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BLA Clinical Review Memorandum

Application Type	Supplement
STN	BLA 125640/220
CBER Received Date	July 4, 2023
PDUFA Goal Date	September 27, 2024
Division / Office	CBER/OTP/OCE/DCEGM
Priority Review (Yes/No)	No
Reviewer Name	Elizabeth Sharpe, MD
Review Completion Date / Stamped Date	August 30, 2024
Supervisory Concurrence	Vijay Kumar, MD, MMM, Team Leader Gavin Imperato, MD, PhD, Branch Chief Patroula Smpokou, MD, Division Director
Applicant	Instituto Grifols, S.A.
Established Name	Fibrin sealant (human)
Trade Name	VISTASEAL
Pharmacologic Class	Fibrin Sealant
Formulation(s), including Adjuvants, etc.	Frozen solutions
Dosage Form(s) and Route(s) of Administration	Two prefilled syringes containing sterile frozen solutions of human fibrinogen (component 1) and human thrombin with calcium chloride (component 2), which are assembled in a syringe holder for single use for topical administration.
Dosing Regimen	N/A
Indication(s) and Intended Population(s)	As an adjunct to hemostasis for mild to moderate bleeding in patients undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical.
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

GLOSSARY

ADR	adverse drug reaction
AE	adverse event
BLA	Biologics License Application
FDA	Food and Drug Administration
HF	human factors
IP	investigational product
iPSP	initial pediatric study plan
IR	information request
ITT	intent-to-treat
MC	manual compression
mITT	modified intent-to-treat
PMR	postmarketing requirement
PP	per protocol
PREA	Pediatric Research Equity Act
SAE	serious adverse event
STN	Submission Tracking Number
TBS	target bleeding site
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TTH	time to hemostasis

1. EXECUTIVE SUMMARY

Instituto Grifols, S.A. submitted the supplement to Biologics License Application (sBLA) 125640/220 to expand the indication for VISTASEAL to include the pediatric population. The product is being marketed under the name "VISTASEAL." The product was referred to as "FS Grifols" in the clinical studies. The Applicant refers to the product in the supplement as "FS Grifols."

VISTASEAL was approved on November 1, 2017, for use as an adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. In this BLA supplement the Applicant submitted the results of their required postmarketing study in pediatric subjects (Pediatric Research Equity Act [PREA] postmarketing requirement [PMR]) and would like to expand the indication to include pediatric patients ages 0 to <18 years based on data in the postmarketing study and data from the studies that supported the original marketing application for adults.

VISTASEAL is a frozen, sterile, two-component fibrin sealant solution obtained from human plasma pools. VISTASEAL consists of human fibrinogen (component 1) and human thrombin with calcium chloride (component 2) solutions in filled syringes and assembled on a syringe holder. VISTASEAL is a combination product; it is packaged with a drip applicator tip that is generally used for soft tissue and vascular surgery and a spray applicator tip that is generally used for parenchymal surgery.

VISTASEAL is intended for topical application to exert a local effect by dripping or spraying. When applied to a bleeding surface, the solutions generate a crosslinked fibrin clot in a process that mimics the last stage of the human coagulation system. VISTASEAL is intended for use intraoperatively only by a surgeon or qualified health care provider.

The clinical development program of VISTASEAL in pediatric patients consists of four pivotal Phase 3 clinical studies. The main study reviewed for this pediatric efficacy supplement is the PREA PMR Study IG1405 that enrolled 186 pediatric subjects. Three pivotal studies (IG1101, IG1102, and IG1103) supported the safety and efficacy of VISTASEAL for the original biologics license for the indication of adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. High-level summaries of these studies are provided below. Collectively, these three studies that supported the original BLA enrolled twenty-three pediatric subjects. Of the 23 pediatric subjects enrolled, 10 received VISTASEAL and only 1 pediatric subject received VISTASEAL as part of the randomized-controlled parts of the

of the studies. Table 1 summarizes the four pivotal studies that support VISTASEAL for the intended indication:

