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ORIGINAL ARTICLE *Gynaecology*

Gynaecological endoscopic evaluation of 4% icodextrin solution: a European, multicentre, double-blind, randomized study of the efficacy and safety in the reduction of *de novo* adhesions after laparoscopic gynaecological surgery

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BACKGROUND: Gynaecological laparoscopic surgery outcomes can be compromised by the formation of *de novo* adhesions. This randomized, double-blind study was designed to assess the efficacy and safety of 4% icodextrin solution (Adept®) in the reduction of *de novo* adhesion incidence compared to lactated Ringer's solution (LRS).

METHODS: Patients undergoing laparoscopic surgery for removal of myomas or endometriotic cysts were treated with randomized solution as an intra-operative irrigant and 1l post-operative instillate. *De novo* adhesion incidence (number of sites with adhesions), severity and extent were independently scored at a second-look procedure and the efficacy of the two solutions compared. The effect of surgical covariates on adhesion formation was also investigated. Initial exploratory analysis of individual anatomical sites of clinical importance was progressed.

RESULTS: Of 498 patients randomized, 330 were evaluable (160 LRS – 75% myomectomy/25% endometriotic cysts; 170 Adept – 79% myomectomy/21% endometriotic cysts). At study completion, 76.2% LRS and 77.6% Adept had ≥1 *de novo* adhesion. The mean (SD) number of *de novo* adhesions was 2.58 (2.11) for Adept and 2.58 (2.38) for LRS. The treatment effect difference was not significant ($P = 0.909$). Assessment of surgical covariates identified significant influences on the mean number of *de novo* adhesions regardless of treatment, including surgery duration ($P = 0.048$), blood loss in myomectomy patients ($P = 0.019$), length of uterine incision in myomectomy patients ($P < 0.001$) and number of suture knots ($P < 0.001$). There were 15 adverse events considered treatment-related in the LRS patients (7.2%) and 18 in the Adept group (8.3%). Of 17 reported serious adverse events (9 LRS; 8 Adept) none were considered treatment-related.

CONCLUSIONS: The study confirmed the safety of Adept in laparoscopic surgery. The proportion of patients with *de novo* adhesion formation was considerably higher than previous literature suggested. Overall there was no evidence of a clinical effect but various surgical covariates including surgery duration, blood loss, number and size of incisions, suturing and number of knots were found to influence *de novo* adhesion formation. The study provides direction for future research into adhesion reduction strategies in site specific surgery.

Key words: adhesions / icodextrin / laparoscopy / myomas / endometriotic cysts

Introduction

Adhesion formation is an almost inevitable consequence of abdominopelvic surgery, posing considerable morbidity and mortality risks for patients and an associated clinical workload and cost burden (Ellis *et al*., 1999; Lower *et al*, 2000; Lower *et al*., 2004). Despite the development and implementation of strategies to reduce adhesions, they remain the most frequent complication of abdominopelvic surgery (DeWilde and Trew, 2007). Adhesiolysis is the only treatment, although adhesions reform in most patients (mean 85%) regardless of the method of adhesiolysis used or the type of adhesion being lysed (Diamond and Freeman, 2001).

Laparoscopy is believed to be less adhesiogenic and causes fewer *de novo* adhesions compared with laparotomy. However, although the number of adhesions forming may be reduced (Nappi *et al*., 2007), the comparative risk of adhesion-related complications following open and laparoscopic gynaecological surgery is similar for most procedures (Lower *et al*., 2004; Nappi *et al*., 2007). Laparoscopy has many advantages over open surgery and is certainly the preferred current operative approach, especially in women wishing to become pregnant. Many patients undergoing laparoscopic myomectomy or laparoscopy for endometriotic cysts do so with an aim to improve their fertility. However, even adopting the laparoscopic approach, these procedures are known to be compromised by a significant rate of *de novo* adhesion formation, which could have an impact on successful fertility outcomes for the patient, as well as putting them at risk of other adhesion-related complications (Nezhat *et al*., 1991; Redwine, 1991; Canis *et al*., 1992; Hasson *et al*., 1992; Mais *et al*., 1995; Dubuisson *et al*., 1998).

Because of the risk of adhesions forming, myomectomy and removal of endometriotic cysts are procedures where a second-look laparoscopy may be recommended for patients wishing to retain fertility. Following laparoscopic myomectomy, it would allow for evaluation of the quality of the uterine scar, which may be an important consideration in patients wishing to become pregnant (Nezhat *et al*., 1991; Harris, 1992; Dubuisson *et al*., 1995; Dubuisson *et al*., 2000; Jin *et al*., 2009) and in patients with endometriotic cysts, it would allow the opportunity for lysing of any newly formed adnexal adhesions that could compromise fertility or induce pelvic pain.

Adept (4% icodextrin solution) is a non-viscous, iso-osmotic, clear solution that has been proven safe and effective as an anti-adhesion device when used as an irrigant fluid during surgery (minimum 100 ml/30 min) and then at the end of surgery as a 1000 ml post-operative instillate providing a fluid reservoir in the peritoneal cavity with a prolonged residence time of up to 4 days (Brown *et al*., 2007). Adept acts to temporarily separate peritoneal surfaces through the process of hydroflotation, thereby minimizing tissue apposition during the critical period of fibrin formation and mesothelial regeneration following surgery, and thus providing a barrier to adhesion formation.

Adept is approved for use in both open and laparoscopic abdominopelvic surgery in Europe and is currently the only device approved in the USA for adhesion prevention in laparoscopy based on demonstration of safety and efficacy in a double-blind randomized controlled trial (RCT) (Brown *et al*., 2007). The study found that Adept reduced adhesion reformation after laparoscopic adhesiolysis compared with patients treated with lactated Ringer's solution (LRS).

The Gynaecological ENdoscopic EValuation of Adept (GENEVA) study was performed to assess the efficacy and safety of Adept as adhesion reduction prophylaxis to reduce *de novo* adhesions following initial laparoscopic surgical removal of myomas or endometriotic cysts. Patients undergoing primary laparoscopic myomectomy have a high incidence of *de novo* adhesion formation, particularly where the myomectomy requires incisions to the posterior wall of the uterus. Posterior pelvic adhesions also tend to be more dense and severe with the potential for tethering of adjacent bowel and/or adnexa (Tulandi *et al*., 1993; Myomectomy Adhesion Study Group, 1995; Dubuisson *et al*., 1998; Takeuchi and Kinoshita., 2002; Takeuchi *et al*., 2005; Practice Committee ASRM., 2008).

Materials and Methods

GENEVA was a double-blind, comparative, randomized study with 25 European centres enrolling patients to assess the safety and efficacy of Adept compared with LRS when used as an intra-operative irrigating solution (minimum 100 ml/30 min surgery time) and as a 1 l post-operative instillate for the reduction of *de novo* adhesion formation after laparoscopic surgery for myomas or endometriotic cysts. *De novo* adhesions were defined as the formation of adhesions at anatomical locations where there were no adhesions previously.

Investigators in all study centres were experienced in laparoscopic surgery for removal of myomas and endometriotic cysts. The surgery was video recorded according to a detailed protocol to enable all assessments to be made through an independent and blinded review of video recordings.

