# Introduction

Achieving timely hemostasis during surgery is critical to ensure wound healing and minimize blood loss. Complications from perioperative bleeding and associated transfused blood products account for substantial clinical morbidity and economic burden [1-3]. Innovation in surgical techniques has included the development of various topical hemostatic agents (THA), used as adjuncts when conventional techniques such as ligature, sutures or electrocautery are insufficient or impractical [4, 5]. THA are known to improve patient outcome and reduce health care cost [6-8]. Classified by mechanism of action, they include mechanical agents that provide a structural matrix, active agents that contain thrombin, flowables consisting of gelatin matrix with/without thrombin, and fibrin sealants which are based on fibrinogen and thrombin [4, 5].

Fibrin sealants (FSs) have emerged as effective and safe adjuncts for controlling perioperative bleeding in a wide range of open and endoscopic surgical scenarios [9]. Upon mixing, the dual-component thrombin/fibrinogen system mimics the final step in the natural coagulation pathway, forming a stable physiological fibrin clot that assists in tissue healing. Rapid hemostatic action occurs regardless of the patient’s coagulation status, while the biocompatible clot is absorbed through physiological fibrinolysis. Evicel® Fibrin Sealant (Ethicon Inc., Raritan NJ, USA) consists of a human fibrinogen/fibronectin concentrate and human thrombin. The hemostatic effectiveness of Evicel® was demonstrated in adult clinical trials of retroperitoneal, intra-abdominal, orthopedic, vascular and neurosurgery, and no safety concerns emerged [10-13]. In the US and EU, Evicel® is indicated as adjunct to surgical hemostasis when standard surgical techniques are ineffective or impractical [14, 15]. In EU, Evicel® is also indicated as suture support in vascular surgery, and for suture line sealing in dura mater closure; however, it is not yet approved in children [15].

Observational data have supported the efficacy of FSs as sealants/adhesives in children treated for dural puncture leakage [16, 17], peritoneal catheter cuff leakage [18-20] and other conditions [21-26], and these studies did not raise any safety concerns. A shortage of clinical data exists, however, on the use of FSs to control intraoperative bleeding in pediatric patients. Fibrin sealants were shown to be safe and effective as adjunctive hemostats in children undergoing hepatectomy and tonsillectomy [27-29] and to reduce the transfusion need and intensive care hospitalization time after cardiovascular surgery [30]. For other surgical indications, however, studies are scarce. Here, we present a multicenter randomized, controlled clinical trial evaluating the safety and efficacy of Evicel® versus Surgicel® as adjuncts to surgical hemostasis in children undergoing abdominal, retroperitoneal, pelvic, or thoracic surgery.

# Patients and Methods

**Study Design**. This was a multicenter, prospective, randomized controlled study across pediatric surgery centers in the UK, Canada, and Belgium, evaluating Evicel® versus Surgicel® (Ethicon, Inc., Raritan NJ, USA) as adjunctive hemostats for mild-to-moderate intraoperative bleeding in children undergoing open or laparoscopic procedures in multiple surgical subspecialties. The ‘target bleeding site’ (TBS) was defined as ‘the first active bleeding site identified during soft tissue or parenchymal organ dissection (kidney, liver, spleen, pancreas) that was related to the operative procedure and required the use of an adjunctive hemostat because conventional hemostatic methods were considered ineffective or impractical to use’. Concurrent with prior hemostasis trials in adults, mild bleeding was defined as a ‘small area of capillary, arteriole or venule oozing’, and moderate bleeding as ‘bleeding that was considered challenging because of a larger area of capillary, arteriolar or venular oozing, or bleeding that was more pronounced than oozing, possibly originating from a small artery or vein, but not massive, pulsatile or flowing’. As required by the European Medicines Agency Pediatric Investigation Plan for Evicel®, a descriptive analysis on a randomized sample of 40 subjects (³20 subjects per arm) was needed to demonstrate safety of the product in pediatric population. In alignment with EU Guidance on the clinical investigation of plasma-derived FSs [31], control subjects received standard treatment without FS, and the clinical situations represented those encountered in actual clinical practice. The performance and safety profile of the Surgicel® family of products are supported by clinical studies in a wide spectrum of surgical procedures [32]. As a widely available product, Surgicel® is considered a reasonable and acceptable international standard of care. This study was performed in accordance with the ICH tripartite guideline for Good Clinical Practice (1996), the US FDA regulations (Title 21 CFR Parts 50, 54, 56, 312), the Declaration of Helsinki (2013), the European Union Clinical Trial Directive (2001/20/EC, May 2001), and the EU GCP Directive (2005/28/EC). Clinical Trial Application (CTA) approval was obtained from the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK (2 January 2014), the Federal Agency for Medicines and Health Products, Belgium (27 January 2014), and Health Canada (11 February 2014). Protocols and informed consent forms were approved by independent ethics committees/institutional review boards at participating sites (Supplementary Material 1). The trial was registered as EudraCT 2013-003401-26 and NCT 02227706.