Table 1. All Pivotal Phase 3 Clinical Studies

Study No.	Surgery Type	Active Control	Hypothesis Testing	Target Bleeding Site Intensity	Number of Children Enrolled	Number of Children Who Received VISTASEAL
IG1405	Parenchymous (hepatic) and soft tissue	EVICEL	Noninferiority	Mild or Moderate	186	91
IG1101	Vascular	Manual compression	Superiority	Moderate	0	0
IG1102	Parenchymous (hepatic)	SURGICEL	Noninferiority	Moderate	5	2
IG1103	Soft tissue	SURGICEL	Noninferiority	Moderate	18	9

Source: Original table by clinical reviewer; data extracted from the Clinical Overview document

Study IG1405 Overview

Pediatric Study IG1405 was a Phase 3, multicenter, patient-blinded, prospective, randomized active-controlled noninferiority study comparing VISTASEAL to EVICEL, a fibrin sealant (human) that is FDA-approved as an adjunct to hemostasis for use in patients undergoing surgery, when control of bleeding by standard surgical techniques (such as suture, ligature, or cautery) is ineffective or impractical.

The primary efficacy endpoint was the proportion of subjects achieving hemostasis at the target bleeding site (TBS) by four minutes after product application (T4), with no occurrence of rebleeding until the completion of the surgical closure ($T_{Closure}$).

The study enrolled subjects aged <18 years who required an elective (nonemergency), open pelvic, abdominal, or thoracic (noncardiac) surgical procedure, wherein a TBS was identified, and a topical hemostatic agent was indicated. The study treatments were applied on the cut parenchymous surface of a solid organ (i.e., liver) or in soft tissue (i.e., fat, muscle, or connective tissue). Emergency surgery was included only in subjects aged ≤27 days to increase the chance of enrolling subjects in this age group. The maximum allowable volume of VISTASEAL was 12 mL for subjects ≥2 years of age and 6 mL for subjects <2 years of age.

Of the 186 pediatric subjects enrolled, 91 received VISTASEAL and 87 received EVICEL. The remaining eight subjects (four in the VISTASEAL group and four in the EVICEL group) did not receive fibrin sealant either because no TBS that met eligibility criteria was identified intraoperatively or because the product was not available during surgery. The primary analyses, as predefined in the study protocol, included the modified intent-to-treat (mITT) population which included all subjects who received either VISTASEAL or EVICEL during the study. The predefined noninferiority margin was 0.8 for the ratio of proportions of subjects achieving hemostasis by T4.

Study IG1405: Summary of Efficacy

In Study IG1405, the proportion of hemostasis by T4 (primary efficacy) in all types of bleeding sites was 96.7% (88/91 subjects) in the VISTASEAL group and 95.4% (83/87 subjects) in the EVICEL group. The 95% confidence interval (CI) of proportion of subjects meeting the primary efficacy endpoint in subjects receiving VISTASEAL relative to EVICEL was 1.01 (0.96 to 1.07).

The proportion of hemostasis by T4 in subjects with a parenchymous bleeding site was 100% in both the VISTASEAL group (46/46 subjects) and the EVICEL group (43/43 subjects). The 95% CI of proportion of subjects with a parenchymous TBS meeting the primary efficacy endpoint in subjects receiving VISTASEAL relative to EVICEL was 1.00 (0.92 to 1.09), indicating that VISTASEAL is noninferior.

The proportion of hemostasis by T4 in subjects with a soft tissue bleeding site was 93.3% (42/45 subjects) in the VISTASEAL group and 90.9% (40/44 subjects) in the EVICEL group. The 95% CI of proportion of subjects with a soft tissue TBS meeting the primary efficacy endpoint in subjects receiving VISTASEAL relative to EVICEL was 1.03 (0.91 to 1.16).