The study protocol and conduct was directed by an independent steering panel (see Appendix 1) who were keen to ensure as homologous a

study population as possible in the design and conduct of the study. Blinded *de novo* adhesion incidence and baseline characteristics of randomized patients were monitored by a Data and Safety Monitoring Board (DSMB, see Appendix 1) on an ongoing basis throughout the study to establish whether or not the observed *de novo* adhesion incidence rates were compatible with the assumptions made for study powering. The study protocol received written approval from the institutional ethics committee or institutional review board at each study centre.

Participants

Eligibility criteria required patients to be female, aged 18–45 years, and undergoing primary removal of myomas or endometriotic cysts. All patients had a negative pregnancy test prior to entering the study and agreed to use adequate forms of contraception throughout the study. Patients underwent a planned second-look laparoscopy 4–16 weeks after the primary procedure. Before completing any study-related procedures, all patients were required to give their written, signed informed consent to participate in the study in accordance with the International Conference of Harmonization Good Clinical Practice Guidelines. Patients were free to withdraw from the study at any time for any reason.

Pre-operative exclusions included current pregnancy including ectopic pregnancy; serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase and/or bilirubin >20% above the upper range of normal and considered clinically significant by the study site's principle investigator; blood urea nitrogen and creatinine >30% above the upper range of normal and considered clinically significant; concurrent use of systemic corticosteroids, antineoplastic drugs and/or radiation; GNRH agonist/antagonists (except oral contraceptive—combined estrogen/progesterone) in the 4 weeks prior to study; active pelvic or abdominal infection; known allergy to starch-based polymers; known or suspected intolerance or hypersensitivity to the study materials (or closely related compounds) or any of their stated ingredients; prior surgery for endometriotic cysts or myomas; non-gynaecological surgical procedure planned to be performed during the laparoscopic procedure; more than four myomas on pre-operative ultrasound; largest myoma less than two or >8 cm diameter on pre-operative ultrasound; endometriotic cysts less than three or >7 cm on pre-operative ultrasound; history of alcohol or other substance abuse within the last year; use of another investigational agent; or participation in a clinical trial within the last 30 days prior to study enrolment. At centres in France, patients with diabetes mellitus were excluded.

Intra-operative exclusions were: clinical evidence of cancer, pregnancy including ectopic pregnancy, rectovaginal endometriosis, or endometriosis American Fertility Society (AFS) class III or IV (other than endometriotic cysts); conversion to laparotomy; unplanned surgery involving opening of the bowel (excluding appendectomy); extensive pelvic adhesions (AFS adhesion scores moderate or severe) (American Fertility Society, 1988); use, during the procedure, of any approved or unapproved anti-adhesion agent; use of O_2 enhanced insufflation; adhesions that would require lysing during planned myomectomy or planned endometriotic cyst removal—other than those around the ovarian fossa, which would need to be lysed prior to cyst removal; endometriotic cysts not removed and ovary not left open; suturing the ovarian capsule; pedunculated cysts; use of glue; or peritoneum sutured to fascia (with the exception of the trocar port). Post-operative exclusions were use of drains and post-operative ovarian histology consistent with a non-endometriotic cyst.

Reasons for withdrawal included: removal of consent; serious adverse events or other investigator safety concerns; violation of inclusion/exclusion criteria; or pregnancy.

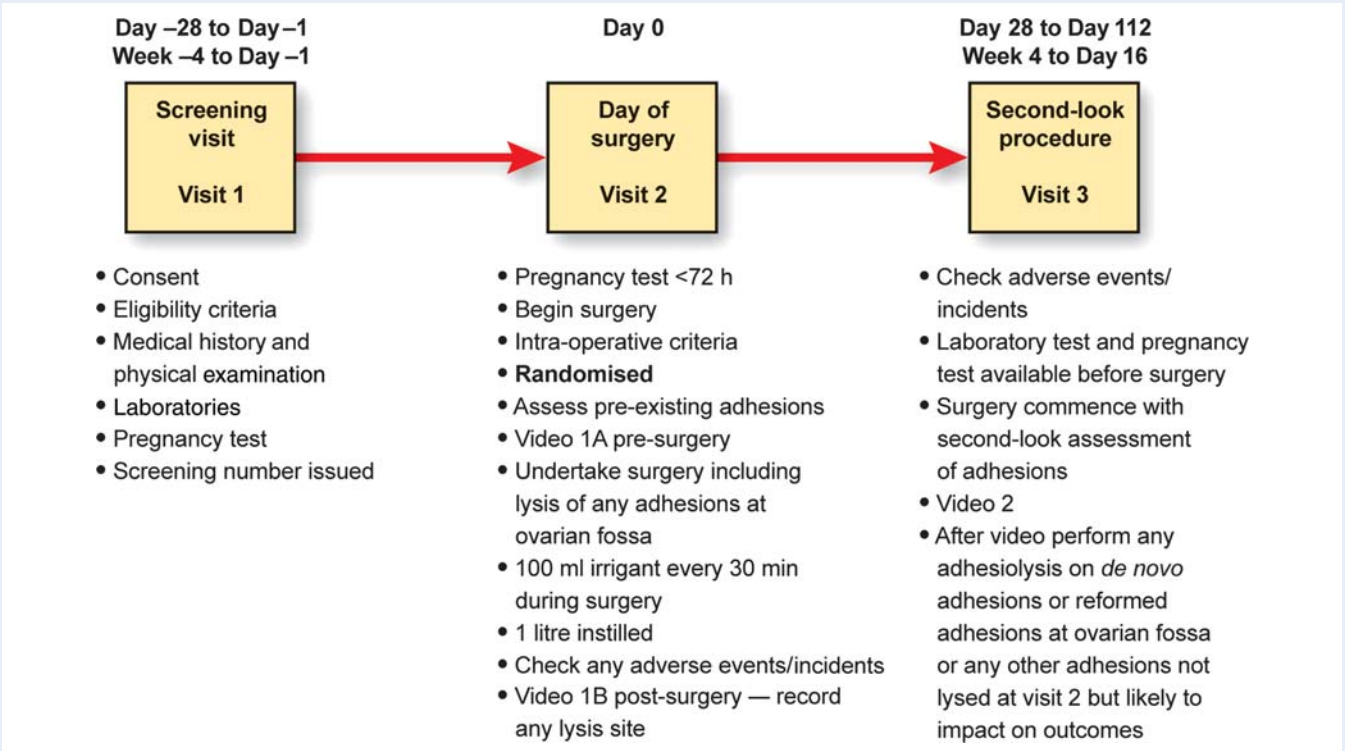

Figure 1 Study schedule.

Study schedule

The study duration was up to 20 weeks, allowing for the patient to visit the study site on three occasions: for a screening/baseline visit, on the day of surgery and finally for follow-up laparoscopy 4–16 weeks after primary surgery. The study schedule is illustrated in Fig. 1.

Treatments and allocation

Adept (4% icodextrin solution—Baxter Healthcare, Deerfield, IL, USA) and LRS were presented in identical 1 l infusion bags provided with an injection port and a connection point for the irrigation set. Each bag was labelled according to EC Good Manufacturing Practice requirements for investigational medicinal products. Each bag had an outer wrap that contained the study code and patient number on an identification label, along with product expiry date. Double-blinding was possible as both fluids are clear and odourless solutions with similar viscosities to water and they were packaged identically.

Each centre was assigned an adequate stock of blinded treatment packs containing 3 × 1 l blinded bags of Adept or LRS, with additional packs provided during the study as required.

