, whereas the inoculation model requires only one surgery.

The sponsor's response/justification was deemed acceptable.

iii) **Reproductive Toxicity Testing**

Preliminary feasibility study in the pregnant CD rat by intraperitoneal administration (Vol 6/pg 2)

This study was performed to assess the effects of intraperitoneal icodextrin administration on progress and outcome of pregnancy in rats treated up to day 17 of gestation. Icodextrin (20% solution) was administered by intraperitoneal injection at dose volumes of 5 or 10 ml/kg/day to groups of 8 pregnant rats from day 6 to 17 of gestation. Control animals received electrolyte solution only at a dosage of 10 ml/kg/day throughout the same period. Rats were euthanized on day 20 of gestation for examination of their uterine contents.

Results of this study showed that there were no adverse treatment effects on maternal body weight or food consumption. Necropsy of dams at day 20 of gestation did not reveal any macroscopic differences between treated and control animals. Additionally, litter responses and examination of fetuses at day 20 of gestation suggested that there had been no obvious adverse effects of treatment on embryo-fetal survival or development.

Conclusion: Peritoneal injection of 20% icodextrin does not have an apparent adverse effect on the developing embryo or fetus.

The results of this study were acceptable.

Icodextrin combined study of effects on fertility and embryo-fetal toxicity in CD rats by intraperitoneal administration (Vol 6, page 61)

The purpose of this study was to investigate the influence of icodextrin on the reproductive performance and fertility of male and female CD rats. To test this 20% icodextrin solution was administered by intraperitoneal injections at doses of 5 or 10 ml/kg/day to groups of 22 sexually mature paired male and female rats. Another group of 22 sexually mature male rats received a 20% icodextrin solution at a dose of 20 ml/kg/day and were paired with 22 untreated females.

Controls consisted of 22 mature male and female rats received peritoneal injections at a dose of 10 ml/kg/day of the electrolyte solution used to suspend icodextrin in the treatment groups.

Male rats were treated for 29 days before pairing and until termination at approximately 7 weeks of treatment, throughout pairing, and until termination. Female rats were treated daily for 15 days prior to pairing, throughout pairing, and up to day 17 of gestation. Control rats received the electrolyte solution alone over the same time course reported above.

Female rats were euthanized on day 20 of gestation for examination of their uterine contents and necropsies of fetuses. Male rats were euthanized after 7 weeks of treatment, and the testes were weighed and preserved.

The results of this study demonstrated that 10 ml/kg/day of a 20% icodextrin solution had no adverse effects of female condition, mating performance, fertility and embryo-fetal development. For the males, a dose of 20 ml/kg/day had no adverse effects on general condition, mating performance or fertility.

The results of this study were acceptable.

iv) **Carcinogenesis/metastasis effects (Vol 6, pg 230)**

The sponsor has not provided any testing for carcinogenesis/metastasis effects associated with Adept®. The sponsor makes the following justification:

"Adept® is administered on a single occasion and is not a long term treatment. Because of the bland chemical structure of icodextrin, and its breakdown products *in vitro,* its lack of genotoxic effect *in vitro,* and the impossibility of devising an appropriate and realistic animal experiment that would be physiologically acceptable, no experiment has been done."

In addition, a search of Medline (from 1996), Embase (from 1972), Biological Abstracts (from 1976), Toxline (from 1964) and the RTECS database using the terms dextrin, icodextrin, maltodextrin, and starch with carcinogenic, carcinoma, metastatic, metastasis provided no published information of apparent relevance.

This justification in combination with acceptable genotoxicity test results (chromosomal aberration, assay, Ames assay, micronucleus assay), and the safe use of a similar icodextrin product in peritoneal dialysis patients was sufficient evidence to demonstrate the Adept® has little if any carcinogenic/metastatic potential.
The results of this justification were acceptable.

v) **Pharmacokinetics Testing**

Report on the pharmacokinetic studies of dextrin 20 (identical to icodextrin used in Adept®) in the rat. (Vol 6, Page 232)

Twenty-four rats received twice daily intraperitoneal injections of Dextrin 20 (14 or 20%) or electrolyte solution at a dose of 30ml/kg for a minimum of 28 consecutive days. Blood and urine samples were collected from 2 male and 2 female rats from the electrolyte and Dextrin polymer treated groups at 24 hours after the first administration of test material and 24 hours after the first dose on day 28 of treatment. Attempts to collect peritoneal fluid were only made if animals showed a distended abdomen or signs of discomfort.