The primary clinical efficacy endpoint was supported by secondary efficacy endpoints, including the cumulative proportion of subjects achieving hemostasis at the TBS by T7 and T10 and the prevalence of treatment failures, defined as:

- Persistent bleeding at the TBS beyond the 4-minute observation time point
- Grade 3 or 4 breakthrough bleeding at the TBS that jeopardizes subject safety, according to the investigator's (the surgeon's) judgment, at any moment during the 10-minute observation period and until $T_{Closure}$
- Use of alternative topical hemostatic agents or maneuvers (other than the study treatment) at the TBS during the 10-minute observation period and until $T_{Closure}$ or use of study treatment at the TBS beyond the assessment of the primary efficacy endpoint at T4 and until $T_{Closure}$
- Rebleeding (Grade ≥1) at the TBS after the assessment of the primary efficacy endpoint at T4 and until $T_{Closure}$

Hemostasis by T7: All 91 (100.0%) subjects from the VISTASEAL group (46 subjects in parenchymous surgery and 43 subjects in soft tissue surgery), and all 87 (100.0%) subjects from the EVICEL group (43 subjects in parenchymous surgery and 44 subjects in soft tissue surgery) met the secondary efficacy endpoint and achieved hemostasis at the TBS by T7.

Hemostasis by T10: A total of 90/91 (98.9%) subjects from the VISTASEAL group, and all 87 (100.0%) subjects from the EVICEL group met the secondary efficacy endpoint and achieved hemostasis at the TBS by T10. In parenchymous surgery, 45/46 (97.8%) subjects in VISTASEAL group and all 43 (100.0%) subjects in EVICEL group achieved hemostasis. In soft tissue surgery, all 45 (100.0%) subjects in VISTASEAL group and all 44 (100%) subjects in EVICEL group achieved hemostasis. The only subject who did

not achieve hemostasis at T10 was Subject (b) (6) in VISTASEAL group. This subject missed hemostasis assessment at T10; hence the missing assessment was considered not to have achieved hemostasis. However, this subject achieved hemostasis at T4 and T7

Prevalence of treatment failures: There were no treatment failures in either arm of the study.

Conclusion Regarding Efficacy Data in Study IG1405

These data indicate that VISTASEAL is noninferior to EVICEL in parenchymous and soft tissue surgery in pediatric patients.

Study IG1405 Summary of Safety

Deaths in Study IG1405

A total of three deaths occurred in the study, one (1/91 [1.1%]) in VISTASEAL group and two (2/87 [2.3%]) in the EVICEL group. All deaths were considered by the investigator, Applicant, and clinical reviewer as unrelated to study treatment. See Section 6.1.12.3 for a review of the deaths that occurred in this study.

Nonfatal Serious Adverse Events in Study IG1405

The number and nature of nonfatal treatment-emergent serious adverse events (TESAEs) were similar in the VISTASEAL and EVICEL groups. Fifteen subjects experienced TESAEs: seven (7.7%) subjects in VISTASEAL group and eight (9.2%)subjects in EVICEL group. All serious adverse events (SAEs) were considered unrelated to the study treatment by the investigator and the Applicant. The clinical reviewer assessed one TESAE (ileoileal intussusception that occurred in an 8-month-old male 2 days after application of VISTASEAL) as possibly related to VISTASEAL and two TESAEs (pulmonary embolism that occurred in a 1-year-old female 7 days after EVICEL application and paralytic sepsis that occurred 2 to 3 days after application of EVICEL) as unlikely related to EVICEL. Table 32 in Section 6.1.12.4 of this memo includes details regarding all TESAEs reported in Study IG1405.

Adverse Drug Reactions in Pediatric Study IG1405

The pediatric study protocol for IG1405 defined adverse drug reaction (ADR) as any adverse event (AE) considered by the investigator to be related to VISTASEAL or EVICEL. With this definition, only one adverse reaction of postoperative procedural pain occurred during the study. All other AEs across all study sites were assessed by the investigator/surgeon as not related to VISTASEAL or EVICEL.

Most Common Treatment-Emergent Adverse Events for Pediatric Study IG1405

Table 2 lists the most common treatment-emergent adverse events (TEAEs) that were recorded in subjects in pediatric Study IG1405, defined as occurring in ≥2 patients. The table reflects grouped like-terms.