Treatment was randomized through a 24-h central randomization telephone system, which centres contacted within 24 h prior to visit 2. Patients were stratified according to their diagnosis of either myomas or endometriotic cysts and were randomized in a 1:1 ratio to separate randomization lists. In the event that the intra-operative criteria were not met after randomization, the treatment pack assigned was not permitted for allocation to any other patient in the study. The system was administered by the study Clinical Research Organization.

Surgical technique

In order to mitigate against any potential inter-surgeon variables, surgical management was standardized as far as possible (see Table I).

Study treatment

Prior to surgery at visit 2, the treatment packs were pre-warmed in a theatre-warming cabinet and maintained at approximately body temperature until use. At surgery, following initial video recording, the abdomen was washed with study solution and this washing/irrigation of the abdominal cavity was repeated/continued with a minimum of 100 ml of study solution at intervals of at least once every 30 min. At the end of surgery, after a final irrigation with a minimum 100 ml followed by reversal of Trendelenburg position and evacuation of any intraoperative solution, a final 1000 ml was instilled from a fresh treatment bag. All trocar ports ≥10 mm were double sutured to the fascia to help minimize any leakage.

Intra-operative variables

During surgery, the following were recorded: duration of operation (defined as time from commencement of insufflation to skin closure); estimated blood loss during surgery (defined as anaesthetist's/theatre sister's estimate of loss); number and length of incisions made during laparoscopic myomectomy (measured according to local practice using calibrated instruments, e.g. probe, ruler) and the number of sutures used following laparoscopic myomectomy (where interrupted suturing of serosa was undertaken, this was defined as the number of knots).

Video recording

A comprehensive video protocol was established including investigator training. Video recordings of 23 adhesion sites designated by the modified AFS (mAFS) (Brown *et al.*, 2007) and the site of surgery were made at first and second laparoscopy (see Appendix 2). This allowed for independent blinded video review and scoring of the number, extent and severity of adhesions at any of the anatomical study sites throughout the abdominopelvic cavity.

At the second-look laparoscopy, the pre-surgery orientation survey of eight organ sites followed by filming of 23 adhesion scoring sites was repeated.

Investigators were advised that should any additional surgical interventions be required at the second-look laparoscopy, these should be undertaken after the filming.

Independent video reviews

Videos were scored by two primary independent reviewers: Prof Ian Cooke, University of Sheffield, UK and Mr Jonathan Skull, The Royal Hallamshire Hospital, Sheffield, UK.

Adhesion scoring was undertaken in accordance with a separate protocol to ensure minimal inter-observer variability.

Reviewers were blinded to the study treatment assignment (study arm), subject confidential information and investigator site identifiers. They were not blinded to the sequence of visits. However, first and second procedures were scored independently. All efficacy assessments were made from the independent reviewers' video scoring of the 23 specified

Table I Surgical technique.

	Standardized technique	Local practice
Myomas and endometriotic cysts	Insufflation pressure 10–15 mmHg	Use of a humidifier
	Use of supplied polydioxanone (PDS) sutures	Serosal incision
	Suture tail lengths <3 mm	Use of pitressin
	Suture knots with three throws	
Myomas	Strip away from underlying myometrium using grasping forceps or myoma screw	
	Close healthy serosa in two layers using supplied sutures—PDS 2.0 or 3.0	
	Close small serosal defects in one layer	Suturing of deep tissue and serosa
		Interrupted or continuous suturing
Endometriotic cysts	Only uncomplicated unilateral or bilateral endometriotic cysts	
	Incise cyst capsule and drain with the contents aspirated	
	Strip away capsule from the normal ovarian tissue	
	Ovary left open	
	Arrest any bleeding from the ovary with bipolar diathermy where possible	
	Where bleeding continues use a haemostatic figure-of-eight PDS 2.0 suture placed inside the ovary at the base but the capsule itself should not be closed	
	No suturing outside the ovary	
	No use of glue	

adhesion sites and the independent reviewers identified any potential protocol violations.

Efficacy and safety assessment

The incidence (presence or absence), severity ('filmy' or 'dense and vascular') and extent ('<1/3', '1/3–2/3' or '>2/3') of *de novo* adhesions were recorded and scored at the site of surgery and at each of the 23 anatomical sites in accordance with the mAFS system (Brown *et al*., 2007), allowing calculation of total mAFS and AFS scores, as well as AFS site-specific scores for each evaluable video.

Posterior and anterior uterus

In order to assess the potential for an adhesion prevention device to reduce *de novo* adhesions, an anatomical site that forms sufficient adhesions with the potential to demonstrate treatment differences is required for evaluation. As the literature identified posterior uterine myomectomies as having a high incidence of *de novo* adhesions that typically involve clinically significant sites such as the adnexa and/or bowel (Dubuisson *et al*., 1998; Takeuchi and Kinoshita., 2002; Takeuchi *et al*., 2005), a focused exploratory analysis was undertaken to assess incidence, severity and extent of adhesions in patients undergoing myomectomy with incisions to the posterior and/or or anterior uterus. No allowance was made for multiplicity.

Safety

Safety was assessed individually and each event/incident classified by body system and preferred term using MedDRA (Medical Dictionary for Regulatory Activities). The number of events and numbers of patients reporting at least one event were summarized. Clinically significant abnormal values from laboratory tests were also assessed as adverse events, as were any clinically significant changes from baseline.