**Study Subjects and Procedures.** Patients younger than 18 years, requiring non-emergent open/ laparoscopic, and abdominal, retroperitoneal, pelvic or thoracic (non-cardiac) surgery, were considered. The patient’s parent or legal guardian provided informed consent, as required by local regulations. Assent was obtained from patients possessing the intellectual and emotional ability to comprehend the study concepts. Patients in whom an appropriate TBS was identified intra-operatively were enrolled if none of the exclusion criteria were met, which included known intolerance to blood products or study product component(s), unwillingness to receive blood products, surgery indicated for trauma, TBS in an actively infected field [33]) or in an anastomotic bleeding site (full list of exclusion criteria is given in Supplementary Material 2).

The study sponsor provided computer-generated randomization envelopes. For each subject, at least 1 Evicel® and 1 Surgicel® kit were prepared in the operation field room before randomization. Upon encounter of the first TBS, the subject was randomized. Neither investigators nor study subjects were blinded to treatment. Evicel® was applied according to manufacturers’ instructions [34] using the Evicel® application device, tips and/or airless spray accessory [14], the amount of study product being dependent on the area to be treated. The TBS was assessed at 4, 7, and 10 min after randomization. If, during the 10-min assessment, hemostasis was not achieved or if break-through bleeding occurred, a second application of the assigned study product was allowed (with a 1-2 min cure time between applications); if indicated, the surgeon could revert to standard of care. If, beyond the 10-min observation period, bleeding persisted or re-bleeding occurred, the use of any hemostatic method was allowed, per the surgeon’s standard of care. Post-operatively, study subjects were followed until hospital discharge, and re-evaluated at postoperative day 30 (+14) via an in-office visit or a phone call.

**Safety Endpoints**. All adverse events (AE) and serious adverse events (SAE) occurring within the 30-day postoperative follow-up were captured and adjudicated for relationship with study product and procedure. The sponsor was required to submit any reportable events to Health Regulatory Authorities per local regulations. For reportable events, investigator causality assessment was not to be changed by the Sponsor, and if there was a difference in opinion, both assessments were to be presented. Adverse events were summarized using Medical Dictionary for Regulatory Activities (MedDRA) terms. Specific safety endpoints were the proportions of subjects with thrombotic and TBS re-bleeding events, the estimated volume of blood loss, and the quantity of transfused blood and blood products.

**Efficacy Endpoints.** The primary efficacy endpoint was the time to hemostasis (TTH), defined as the time between randomization and cessation of bleeding at the TBS. The secondary effectiveness endpoints were the proportions of subjects achieving hemostasis (“treatment success”) at the TBS at 4, 7 and 10 min, and the proportion of subjects who failed to achieve hemostasis within 10 min, or who required hemostatic treatment at the TBS other than re-application of the assigned study product (“treatment failure”) [10].