Table 2. Most Common Treatment-Emergent Adverse Events Defined as Occurring in ≥2 Subjects, IG1405

Grouped Term (Revised)	Terms Reported in CSR
Anemia	anemia anemia postoperative hemoglobin decreased
Upper respiratory infection	respiratory syncytial virus infection respiratory tract infection rhinovirus infection upper respiratory tract infection viral upper respiratory tract infection
Wound complication	wound complication wound infection wound dehiscence postoperative wound infection
Bleeding	post procedural hemorrhage procedural hemorrhage
Low platelets	thrombocytosis platelet count increased
Ileus	Ileus paralytic ileus
Vomiting	vomiting procedural vomiting

Source: Original table by clinical reviewer
Abbreviations: CSR, complete study report; TEAE, treatment-emergent adverse event

Studies IG1101, 1102, 1103

The following summarizes efficacy and safety data from the three pivotal studies that supported approval of VISTASEAL for use in adults in the original BLA. All three pivotal studies had similar study designs. Each study was a Phase 3, multicenter, patient-blind, prospective randomized controlled study that consisted of two parts: a Preliminary Part I and a Primary Part II. The purpose of the Preliminary Part I was to ensure that local study teams familiarized themselves with the technique for VISTASEAL application and with intra-operative procedures required by the protocol of the clinical study. In Study IG1101, all subjects enrolled in the Preliminary Part I were treated with VISTASEAL. In Studies IG1102 and IG1103, subjects were randomized in Preliminary Part I to a 1:1 ratio into one of two treatment groups: VISTASEAL or SURGICEL.

Part II of the studies was designed to provide sufficient evidence to support the safety and efficacy of VISTASEAL as an adjunct to hemostasis in surgery and was to start only after enrollment of two subjects in Part I in Study IG1101 and four subjects in Studies IG1102 and IG1103.

The primary efficacy endpoint for all three clinical studies was the proportion of subjects achieving hemostasis at the TBS by 4 minutes (T4) following the start of treatment application (T_{Start}), without occurrence of rebleeding and reapplication of study treatment after T4 and until the completion of the surgical closure ($T_{Closure}$).

Efficacy Data From Studies IG1101, 1102, and 1103

Study IG1101 (Vascular)

Study IG1101 was a superiority study to evaluate the efficacy and safety of VISTASEAL compared to manual compression (MC) as an adjunct to hemostasis during vascular surgery. The study enrolled 225 adults undergoing an elective, open peripheral vascular surgical procedure who had a TBS with moderate bleeding for which conventional surgical techniques (including suture, ligature, and cautery) were ineffective or impractical and required an adjunct treatment to achieve hemostasis. No pediatric subjects enrolled in the study, although eligibility criteria included children. The absence of pediatric enrollment was attributed to the low prevalence of children who undergo peripheral vascular surgery. Subjects were randomized 1:1 to receive VISTASEAL or MC.

The proportion of hemostasis by T4 (primary efficacy) was 76.1% (83/109 subjects) in the VISTASEAL group and 22.8% (13/57 subjects) in the MC control group. The 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving VISTASEAL relative to MC was 3.339 (2.047, 5.445). The proportion of hemostasis by T4 was significantly higher in the VISTASEAL group compared to the MC group (p-value<0.001), indicating that VISTASEAL is superior to MC and that the primary efficacy objective was achieved.

The primary clinical efficacy endpoint was supported by secondary efficacy endpoints including time to hemostasis (TTH), hemostasis by T5, T7, and T10 and the rate of treatment failures.

Study IG1102 (Parenchymous)

Study IG1102 was a noninferiority study to evaluate the efficacy and safety of VISTASEAL compared to SURGICEL, an FDA-approved hemostatic agent, as an adjunct to hemostasis during parenchymous surgery. The study enrolled 320 adults and five children undergoing parenchymous surgery with a TBS that had moderate bleeding for which conventional surgical techniques (including suture, ligature, and cautery) were ineffective or impractical and that required an adjunct treatment to achieve hemostasis. The noninferiority margin was 0.8 for the ratio of proportions of subjects achieving hemostasis by T4.