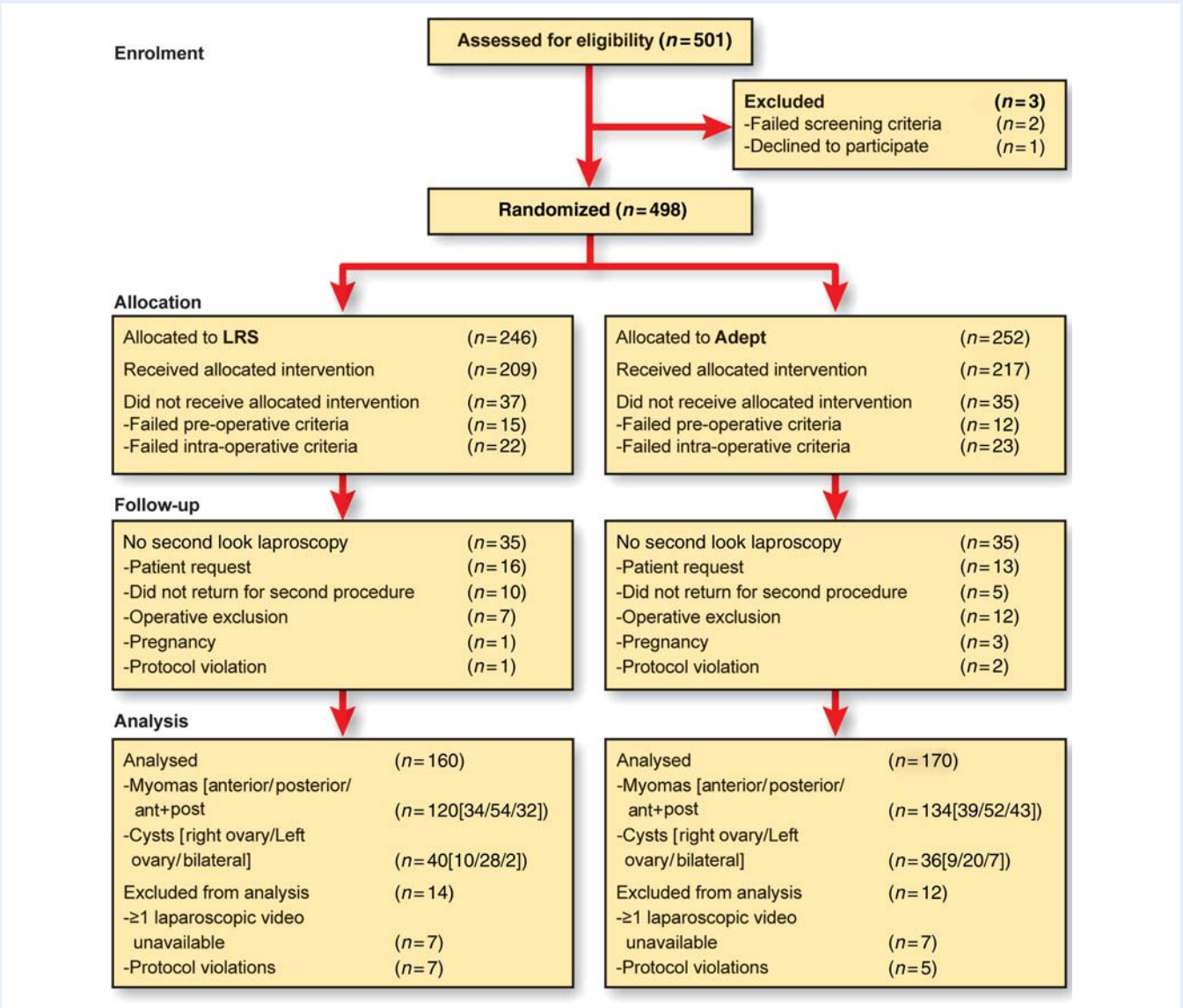

Figure 2 Patient flow illustrating treatment group comparability.

Statistical analysis

The statistical analysis was based on a predefined statistical analysis plan. The efficacy analysis was conducted on an evaluable population of patients with pre-surgery, post-surgery and second-look video assessments who had no protocol violations. The safety population consisted of all consenting patients who received randomized treatment.

A sample size of 330 evaluable patients (165 per treatment arm) was estimated to be required to detect a relative risk reduction of 50% (i.e. an absolute risk reduction of 15% assuming *de novo* adhesion formation in 30% of patients for LRS and 15% with Adept), with at least 90% power. The LRS rate was based on a review of the literature of adhesion incidence in the absence of treatment with anti-adhesion agents or LRS, which identified a per-patient *de novo* adhesion incidence of ~35% following laparoscopic myomectomy (Dubuisson *et al.*, 1998) and ~21% *de novo* formation following laparoscopic removal of endometriotic cysts (Canis *et al.*, 1992).

A patient recruitment ratio of 2:1 was adopted to recruit approximately 220 myomectomy patients and 110 endometriotic cyst patients with an estimated control adhesion formation rate of 30%. It was assumed that using LRS as an irrigant and instillate would not influence this rate.

The DSMB reviewed and monitored unblinded safety data. They set a level for statistical significance of $P < 0.001$ on the primary end-point for benefit of Adept relative to LRS, to recommend early termination of the study. This conservative approach had no impact on the study sample size requirements. Following an interim, blinded review of data, it became clear that the prior assumptions on adhesion rates were incorrect. For this reason, the DSMB recommended to the study steering panel that for the study to progress, the primary end-point ought to be modified to correct for a much higher proportion of patients with *de novo* adhesions (75.4% myomas, 86.1% endometriotic cysts, 80% for combined treatment groups) than predicted from the literature (30%). The steering panel accepted this recommendation and the revised primary end-point was the total number of incident *de novo* adhesions for each patient: the number of evaluable patients required to complete the study was not amended and the study power did not require changing.

The primary analysis consisted of an analysis of covariance, adjusting for the randomization stratification variable, to compare the mean patient total incidence of *de novo* adhesions between the Adept and LRS groups, generating an estimate of treatment effect difference with a 95% confidence interval (CI) and *P*-value. The methods used for the primary analysis were then applied to the total mAFS score, for the *de novo* adhesions and AFS score in the Adept and LRS groups, and repeated for clinically relevant operative subpopulations and anatomical sites.

Analysis of the original primary outcome was based on a logistic regression model, including the stratification variable and treatment group, providing an estimated treatment effect as an odds ratio (OR) with a 95% CI and *P*-value.

The impact of study covariates and their interaction with treatment on the primary outcome was investigated. Covariates included volume of irrigation solution; surgery duration; blood loss and in myomectomy patients: number of incisions; incision length and number of knots.

Results

Study recruitment ran from September 2003 to June 2005, with the last patient completing follow-up in August 2005. The outcomes of all patients considered for entry into the study are illustrated in Fig. 2.

A total of 501 patients were screened for eligibility, of these 498 were randomized to treatment prior to first laparoscopic surgery, although one of these patients was subsequently found to have failed a screening laboratory test. Of those randomized, 72 patients were excluded from study treatment due to failure to meet pre-operative or intra-operative exclusion criteria. A total of 426 patients met all study criteria and were treated with LRS (209) or Adept (217) at first laparoscopic surgery. These patients constituted the safety population. A total of 70 patients did not undergo a second-look laparoscopy. The majority did not because they either expressed a wish not to be considered for second-look laparoscopic surgery or did not return for surgery within the stipulated time period. This left a total of 356 patients who underwent second-look laparoscopy. Of these, 26 patients were excluded from the evaluable population either because of video assessment anomalies which prevented appropriate adhesion scoring at all sites, or surgery practice deviations. No patients were withdrawn due to adverse events. A total of 330 were

Table II Demographic characteristics—comparable evaluable population.

	LRS			Adept		
	N	Mean (SD)	Minimum, maximum	*N*	Mean (SD)	Minimum, maximum
Age (years)						
All patients	160	34.2 (5.4)	18.1, 45.2	170	34.8 (5.5)	21.1, 45.8
Myomas	120	35.3 (4.9)	21.1, 45.2	134	35.5 (5.1)	21.1, 45.4
Endometriotic cysts	40	31.0 (5.5)	18.1, 43.2	36	32.0 (6.1)	22.5, 45.8
Weight (kg)						
All patients	160	64.5 (11.5)	43.0, 104.0	170	65.1 (11.7)	47.0, 116.0
Myomas	120	65.3 (12.2)	43.0, 104.0	134	66.0 (12.2)	48.5, 116.0
Endometriotic cysts	40	62.0 (8.8)	49.0, 92.0	36	61.9 (9.2)	47.0, 84.5
Height (m)						
All patients	160	1.66 (0.06)	1.45, 1.80	170	1.65 (0.06)	1.50, 1.83
Myomas	120	1.66 (0.06)	1.45, 1.80	134	1.65 (0.06)	1.50, 1.83
Endometriotic cysts	40	1.66 (0.06)	1.52, 1.78	36	1.66 (0.06)	1.52, 1.80

Table III Initial laparoscopic parameters—comparability of efficacy population.