**Statistical Analysis.** Safety and efficacy endpoints were summarized descriptively, in the Safety and Intention-to-treat (ITT) set, respectively. Efficacy endpoints included the median TTH with 2-sided distribution-free 95% confidence interval (CI) (missing data not imputed; analysis in the Per-protocol (PP) set was considered supportive), proportions of subjects with 4-, 7-, and 10-min treatment success and treatment failure, with 2-sided Clopper-Pearson 95% CI (missing data considered as failures). The TTH was also analyzed by age group (neonates [birth-30 days], infants/toddlers [31 days-24 months], children [2-11 years] and adolescents [12-<18years]). The SAS® studio version 9.1 (EG) or higher was used.

# Results

**Study Subjects.** Between November 2014 and May 2019, a total of 130 subjects were screened at 14 centers, and 40 were enrolled at 8 centers in the UK and Canada (1-10 subjects per center) (Figure 1). The ITT set included 20 subjects in each group, and all subjects completed the study. The PP set comprised 18 Evicel® and 20 Surgicel® subjects. Three major protocol deviations occurred in 2 Evicel® subjects, due to alterations in study procedure and randomization. For the first subject, the primary endpoint data were unavailable, but secondary endpoint analysis showed treatment success at 4, 7, and 10 min. For the second subject, data were available for all endpoints. The Safety set included 20 subjects in each group. Patient characteristics are shown in Table 1. The study populations had similar age ranges with subjects in every age group except neonates. Gender distribution was slightly skewed towards females for Evicel® and towards males for Surgicel®. Overall, the indications for surgery were neoplasms/cysts (n=19, 47.5%), abnormalities in the gastrointestinal (n=12, 30.0%) or urinary tract (n=2, 5.0%), splenomegaly due to congenital spherocytosis (n=3, 7.5%), and other indications (n=4, 10.0%).

**Surgical Procedures and Target Bleeding Sites**. Both study arms showed a predominance of open (versus laparoscopic) approaches, and of abdominal procedures (Table 2). The primary method to obtain hemostasis at the TBS was mostly electrocautery, or no other conventional method was used because they were considered impractical. In both groups, TBSs were mostly located in the abdomen, followed by the pelvic and retroperitoneal region in the Evicel® group, and the thoracic and retroperitoneal region in the Surgicel® group (Table 2). The most frequent TBS tissue types in the Evicel® arm were loose areolar connective tissue and liver, followed by fat tissue, and in the Surgicel® arm loose areolar connective tissue followed by other tissues, fat and muscle. In both arms, TBS bleeding intensity was 40% moderate and 60% mild, with a mostly diffuse bleeding pattern. The predominant source of bleeding was venous in both groups, followed by mixed arterial and venous. The THA were applied per manufacturer’s instructions. Surgeons’ preference for Evicel® application method and device tips, as well as the quantities of product used are described in Supplementary Material 3. The median (range) surgery and operating room times were 143.0 (64.0, 506.0) min and 212.5 (106.0, 553.0) min in the Evicel® group, versus 167.0 (47.0, 415.0) and 224.5 (125.0, 496.0) min in the Surgicel® group. Six Surgicel® subjects (30.0%) and 2 Evicel® subjects (10.0%) were admitted to ICU. In all 8 subjects, the reasons for admission to the ICU were adverse events that were classified by both investigator and sponsor as Not Related to study product. Of the adverse events that occurred after their admission to the ICU, only one was classified as possibly related to Evicel®: this subject had been admitted to ICU because of a serious adverse event of possible hypoxic brain injury, which -as mentioned- was considered unrelated to study product. Two days after ICU submission, clotting tests in this subject showed values higher than normal: this was considered a mild, non-serious adverse event and possibly related to Evicel®. In both groups, the median postoperative hospital stay was 5 nights, with a range of (1, 40 nights) for the Evicel® and (1, 13 nights) for the Surgicel® group.