In Study IG1102, the proportion of hemostasis by T4 (primary efficacy) was 92.8% (103/111 subjects) in the VISTASEAL treatment group and 80.5% (91/113 subjects) in the SURGICEL treatment group. The 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving VISTASEAL relative to SURGICEL was 1.152 (1.038, 1.279), indicating that VISTASEAL is both noninferior and superior to SURGICEL. The proportion of hemostasis by T4 was significantly higher in the VISTASEAL group compared to the SURGICEL group (p-value=0.010).

The primary clinical efficacy endpoint was supported by secondary efficacy endpoints including TTH, hemostasis rate by T2, T3, T5, and T7.

Study IG1103 (Soft Tissue)

Study IG1103 was also designed as a noninferiority study to evaluate the efficacy and safety of VISTASEAL compared to SURGICEL as an adjunct to hemostasis in soft tissue (muscle, fat, connective tissue) surgery. The study enrolled 309 adults and 18 children. Nine of the children received VISTASEAL. Only one of the nine received VISTASEAL in the pivotal Part II of the study.

The inferiority margin was 0.8 for the ratio of proportions of subjects achieving hemostasis by T4. The proportion of hemostasis by T4 (primary efficacy) was 82.8% (96/116 subjects) in the VISTASEAL group and 77.8% (84/108 subjects) in the SURGICEL group. The 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving VISTASEAL relative to SURGICEL was 1.064 (0.934, 1.213), indicating that VISTASEAL is noninferior to SURGICEL.

The primary clinical efficacy endpoint was supported by secondary efficacy endpoints including TTH, hemostasis rate by T2, T3, T5, and T7.

Efficacy Conclusion

The positive efficacy results from all four studies support the use of VISTASEAL as an adjunct to hemostasis for mild to moderate bleeding in adult and pediatric patients undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical.

Summary of Safety Studies IG1101, 1102, 1103

The safety evaluations for Studies IG1101, IG1102, and IG1103 were based on the pooled safety population, defined as all subjects enrolled in the studies. A total of approximately 500 subjects were treated with VISTASEAL, 320 subjects were treated with SURGICEL, and 57 subjects were treated with MC over these three pivotal studies.

The overall summary of TEAEs in all three studies is provided in Table 3.

Table 3. Summary of Treatment-Emergent Adverse Events by Treatment Group, Safety Population, All Three Studies

Variable	Pooled Safety VISTASEAL N=500 n (%)	Pooled Safety SURGICEL N=320 n (%)	MC N=57 n (%)
Subjects with any TEAE	419 (83.8)	278 (86.9)	44 (77.2)
Total number of TEAEs	1763	1263	104
Subjects with any ADR	64 (12.8)	27 (8.4)	3 (5.3)
Total number of ADRs	128	65	5
Subjects with any ADR attributable to application technique	1 (0.2)	0	0
Total number of ADRs attributable to application technique	2	0	0
Subjects with any SAE	81 (16.2)	41 (12.8)	11 (19.3)
Total number of SAEs	167	65	14

Variable	Pooled Safety VISTASEAL N=500 n (%)	Pooled Safety SURGICEL N=320 n (%)	MC N=57 n (%)
Subjects with any TEAE with outcome of death	13 (2.6)	4 (1.3)	0
Subjects with any serious ADR	9 (1.8)	0	1 (1.8)
Total number of serious ADRs	15	0	1
Subjects with any AE leading to withdrawal	0	0	0
Total number of AEs leading to withdrawal	0	0	0

Source: Table 5.3/1.2 of ISS in Module 5.3.5.3
Abbreviations: ADR, adverse drug reaction; AE, adverse event; ISS, integrated summary of safety; MC, manual compression; N, study population; n, sample size; SAE, serious adverse event

Deaths

Deaths in Studies IG1101, IG1102, and IG1103

Thirteen of 500 (2.6%) subjects in the VISTASEAL treatment group, 4/320 (1.3%) subjects from the SURGICEL treatment group, and zero subjects from the MC treatment group died from one or more TEAEs. The occurrence of deaths varied from a few days to weeks after treatment administration (see review Section 8.4.1 for more details). All SAEs with a fatal outcome in the three studies, regardless of treatment group, were considered unrelated to study treatment by the Applicant. See Section 8.4.1 for additional information regarding the deaths reported in the three studies.