All patients	LRS			Adept		
	N	Number (%) of patients with adhesions		*N*	Number (%) of patients with adhesions	
Adhesions at initial surgery						
Prior to surgery	160	84 (52.5)		170	99 (58.2)	
Post-surgery	160	65 (40.6)		170	76 (44.7)	
	N	Mean (SD)	Minimim, maximum	*N*	Mean (SD)	Minimim, maximum
Duration of surgery (min)	159	99.9 (43.4)	30.0, 250.0	170	103.4 (46.4)	25.0, 255.0
Blood loss (ml)	153	143.5 (150.0)	5.0, 1000.0	165	123.3 (125.9)	5.0, 800.0
Number of incisions	122	1.48 (0.73)	1.00, 4.00	134	1.75 (1.11)	1.00, 5.0
Length of incisions (mm)	122	57.0 (24.7)	6.0, 155.0	134	61.3 (30.6)	3.0, 185.0
Number of knots	95	4.81 (3.17)	0.00, 16.00	99	5.49 (4.79)	0.00, 26.00
Volume irrigated (ml)	160	1250.7 (699.3)	150.0, 4000.0	170	1351.4 (788.4)	200.0, 4500.0
Volume of instillate (ml)	160	1006.2 (55.7)	1000.0, 1500.0	170	998.9 (15.3)	800.0, 1006.0
Time to second-look laparoscopy (days)	160	59.0 (37.4)	21.0, 356.0	170	56.4 (25.2)	27.0, 203.0

Table IV Number of *de novo* adhesions at second look by treatment and by subgroups.

	LRS			Adept			95% CI	*P*-value
	N	Mean (SD)	Minimum, maximum	*N*	Mean (SD)	Minimum, maximum		
All patients	160	2.58 (2.38)	0, 13	170	2.58 (2.11)	0, 10	0.03 (−0.46, 0.51)	0.909
Myomas	120	2.42 (2.27)	0, 13	134	2.49 (2.12)	0, 10	0.07 (−0.47, 0.61)	0.804
Posterior myomas	54	2.65 (2.36)	0, 13	52	2.44 (1.78)	0, 7	−0.21 (−1.01, 0.60)	0.614
Anterior myomas	34	2.21 (2.24)	0, 11	39	2.21 (2.30)	0, 8	0.00 (−1.06, 1.06)	0.999
Anterior/posterior myomas	32	2.25 (2.18)	0, 9	43	2.79 (2.33)	0, 10	0.54 (−0.51, 1.60)	0.310
Endometriotic cysts	40	3.05 (2.65)	0, 11	36	2.94 (2.10)	0, 7	−0.11 (−1.21, 1.00)	0.849
Right ovary cysts	10	2.5 (1.78)	0, 5	9	3.78 (2.33)	0, 7	1.28 (−0.72, 3.27)	0.194
Left ovary cysts	28	3.14 (2.89)	0, 11	20	2.70 (1.98)	0, 7	−0.44 (−1.95, 1.06)	0.556
Bilateral cysts	2	4.50 (3.54)	2, 7	7	2.57 (2.15)	0, 6	−1.93 (−6.47, 2.62)	0.349

considered as the evaluable population, having been treated with LRS (160) or Adept (170) at first laparoscopy and having undergone a second-look laparoscopy which could be scored according to protocol by the video assessors. The proportion of myomectomy and endometriotic cysts patients was approximately balanced between the two evaluable treatment groups (LRS 75%/25% and Adept 79%/21%).

The two treatment groups were comparable with respect to patient demographics as detailed in Table II.

Surgery parameters during first laparoscopic surgery and treatment volumes are summarized by treatment group for the evaluable population in Table III.

Patients randomized to the Adept treatment group had fewer adhesions in total prior to surgery, but in a slightly higher proportion of patients than the LRS group [LRS—425 adhesions, observed in 84 (52.5%) patients; Adept—387 adhesions, observed in 99 (58.2%) patients]. Surgical necessity required some pre-existing adhesions to be lysed. This was similar in both groups: LRS—116 adhesions lysed (28.8% of total pre-existing adhesions) in 40 (23.1%) patients; Adept 110 adhesions lysed (29.1% of total pre-existing adhesions) in 37 (23.5%) of patients. Post-surgery, 65 (40.6%) LRS patients and 76 (44.7%) Adept patients were observed to have at least one remaining adhesion.

Duration of surgery, blood loss, number of incisions and length of incisions were comparable for each treatment group and also comparable for the myomectomies by treatment group and endometriotic cysts. Both treatment groups were treated with similar volumes of study device as an intra-operative irrigant and as an instillate at close of surgery. There was little difference in follow-up interval between initial surgery and second-look laparoscopy for both treatment groups for all patients and for the subpopulations.

The initial primary efficacy parameter for the study was the proportion of patients reporting *de novo* adhesions at second-look surgery. At the end of the study, 76.2% of LRS-treated patients and 77.6% of Adept-treated patients were observed to have one or

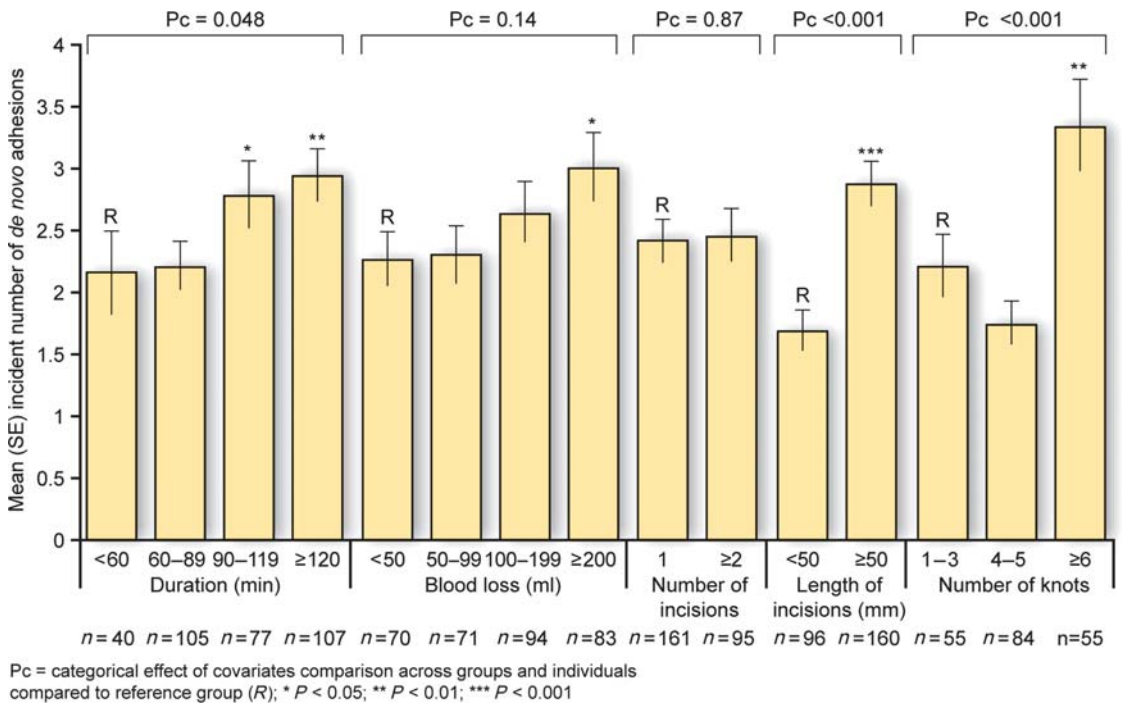

Figure 3 Impact of surgical covariates on mean number of *de novo* adhesions for overall evaluable patient population.