Results of this study showed that there is an extensive loss of Dextrin 20 from the peritoneal cavity, which is in contrast to the human and dog in which prolonged peritoneal retention occurs, and leads to increased peritoneal volume. Dextrin 20 and its hydrolysis products are excreted in urine in varying molecular weight forms (G1 - >G10). In addition, Dextrin 20 and its hydrolysis products do not accumulate and achieve steady plasma levels as compared to those reported in anephric human patients.

The results of this study were acceptable.

Pharmacokinetic Studies of Dextrin 20 (identical to icodextrin used in Adept®) in the Dog; Volume 6, page 262

The study consisted of dogs (n=8/group) that were placed in four study groups (electrolyte solution, 5% glucose, 14% icodextrin, and 20% icodextrin). Dogs were dosed (30 ml/kg) twice daily for 28 days via an "immobilized disk" peritoneal dialysis catheter surgically implanted in the abdominal cavity. Following each "dwell" period, the dialysate (fluid in peritoneal cavity) was collected in measuring cylinder (volume recorded) and sampled for icodextrin concentration. Blood samples were collected on days 1, 7, 14, 21, and 28 with sampling done on each day at the following time points (in hours): predose, +1, +2, +5, +10 (just before 2nd daily infusion), and +24 (just before the 1st dose on the succeeding day). Urine was collected on the same days as blood collection. To collect urine, dogs were housed in special chambers. All of the urine excreted by dogs during the 24-h period was collected and a 10 ml sample was used for analysis.

Dogs treated with 20% icodextrin showed a 2 to 3 fold increase in plasma carbohydrate levels. The rise in total carbohydrate was accounted for by increases in components ranging from glucose to high molecular weight forms of icodextrin. Similarly, increased carbohydrate secretion was also observed in the urine of dogs treated with 20% icodextrin. Carbohydrate in urine from 20% icodextrin-treated dogs ranged from glucose to high molecular weight forms of icodextrin. In most samples tested, 2, 3, and >10 dextrin units accounted for most of the urinary carbohydrate. A comparison of total carbohydrate excreted in the urine (collected over a 24h period) of dogs in the electrolyte and 20% icodextrin groups indicates that the percentage of infused dose excreted by 20% icodextrin-treated dogs was very variable, ranging from 12 to 74%. In addition to the results above, the presence of 20% icodextrin caused fluid accumulation in the peritoneal cavity of dogs, which is similar to findings in humans.

vi) **Effectiveness Studies**

Description of the Rabbit Double Uterine Horn Model

The first six effectiveness studies below utilized the Rabbit Double Uterine Horn Model. In this model, uterine horns were traumatized by abrasion of the serosal surface with gauze until punctuate bleeding developed. Ischemia of both uterine horns was induced by removal of the collateral blood supply. The remaining blood supply to the uterine horns in this model is the ascending branches of the utero-vaginal arterial supply of the myometrium. Seven or more days after surgical injury and experimental treatment, rabbits are euthanized and the extent of adhesion formation assessed.

Evaluation of various volumes of 7.5% and 20% icodextrin solutions in the rabbit uterine horn model (Vol 7, page 2)

In this study, rabbits were randomized into thirteen treatment groups (10 rabbits/group) prior to surgery. Following surgical injury to the uterine horns 10, 15, 25, 50, or 75 ml of a 7.5% or 20% icodextrin solution, or 10 or 75 ml of a placebo solution, or no solution (control) was

administered. After 7 days, the rabbits were euthanized and the extent of adhesion formation assessed by two independent observers. One rabbit treated with 50 ml 20% icodextrin died postoperatively without evidence of inflammation or edema, and was replaced.