Treatment-Emergency Serious Adverse Events

TESAEs (including deaths) were reported in 81/500 (16.2%) subjects in the VISTASEAL treatment group, 41/320 (12.8%) subjects in the SURGICEL treatment group, and 11/57 (19.3%) subjects in the MC treatment group.

Of the TESAEs in the VISTASEAL group (72/81 subjects), the majority were considered unrelated to study treatment by investigators in all except 9 subjects (9/81 subjects). Five subjects had SAEs that were considered unlikely related and four subjects had SAEs that were considered possibly related to the study treatment. SAEs considered unlikely related to study treatment were: postoperative wound infection, wound infection, abdominal abscess, deep vein thromboses (two subjects, including one right femoral vein and one left peroneal vein in one subject), pulmonary embolism (two subjects), postprocedural bile leak (two subjects), and liver abscess (one subject). SAEs considered possibly related to study treatment were: cellulitis, positive parvovirus B19 (B19V) test (determined not to be treatment-emergent viral infection), abdominal wound dehiscence, and peritonitis.

All SAEs in the SURGICEL and all SAEs in the MC treatment groups were considered unrelated to study treatment.

Overall, there were no substantial differences noted in SAE incidences among treatment groups, when these SAEs were reviewed within the context of known potential risk of the class of fibrin sealant products. Please see the clinical review memo from the original BLA for additional discussion regarding attribution of TESAEs. Overall,

the clinical review team assessed that the benefits of VISTASEAL application outweigh the risks.

Treatment-Emergent Adverse Events

The overall number of TEAEs was similar for the VISTASEAL group (83.8%), the SURGICEL group (86.9%), and the MC group (77.2%).

In the VISTASEAL treatment group, 64/500 (12.8%) subjects experienced an ADR, compared with 27/320 (8.4%) subjects in the SURGICEL treatment group and 3/57 (5.3%) subjects in the MC group.

TEAEs reported for at least 5% of subjects occurred with similar incidence in both groups, with procedural pain and nausea occurring most frequently. Serious TEAEs of special interest follow: Myocardial infraction occurred in 0.4% in VISTASEAL versus 0% in SURGICEL versus 1.8% in MC. Respiratory failure occurred in 1.2% in VISTASEAL versus 0.3% in SURGICEL versus 0% in MC. Vascular graft thrombosis occurred in 0.2% in VISTASEAL versus 0% in SURGICEL versus 1.8% in MC. No subject discontinued the study due to an AE in any treatment group in all three studies.

Table 4. Treatment-Emergent Adverse Events Reported for ≥5%, All Three Studies

Variable	VISTASEAL N=500 n (%)	SURGICEL Control N=320 n (%)	MC Control N=57 n (%)
Subjects with any TEAE	419 (83.8)	278 (86.9)	44 (77.2)
Total number of TEAEs	1763	1263	104
Subjects with any ADR	64 (12.8)	27 (8.4)	3 (5.3)
Total number of ADRs	128	65	5
Subjects with any ADR attributable to application technique	1 (0.2)	0	0
Total number of ADRs attributable to application technique	2	0	0
Subjects with any SAE	81 (16.2)	41 (12.8)	11 (19.3)
Total number of SAEs	167	65	14
Subjects with any TEAE with outcome of death	13 (2.6)	4 (1.3)	0
Subjects with any serious ADR	9 (1.8)	0	1 (1.8)
Total number of serious ADRs	15	0	1
Subjects with any AE leading to withdrawal	0	0	0
Total number of AEs leading to withdrawal	0	0	0

Source: 5.3/1.2 of ISS in Module 5.3.5.3
Abbreviations: ADR, adverse drug reaction; AE, adverse event; ISS, integrated summary of safety; MC, manual compression; N, study population; n, sample size; SAE, serious adverse event; TEAE, treatment-emergent adverse event

TEAEs reported for least 5% of subjects within a treatment group for all clinical studies combined were procedural pain, 209/500 (41.8%); nausea, 67/500 (13.4%); and pyrexia, 50/500 (10%). Overall, the incidences of the most frequently reported TEAEs were generally similar among the VISTASEAL, SURGICEL, and MC treatment groups.