Table V Number of *de novo* adhesions at second look by categorical covariates and by treatment.

Covariate	Category	Overall			LRS		Adept	
		N	Mean (SD)	Effect estimate (95% CI), *P*-value	*N*	Mean (SD)	*N*	Mean (SD)
Duration (min)	<60	40	2.17 (2.19)	Reference	21	2.10 (2.34)	19	2.26 (2.08)
	60–89	105	2.22 (2.09)	0.08 (−0.73, 0.88), 0.850	48	2.48 (2.19)	57	2.00 (1.99)
	90–119	77	2.79 (2.43)	0.88 (0.02, 1.73), 0.045	42	3.07 (2.69)	35	2.46 (2.06)
	≥120	107	2.95 (2.21)	1.13 (0.30, 1.97), 0.008	48	2.50 (2.28)	59	3.32 (2.10)
Blood loss (ml)	<50	70	2.27 (1.87)	Reference	34	2.32 (1.97)	36	2.22 (1.81)
	50–99	71	2.31 (1.97)	0.10 (−0.64, 0.85), 0.787	29	2.79 (2.13)	42	1.98 (1.80)
	100–199	94	2.65 (2.37)	0.47 (−0.23, 1.17), 0.185	44	2.59 (2.47)	50	2.70 (2.30)
	≥200	83	3.01 (2.59)	0.86 (0.14, 1.59), 0.019	46	2.70 (2.83)	37	3.41 (2.23)
Number of incisions	1	161	2.42 (2.16)	Reference	79	2.54 (2.35)	82	2.29 (1.97)
	≥2	95	2.46 (2.17)	0.05 (−0.51, 0.60), 0.872	43	2.19 (2.07)	52	2.69 (2.24)
Length of incisions (mm)	<50	96	1.70 (1.62)	Reference	47	1.89 (1.75)	49	1.51 (1.47)
	≥50	160	2.88 (2.32)	1.18 (0.65, 1.71), <0.001	75	2.75 (2.47)	85	2.99 (2.19)
Number of knots	1–3	55	2.22 (1.89)	Reference	26	1.85 (1.67)	29	2.55 (2.05)
	4–5	84	1.75 (1.63)	−0.28 (−1.07, 0.52), 0.495	45	1.87 (1.82)	39	1.62 (1.39)
	≥6	55	3.35 (2.76)	1.31 (0.46, 2.16), 0.003	24	3.58 (2.89)	31	3.16 (2.68)
Volume irrigated (ml)	<1000	88	1.84 (1.75)	Reference	45	1.71 (1.58)	43	1.98 (1.92)
	1000–1999	141	2.67 (2.11)	0.77 (0.18, 1.37), 0.011	68	2.53 (2.18)	73	2.79 (2.05)
	≥2000	101	3.10 (2.62)	1.19 (0.55, 1.83), <0.001	47	3.47 (2.95)	54	2.78 (2.28)

more *de novo* adhesions. The OR (CI) of 1.11 (0.66, 1.86) was not significant ($P = 0.693$). For myoma and cyst patients, 75.4% and 86.1%, respectively, had one or more *de novo* adhesions. Summaries of the revised primary efficacy parameter, the total number of *de novo* adhesions at second-look surgery, are presented for all patients, surgery subgroup and anatomical sites, by treatment in Table IV. The mean (CI) estimated difference (Adept-LRS) for all patients of 0.028 (−0.46, 0.51) was not significant ($P = 0.909$).

Figure 3 shows the number of *de novo* adhesions by subgroups of the study population (both treatments combined), with *P*-values for comparisons between increasing levels of each covariate and the lowest, reference group, as well as *P*-values indicating the overall

Table VI ***De novo*** **adhesion scoring at second-look laparoscopy.**

	LRS			Adept			Adept-LRS (95% CI), *P*-value
	N	Mean (SD)	Minimum, maximum	*N*	Mean (SD)	Minimum, maximum	
All patients							
Total mAFS (23 sites)	153	8.42 (11.80)	0, 82	159	8.13 (12.37)	0, 71	−0.15 (−2.84, 2.54), 0.911
AFS score (adnexal sites only)	158	0.78 (2.32)	0, 16	164	0.61 (3.00)	0, 32	−0.12 (−0.70, 0.46), 0.690
Posterior myomectomy							
Total mAFS (23 sites)	51	9.31 (13.44)	0, 66	48	6.73 (9.81)	0, 58	−2.58 (−7.30, 2.13), 0.280
AFS score (adnexal sites only)	53	0.38 (1.72)	0, 12	48	0.10 (0.42)	0, 2	−0.27 (−0.78, 0.23), 0.288
AFS site-specific scores							
Posterior uterus	27	5.04 (4.13)	1, 16	31	2.71 (2.04)	1, 8	−2.33 (−4.01, −0.65), 0.007
Rectosigmoid	22	5.18 (3.75)	1, 16	15	3.20 (2.81)	1, 8	−1.98 (−4.30, 0.33), 0.091
Omentum	10	2.80 (1.55)	1, 4	9	2.33 (1.58)	1, 4	−0.47 (−1.98, 1.05), 0.525
Anterior uterus	6	4.17 (2.23)	1, 8	6	3.83 (3.43)	1, 8	−0.33 (−4.05, 3.39), 0.846
Cul-de-sac (posterior)	5	3.00 (3.08)	1, 8	6	1.00 (0.00)	1, 1	−2.00 (−4.81, 0.81), 0.142
Small bowel	0	– (–)	–, –	1	4.00 (–)	4, 4	N/A

All patients, posterior myomectomy subgroup and posterior scoring sites, by treatment group.

significance of each covariate. It illustrates that there is an increasing number of *de novo* adhesions with longer duration of surgery ($P = 0.048$), with approximately 3 *de novo* adhesions per patient for those in surgery for over 2 h. Overall, blood loss was not found to be significantly associated with *de novo* adhesion incidence ($P = 0.14$), though there were signs of a trend (linear effect of blood loss, $P = 0.058$), with patients losing in excess of 200 ml developing a higher number of adhesions than those with <50 ml blood loss during surgery ($P = 0.019$) (Fig. 3). In myomectomy patients, the overall association reached statistical significance ($P = 0.019$).

While the number of incisions made during surgery was not found to be associated with the number of *de novo* adhesions, the total length of incisions did appear to be an important factor ($P < 0.001$). Also, the number of knots used at myomectomy or endometriotic cyst surgery sites showed an association with the numbers of *de novo* adhesions ($P < 0.001$), though the effect was not linear, with a marked increase when six or more knots were used.

Although no treatment effects were found in the population as a whole, several covariate effects were evident (Table V). These were also tested for evidence of differences between treatment groups according to levels of each covariate (i.e. treatment-by-covariate interaction). However none of the covariates studied showed a significant interaction with treatment on the number of *de novo* adhesions.

Secondary efficacy parameters, including total mAFS score and AFS are presented by treatment in Table VI together with details for posterior myomectomy. In patients undergoing posterior myomectomy and where *de novo* adhesions were observed, the AFS scores for individual posterior adhesion scoring sites were examined. The mean *de novo* adhesion score was reduced by 46% in Adept patients compared with LRS at the posterior uterus (AFS site score LRS 5.04: Adept 2.71: $P = 0.007$). This reduction in adhesion burden was supported by similar trends at other adjacent sites where the score of *de novo* adhesion burden was lower.