**Safety Endpoints.** Nearly all Evicel® and Surgicel® subjects experienced at least 1 AE, but SAE were few in both groups (Table 3). There were no deaths or thrombotic events in either group, and the frequency of re-bleeding was low (Table 3). Investigators adjudicated 50 AEs in the Evicel® and 60 AEs in the Surgicel® group as (possibly) related to study procedure. Two AEs in 2 Evicel® subjects (10.0%) (coagulopathy (abnormal values on laboratory clotting test) and pyrexia) and two AEs in 2 Surgicel® subjects (10.0%) (tachycardia and hypotension) were considered possibly related to study product by the investigator; the study sponsor considered these events Not Related to study product due to the lack of a plausible causal mechanism (Table 3). The median estimated blood loss (for the entire surgical procedure) was 50.0 mL in both groups, with a range of (0.0, 2,000.0 mL) for Evicel® and (0.0, 400.0 mL) for Surgicel®. Two Evicel® subjects experienced excessive blood loss, but in neither subject was this related to the TBS. The first subject experienced a 2,000 mL procedural hemorrhage prior to being randomized. The second subject had a mild TBS bleeding but suffered a total operative blood loss of ±1,500 mL. In both subjects, the TBS showed hemostasis at 4 min with no re-bleeding. Between randomization and study completion, 7 Evicel® subjects (35.0%) received a total of 13 units of blood products and 3 Surgicel® subjects (15.0%) a total of 5 units.

**Effectiveness Endpoints.** The median (range) TTH was 4.0 min (1.8, 27.1) (95% CI 3.3, 4.7) for the Evicel® group and 4.0 min (1.1, 115.5) (95% CI 2.9, 8.1) for the Surgicel® group (Figure 2). One Surgicel® subject experienced rebleeding at 114 min, as described below. By age group, the TTH in the Evicel® and Surgicel® groups were 4.0 min (2.8, 6.3) versus 61.8 min (8.1, 115.5) for infants/toddlers, 4.0 min (2.6, 6.0) versus 4.0 min (1.1, 11.2) for children, and 4.0 min (1.8, 27.1) versus 7.0 min (1.2, 16.0) for adolescents, respectively (Figure 2). Effectiveness analyses in the PP set showed similar results (not shown).

The treatment success rates in the Evicel® and Surgicel® groups were 16/20 subjects (80.0%, 95%CI 56.3, 94.3) versus 13/20 subjects (65.0%, 95%CI 40.8, 84.6) at 4 min, 20/20 subjects (100.0%, 95%CI 83.2, 100.0) versus 16/20 subjects (80.0%, 95%CI 56.3, 94.3) at 7 min, and 19/20 subjects (95.0%, 95%CI 75.1, 99.9) versus 18/20 subjects (90.0%, 95%CI 68.3, 98.8) at 10 min, respectively (Figure 3). For 1 Surgicel® subject, the 10-min assessment was not completed, but with a 7-min TTH and no re-bleeding, the subject was considered a treatment success. The treatment failure rates were 1/20 (5.0%) Evicel® and 5/20 (25.0%) Surgicel® subjects. One Evicel® subject exhibited TBS re-bleeding at 10 min but did not require additional hemostatic treatment. In the Surgicel® group, 6/20 subjects (30.0%) received additional hemostatic treatment. One of these subjects received additional Surgicel® but was not considered a treatment failure. The 5 other subjects were treatment failures: 3 required electrocautery and manual compression; 1 required additional Surgicel®, manual compression and electrocautery, 1 required additional Surgicel®, manual compression and FS patch; the remaining 2 subjects, after achieving hemostasis at 10 min, showed re-bleeding at 14 min and 114 min that required additional Surgicel® and diathermy, respectively.