Results of the study showed that several rabbits treated with greater volumes of icodextrin had distended abdomens for the first few days after surgery. Results also showed that increased volumes of icodextrin solution (25 to 75 ml) resulted in a greater reduction in the formation of adhesions. However, no difference in between 7.5% and 20% solutions was noted in this study.

The results of this study were acceptable.

Evaluation of 50 ml of various percentages of icodextrin (2.5%, 4%, 7.5%. 10%. 15%, and 20%) in the rabbit uterine horn model (Vol 7, pg 12)

In this study, rabbits were randomized into nine treatment groups (10 rabbits/group) prior to surgery. Following surgical injury to the uterine horns 50 ml of a 2.5%, 4%, 7.5%, 10%, 15%, or 20% icodextrin solution, 50 ml placebo solution, 50 ml Lactated Ringer's solution, or no treatment (control) was administered. After 7 days, the rabbits were euthanized and the extent of adhesion formation assessed by two independent observers.

As in the previous study, this study demonstrated that a 50 ml volume of an icodextrin solution at various concentrations was able to reduce the extent, tenacity, and incidence of adhesion formation. However, it was shown that the 2.5% icodextrin dose had reduced efficacy as compared with more concentrated icodextrin solutions (≥4%).

The results of this study were acceptable.

Evaluation of administration of 4% and 20% icodextrin during the operative procedure (as a lavage) and postoperatively (as an instillate) of the rabbit uterine horn model (Vol 7, pg 20)

In this study, rabbits were randomized into ten treatment groups (10 rabbits/group) prior to surgery. Following surgical injury to the uterine horns 50 ml of 4% or 20% icodextrin solution, 50 ml saline, 50 ml LRS solution or no treatment (control) was administered at various times as shown in the table below:

Table 21: Randomized of rabbits into treatment groups

	Perioperative washing and final peritoneal cavity rinse	50 ml of instillate at the end of the operative procedure
Surgical Control-Group 1	None	None
Group 2	None	Placebo = RLS
Group 3	None	Placebo = saline
Group 4	None	4% icodextrin
Group 5	Placebo = RLS	Placebo = RLS
Group 6	Placebo = saline	Placebo = saline
Group 7	4% icodextrin	4% icodextrin
Group 8	Placebo = RLS	4% icodextrin
Group 9	Placebo = saline	4% icodextrin
Group 10	20% icodextrin	20% icodextrin

After 7 days, the rabbits were euthanized and the extent of adhesion formation assessed by two independent observers. Results of the study showed that a slight reduction in adhesion formation was achieved when LRS or saline were used as both an inter-operative lavage and as

an instillate. However, rabbits treated intra-operatively and post-operatively with 4 or 20% icodextrin solutions were shown to have significantly lower adhesion scores. The investigators also noted that when LRS or saline was used intra-operatively and then 4% icodextrin solution was used as an instillate, there was no significant difference when compared to either of the groups where icodextrin was used for both intra- and postoperative procedures.

The results of this study were acceptable.

Evaluation of administration of 4% and 20% icodextrin during the operative procedure (as a lavage) and postoperatively (as an instillate) of the rabbit uterine horn model (Vol 7/pg 37; Note: This study is an extension to the study presented on pg 20 of Vol 7)

Thirty rabbits were randomized into three treatment groups (Group 1 - surgical control; Group 2 - 4% icodextrin washing during surgery, no instillation after surgery; Group 3 – 4% icodextrin washing during surgery with 50 ml instilled after surgery). After 7 days, the rabbits were euthanized and the extent of adhesion formation assessed by two independent observers.

Results of this study showed that administration of a 50 ml icodextrin instillate post-surgery with icodextrin as a lavage during surgery reduced the extent, tenacity, and incidence of adhesion formation. This reduction in adhesions was not observed when icodextrin lavage alone was performed during surgery.

Conclusion: Reduction of adhesion severity is best achieved when icodextrin solution is used as a lavage during surgery and as an instillate following the surgical procedure.

The results of this study were acceptable.