Table VII Adverse events by treatment group.

	LRS	Adept
Number of patients (safety population)	209	217
Number (%) of patients reporting an adverse event	72 (34.4)	71 (32.7)
Number (%) of patients reporting a treatment-related adverse event	15 (7.2)	18 (8.3)
Treatment-related adverse events (>1 incidence in study)		
Post-procedural pain	7 (3.3)	6 (2.8)
Nausea	3 (1.4)	4 (1.8)
Pain non-specific	2 (1.0)	3 (1.4)
Abdominal pain non-specific	2 (1.0)	0 (0.0)
Vomiting non-specific	1 (0.5)	1 (0.5)
Wound infection	1 (0.5)	1 (0.5)
Nausea post-operative	2 (1.0)	0 (0.0)
Headache	1 (0.5)	1 (0.5)
Urinary retention	2 (1.0)	0 (0.0)
Vulval/genital oedema	0 (0.0)	4 (1.8)

Treatment-related adverse events reported for the safety population are summarized in Table VII. The number (%) of patients reporting one or more such events was 15 (7.2%) with LRS and 18 (8.3%) with Adept. Post-procedural pain was the only event reported in ≥2% of patients in both treatment groups. There were 17 adverse events reported (9 following LRS and 8 following Adept, Table VIII), which were designated serious due to a requirement for prolonged hospitalization and/or surgery.

Table VIII Adverse events designated serious due to a requirement for prolonged hospitalization and/or surgery.

LRS		Adept	
Event designated serious	***N***	**Event designated serious**	***N***
Abdominal pain	5	Abdominal pain	2
With pneumoperitoneum (including post-operative anaesthetic-related hypotension)	3 (1)	With abdominal distension and flatulence	1
Bowel obstruction	1	Post-operative peritonitis and bowel perforation	1
Port-site haematoma	1	Post-operative anaesthetic-related hypotension	1
Clinically confirmed missed miscarriage	1	Wound infection and vomiting	2
Leg pain	1	With faecal impaction	1
		Thrombosis	1
		Intra-operative bleeding	1

None of these serious adverse events were deemed to be treatment related. There were no significant differences in laboratory investigations. No patients died in the study.

Discussion

This was the first double-blind, randomized and controlled study of an anti-adhesion agent specifically investigating reduction of *de novo* adhesions in laparoscopic surgery. Most studies of anti-adhesion agents compare them with surgical technique alone. Importantly, this study compared Adept with LRS, which has been used as a crystalloid for irrigation and hydroflotation. The similarity of the two fluids enabled double-blinding. The study also included blinded and independent video review with comprehensive adhesion scoring of sites throughout the abdominopelvic cavity.

During the GENEVA study, the proportion of patients with *de novo* adhesion formation following laparoscopic myomectomy (75.4%) and ovarian cystectomy (86.1%) was considerable and higher than expected from the literature. On the advice of the DSMB, to enable the study to progress, the study steering panel changed the primary end-point to the total number of *de novo* adhesions for each patient.

The study is distinct from previous research with Adept and with many other anti-adhesion agents, which focused largely on the reformation of adhesions following surgery with adhesiolysis. The study sought to focus on *de novo* adhesion formation. However, 55% of patients had pre-existing adhesions and to enable surgery to be undertaken some pre-existing adhesions had to be lysed in ~25% of patients. Adhesions which reformed at these sites of lysis were not counted within the study analyses. However, it is recognized that the lysis process may have influenced the observed adhesion incidence.

We questioned if the reasons for the high number of adhesions reported reflected differences in the specificity and sensitivity of this study. The adhesion measures employed in the study, included scoring throughout the abdominopelvic cavity. Canis *et al* assessed adnexal adhesions alone (Canis *et al*., 1992) and Dubuisson, while examining adhesions at other sites, including the uterine scar and pouch of Douglas, appeared to focus on sites adherent to the uterus and the adnexa (Dubuisson *et al*., 1998). The GENEVA study employed more sensitive measures and quantifiable scores of adhesions, including systematic video reading of 23 sites plus the site of surgery, independent video assessment and robust scoring compared with the evidence base.

The study was sensitive enough to demonstrate that factors such as surgery duration, blood loss, suture knots and length of incision influenced *de novo* adhesion formation. The wide variations in these factors may have contributed to poor sensitivity to detect changes in the number of *de novo* adhesions between treatments.

While the study provided further confirmation of the safety of Adept in routine surgery, it did not show significant differences between Adept and LRS in terms of the mean number of *de novo* adhesions. Exploratory analysis of the posterior uterus was undertaken as it was considered clinically valid given it is the most adhesiogenic of the three sites of myomectomy. Scoring of *de novo* adhesions at the posterior uterus following removal of a posterior uterine myoma, identified a benefit with Adept over LRS.

A possible reason for limited treatment differences may be explained by some anti-adhesion effect with LRS. This was reported in the PAMELA study (Brown *et al*., 2007), although in this study Adept was shown to reduce adhesion reformation significantly more than LRS. Conversely, a meta-analysis of the effects of crystalloid solutions on abdominopelvic adhesion development reported that they did not increase adhesion-free outcomes, possibly because of rapid absorption of the limited volumes used (Wiseman *et al*., 1998). The higher volumes of LRS used in the PAMELA (Brown *et al*., 2007) and GENEVA studies and meticulous irrigation throughout surgery may have had a beneficial impact.

It was clear from the independent video-review process and the numbers of re-reviews of videos required that this was both a difficult patient group to study and that the independent review process, while robust was not without problems in the reading and scoring of adhesions throughout the abdominopelvic cavity.

Most surgeons do not have the opportunity to undertake second-look therapeutic laparoscopies. In addition, many surgeons do not have the opportunity to see others operating and thus do not see differences in techniques that they may then consider adopting to improve outcomes. The high number of adhesions seen in the study highlights the potential for onward clinical problems due to *de novo* adhesion formation. Adhesions were observed most commonly at the posterior uterus and rectosigmoid and although neither treatment reduced the number of adhesions at these sites, for those adhesions that were found, the extent and severity (as measured by AFS scores for individual anatomical sites) was lower in the Adept group, reaching nominal statistical significance at the posterior uterus.

The study indicates that the duration of surgery, size of incisions, suturing and number of knots, and blood loss are all factors influencing adhesion outcomes. Although the study did not assess the

pneumoperitoneum as a covariate, there is mounting evidence that its environment is also an important adhesiogenic factor.

The published efficacy of Adept in reducing adhesion reformation, including in patients with a high adhesion burden and in difficult clinical cases such as patients with inflammatory endometriosis, pain, infertility and combinations thereof, are not challenged by this study as it only focused on *de novo* adhesion formation (Brown *et al*., 2007). There is good data to support continued use of Adept for reduction of reformed adhesions. In relation to prevention of *de novo* adhesions following primary laparoscopic myomectomy, it seems apparent that surgeons need to carefully consider the size and number of myomas and incision length when deciding whether open or laparoscopic surgery is the better option.

For future research, the study allows us to recommend the need to take careful steps to ensure as homologous a study population as possible. This may include limiting the number of centres, the surgery types and ensure they are narrowly defined to minimize intra- and inter-centre surgery variables and improve study sensitivity. Focusing on a single-patient population will further assist.