# Discussion

This phase III study was done as a regulatory requirement to support a clinical indication for Evicel® Fibrin Sealant in the treatment of mild-to-moderate soft-tissue and parenchymatous surgical bleeding in children. The randomized study, albeit small-scale, supports that Evicel® is safe and performs comparably to the widely used oxidized regenerated cellulose THA Surgicel®, in a wide range of surgical procedures.

Hemostatic efficacy was evident from a similar time-to-hemostasis in both Evicel® and Surgicel® groups, and a comparable increase in success rates, reaching 100% for Evicel® and 90% for Surgicel® at 10 min. The efficacy of Evicel® across age groups, surgical indications, procedure types, and bleeding site characteristics support its value in the general pediatric surgery setting. The surgical indications varied and concerned mostly tumors or cysts, and gastro-intestinal or genito-urinary abnormalities. The TBSs included similar proportions of mild and moderate bleeding intensities, were mostly diffuse in nature and occurred mostly in loose areolar tissue or liver parenchyma, but a wide range of bleeding types and tissues were represented.

Small between-group differences were noted in patient demographics and procedure characteristics, but intra-operative randomization ensured that investigator bias was excluded. Despite a slight difference in median age, the age ranges were similar. Developmental hemostasis is recognized as the physiological maturation of the coagulation system,[35-37] but age-related changes of coagulation and fibrinolysis are most prominent before the age of 6 months [35, 38]. No neonates were enrolled but the Evicel® arm counted 5 subjects aged 1-24 months. While very small, age groups did not show major differences in efficacy.

In a substantial proportion of subjects in both study arms, the adjunctive hemostat was used as a primary hemostatic method because any other method was considered impractical to use due to a (fragile) tissue condition, a large TBS area or an anatomical location impractical for conventional methods. This underscores the value of topical hemostats in the control of mild-to-moderate surgical bleeding [14, 15].

Similar to the adult Evicel® phase III trial, new safety signals were not identified [10]. Most AE were considered (possibly) related to surgical procedure and could be anticipated in the populations treated. In the Evicel® group, variability was noted in surgical parameters such as total procedural blood loss, but none of the outlier values were related to the TBS. Rather, the limited overall blood loss is consistent with the inclusion criteria of mild-to-moderate bleeding, and supports the efficacy of the THA. Documentation of blood loss was not standardized. Total blood loss of zero mL in 3 Evicel® and 1 Surgicel® subject probably related to non-bloody surgical procedures, meticulous dissection and/or the use of energy-based sources.

Although this clinical trial is limited by its descriptive design and small sample size, the favorable outcomes were associated with critical surgical markers supporting the efficacy of Evicel®, including a larger median TBS area, and lower rates of treatment failure and additional treatment relative to the Surgicel® group, arguing in favor of Evicel’s place amongst THAs used in the pediatric population. Due to the nature of the study products, the investigators could not be blinded. This limitation was addressed by the randomization process which occurred intra-operatively, after the TBS had been identified. While the limited sample size did not allow stratification for procedure type, the heterogeneity of surgical indications supports the THA’s safety.

# Conclusion

In accordance with clinical studies in adults, this phase III study supports the safety and efficacy of Evicel® in achieving rapid and sustained hemostasis of mild-to-moderate surgical bleeding in a pediatric population undergoing a broad range of surgical procedures.

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# Table Captions

Table 1. Subject Demographics.

Table 2. Surgical Procedure and Target Bleeding Site Characteristics.

Table 3. Adverse Events

# Figure Legends

Fig. 1. Disposition of study subjects.

Fig. 2. Time to hemostasis (ITT Set). Shown is the TTH for (a) the total group (values indicate the median TTH (min) with distribution-free 95% CI) (n=1 missing data in EVICEL®), and (b) the subgroups according to age (values indicate the median TTH (min) and range) (n=1 missing data in the EVICEL® Adolescents).

Fig. 3. Treatment success (ITT Set). Shown is the percentage of subjects who showed hemostasis at 4, 7 and 10 min after randomization, with 2-sided Clopper-Pearson 95% CI.