Evaluation of 50 ml of various percentages of icodextrin (blinded samples) and placebo in the rabbit uterine horn model (Vol 7, pg 42)

In this study, rabbits were randomized into five treatment groups (10 rabbits/group) prior to surgery. Following surgical injury to the uterine horns 50 ml of a 2.5%, 4%, 7.5%, 10%, 15%, or 20% icodextrin solution, 50 ml placebo solution, 50 ml of each of four blinded solutions (A =4% icodextrin, B=placebo, C=2.5% icodextrin, and D=15% icodextrin), or no treatment (control) was administered. After 7 days, the rabbits were euthanized and the extent of adhesion formation assessed by two independent observers.

Administration of solutions A and D were shown to reduce the formation of adhesions and increased the number of adhesion-free sites. Solutions B and C also reduced adhesion formation, but not to the extent of Solutions A and D. Solution B and C treated animals also had fewer adhesion-free sites as compared to solution A and D treated rabbits. Once the blind was broken, it was determined that the study results were consistent with expectations for the various test solutions.

The results of this study were acceptable.

Comparison of administration of 4% icodextrin and Intergel (another firm's ferric hyaluronate adhesion barrier product) on the rabbit uterine horn model (Vol 7, pg 48)

In this study, rabbits were randomized into three treatment groups (10 rabbits/group) prior to surgery. During the surgical procedure, rabbits receiving 4% icodextrin at the end of surgery also received 4% icodextrin solution washes during the surgery (30 ml preoperatively and aspirated prior to surgery, four 5 ml washes during the surgical procedure, and a 30 ml wash at

the end of surgery). Rabbits receiving Intergel were untreated during surgery. Following surgery, 30 ml of 4% icodextrin solution, 15 ml of Intergel, or no treatment (control) was administered. After 6-9 days, the rabbits were euthanized and the extent of adhesion formation assessed by two independent observers.

Both 4% icodextrin and Intergel had similar abilities to reduce adhesion formation in rabbits. It was noted that some rabbits in the Intergel group had small amounts of orange material visible in the peritoneal cavity in animals necropsied on day 7, but not on day 9.

The results of this study were acceptable.

Evaluation of 4% icodextrin in the prevention of adhesions in the rabbit sidewall formation and reformation model (Vol 7, pg 54).

The following study utilizes the Rabbit Sidewall Formation and Reformation Model. In this model, the cecum and bowel are exteriorized and digital pressure is exerted to create subserosal hemorrhages over all surfaces. The damaged intestine is then lightly abraded with sterile gauze until punctuate bleeding observed. The cecum and bowel are returned to their normal anatomic location. A 5 x 3 cm area of the peritoneum and transverse abdominus muscle are removed from the lateral abdominal wall. Prior to muscle layer incision closure, 13 of the 40 of the total number of rabbits in the study were randomized to receive 50 ml of 4% icodextrin solution. The remaining rabbits served as controls and rabbits upon which adhesiolysis was performed. One-week later, the animals to receive a second laparotomy were anesthetized, adhesions scored, and lysed using blunt and sharp dissection. Following adhesiolysis, 50 ml of 4% icodextrin was administered to half of the rabbits. The remaining rabbits served as surgical controls. After 7 days, the rabbits were euthanized and the extent of adhesion formation assessed.

Administration of 4% icodextrin at the end of the initial surgery or after adhesiolysis was effective in reducing adhesion formation.

The results of this study were acceptable.

Evaluation of peritoneal histology after administration of 4% icodextrin in the rabbit sidewall formation model (Vol 7, pg 58).

The purpose of this study was to evaluate the effect of 50 ml of 4% icodextrin on the histologic appearance of the parietal peritoneum. The following study utilized the Rabbit Sidewall Formation Model, but did not assess adhesion reformation. Following cecum, bowel, and sidewall injury, five of the ten rabbits had 50 ml of 4% icodextrin instilled into the peritoneal cavity just prior to muscle layer closure (control was not specified). After 7 days, the rabbits were euthanized and the site of injury to the parietal peritoneum was excised and fixed in formalin.

Administration of 4% icodextrin at the end of was effective in reducing sidewall adhesion formation. Histologic examination of the excised peritoneal tissues revealed no excess inflammation and normal healing processes comparable to controls.

The results of this study were acceptable.