Although Adept as a fluid agent works throughout the abdominopelvic cavity, for the purposes of future research with this agent, focusing on site-specific changes rather than simply a global effect is likely to provide more important data on clinical efficacy. In GENEVA, while a global reduction in *de novo* adhesions was not seen with Adept compared with LRS, it was found that the severity and extent of adhesions to the posterior uterus was lower in the Adept group. While independent video reviews throughout the abdominopelvic cavity enhance the robust nature of research, for future studies it may be also valuable to have access to surgeon readings to identify anomalies/issues with video reviews and further verify adhesion scorings.

Conclusion

The GENEVA study identified a very high incidence of *de novo* adhesion formation even amongst centres specializing in laparoscopic gynaecological surgery.

The study results provided further confirmation of the safety aspects of Adept use. Although the study found no difference between Adept and LRS in overall *de novo* adhesion formation, scoring of the adhesion severity and extent, it provides direction for future adhesion reduction strategies in site-specific surgery such as myomectomy, where use of a site-specific barrier agent, perhaps in conjunction with Adept, may be a better strategy to reduce adhesions. Further research may be required to examine this.

Authors' roles

All named authors have reviewed the International Committee of Medical Journal Editors (ICMJE) guidelines regarding 'Authorship and Contributorship' and all of them comply with required elements of the three criterion: (1). (a) substantial contributions to conception and design, (b) acquisition of data or (c) analysis and interpretation of data; (2). (a) drafting the article or (b) revising the article critically for important intellectual content; (3) final approval of the submitted manuscript. Their specific contributions against these criteria are detailed below: G.T.: 1a, b, c, 2a, b, 3; G.Pi.: 1a, b, 2b, 3; G.Pa.: 1b, 2b, 3; A.L.: 1a, b, 2b, 3; L.M.: 1b, 2b, 3; D.W.: 1b, 2b, 3; M.K.: 1b, 2b, 3; J.-L.P.: 1a, b, 2b, 3; E.C.: 1b, 2b, 3; A.A.: 1b, 2b, 3; C.N.: 1b, 2b, 3; E.S.: 1b, 2b, 3; E.M.: 1b, 2b, 3; S.L.: 1a, b, 2b, 3; M.D.: 1a, b, 2b, 3; P.K.: 1b, 2b, 3; S.R.: 1b, 2b, 3, C.C.: 1b, 2b, 3; D.D.: 1b, 2b, 3; T.R.: 1b, 2b, 3; A.M.: 1c, 2a,b, 3; I.F.: 1a, c, 2a, b, 3; A.C.: 1a, c, 2a, b, 3; A.K.: 1a, c, 2a, b, 3; G.dZ.: 1a, b, c, 2a, b, 3; R.DW.: 1a, b, 2b, 3.

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Appendix 1

Corvus Communications was appointed by Shire to support recruitment of study centres, manage and provide administrative support to the study steering panel and DSMB and provide support to G.T. as Principal Investigator in centre coordination, communication and motivation. Corvus received ongoing funding from Baxter BioSurgery for work with the Principal Investigator and Robertson Centre for Biostatistics to assist in data analysis and interpretation as well as drafting the study manuscript and coordinating input from all named authors.

Study steering panel

A study steering panel acted as the primary advisory and guiding group. Members included G.T. (chair); I.F. (chair DSMB and biostatistician); M.D. (Principal Investigator Belgium); J.L.P. (Principal Investigator France), R.DW. (Principal Investigator Germany), G.Pi. (Principal Investigator Greece), S.L. (nominee for Prof Luca Minelli, Principal Investigator Italy and A.L. (Principal Investigator UK).

They acted in accordance with a specific charter to ensure that the study progressed optimally and efficiently—to monitor progress and to consider and recommend any protocol or procedural changes in discussions and consultation with the Sponsor, the appointed Clinical Research Organization and the independent DSMB. Any recommendations from the DSMB safety and data reviews were made to the study steering panel as were any recommendations from the Sponsor, to allow the Panel to collectively give guidance on any modifications to the study proceedings.

Data and safety monitoring board

An independent GENEVA DSMB was appointed to review blinded and unblinded adverse event/incident and outcome data for the study. Members included I.F. (chair); G.T. (principal investigator); G.D.; Christopher Sutton, Professor of Gynaecological Surgery, University of Surrey, UK; Per Lundorff, Viborg Hospital, Department of Obstetrics and Gynaecology, Denmark. The primary remit of the DSMB was to protect the interests of the study patients and review all adverse event data and make recommendations, if appropriate, for any changes to the study protocol or, in the case of significant concerns, recommendations for early termination of the study. The DSMB also had the authority to stop the trial because of overwhelming evidence of a difference between treatments if the comparison between the rates of the primary end-point achieved statistical significance ($P < 0.001$ in a two-sided

statistical test) at a second unblinded interim analysis. The DSMB functioned in accordance with a designated charter.

Other investigators and sub-investigators

In addition to the named authors other study investigators included Bernard Blanc, Marseille, France; Herve Dechaud, Montpelier, France; Claude Hocké, Bordeaux, France; Patrick Madelenat, Paris, France; Mario Malzoni, Avellino, Italy and Luca Minelli, Negrar, Italy.

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Contract research organization

PAREXEL International, Uxbridge, Middlesex, UK were the CRO appointed by Shire to coordinate and monitor the study and manage data entry. Their sister organization, Perceptive Informatics, Inc., Berlin Germany was appointed by Shire to manage the independent video reviews.

Appendix 2

Video recording

Systematic review of eight key organ sites: right paracolic gutter and right large bowel (intestinum crassum); cephalad anterior peritoneum right then left; left paracolic gutter and left large bowel; rectosigmoid; omentum and small bowel (intestinum tenue).

Video recording of 23 mAFS adhesion sites

Anatomical site	Description
Cephalad anterior peritoneum—right	Cephalad of uterine fundus and right of midline
Caudal anterior peritoneum	Caudal with respect to fundus of uterus including bladder flap
Right large bowel	Large bowel (intestinum crassum) right of midline
Cephalad anterior peritoneum—left	Cephalad of uterine fundus and left of midline
Left large bowel	Large bowel (intestinum crassum) left of midline
Rectosigmoid	Portion of sigmoid colon in the pelvis
Omentum	
Small bowel	Intestinum tenue
Anterior uterus	Uterine surface anterior to tubal insertion (cornual plane)
Posterior uterus	Uterine surface posterior to tubal insertion (cornual plane)
Cul-de-sac (posterior)	Posterior cul-de-sac medial to the uterosacral ligaments
Medial ovary—right and left side	Most medial portion of the anterior surface of ovary (one-half of the anterior surface closest to the lateral aspect of the uterus)
Lateral ovary—right and left side	Most lateral portion of the anterior surface of ovary (one-half of the anterior surface farthest from the lateral aspect of the uterus)
Sidewall—right and left side	Lateral aspect to the uterosacral ligament
Ovarian fossa—right and left side	That portion of the ovary (all of the posterior surface) which is in contact with the broad ligament
Tube—right and left side	Aspect of the fallopian tube proximal to the ampulla (includes isthmus and cornua)
Ampulla—right and left side	Includes the fallopian tube infundibulum and fimbriae