Additionally, viral nucleic acid testing or viral serology testing did not detect any treatment-emergent viral infection in any of the three clinical studies.

Adverse Drug Reactions

Protocols for Studies IG1101, IG1102, and IG1103 defined ADR as an AE that was assessed by the investigator as definitely related, probably related, possibly related, or unlikely related. Overall, in these three studies, there were no substantial differences in the ADR incidences noted among the VISTASEAL, SURGICEL, or MC groups. For ADRs that occurred in ≥1% in the safety population of the VISTASEAL treatment group, the most common ADRs were procedural pain and nausea (Table 41).

Immunogenicity

No immunogenicity occurred with the treatment with VISTASEAL in Studies IG1101, IG1102, or IG1103. Pediatric Study IG1405 did not assess immunogenicity.

Subject Disposition

In all four clinical studies, subject disposition was consistent among treatment groups. See detailed review of individual studies for details.

Safety Conclusions

The results from all four pivotal studies showed that VISTASEAL was reasonably safe and well-tolerated as a local adjunct hemostatic agent in various surgery types in adults and children. No safety concerns were identified beyond the safety concerns of hemostatic agents in the control groups.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Overall, across the four studies, the percentages or numbers of subjects were balanced regarding sex, age, and race among treatment groups.

Pediatric Study IG1405 is the main study to support use of VISTASEAL in pediatric patients. Demographic characteristics were balanced in both the VISTASEAL and EVICEL comparator groups. Section 6.1.10 includes a table that summarizes the demographic characteristics of the study population. Subjects had a median age of 9.80 years (range: 0.0 to 17.9 years) at randomization and the ages were well-balanced in both the VISTASEAL and EVICEL treatment groups. Overall, 62.4% of the subjects were male. Subjects were primarily White (94.1%).

Across the three studies that supported the original BLA (IG1102, IG1102, IG1103) the percentages of subjects were balanced among treatment groups regarding sex, age, and race. Of 336 subjects who were randomized to VISTASEAL, 89.3% (300/336) of the total enrolled subjects were White, 8.6% (29/336) were Black, and 2.1% (7/336) were Asian. Enrollment in other race groups was too small to permit valid conclusions within these groups. Regarding sex, overall, 48.8% (164/336) were male and 51.2% (172/336) were female, maintaining an approximately equal ratio in both treatment

groups. The mean age of the subjects who were randomized to VISTASEAL was 64 years old in Study IG1101, 60 years old in Study IG1102, and 49 years old in Study IG1103.

There were 0 pediatric subjects enrolled in Study IG1101, 5 pediatric subjects (1 of whom received VISTASEAL) in IG1102, 18 pediatric subjects (9 of whom received VISTASEAL) in Study IG1103, and 186 subjects (91 of whom received VISTASEAL) in pediatric Study IG1405.

1.2 Patient Experience Data

No patient experience data were submitted with the application.

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	-
☐	Observer-reported outcome	-
☐	Clinician-reported outcome	-
☐	Performance outcome	-
☐	Patient-focused drug development meeting summary	-
☐	FDA Patient Listening Session	-
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	-
☐	Observational survey studies	-
☐	Natural history studies	-
☐	Patient preference studies	-
☐	Other: (please specify)	-
☒	**If no patient experience data were submitted by Applicant, indicate here.**	-
☐	Perspectives shared at patient stakeholder meeting	-

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-focused drug development meeting summary report	-
☐	FDA Patient Listening Session	-
☐	Other stakeholder meeting summary report	-
☐	Observational survey studies	-
☐	Other: (please specify)	-

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

VISTASEAL is a fibrin sealant intended to treat mild to moderate bleeding that arises in general surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical.

Reviewer comment: As per FDA Guidance for Industry (May 1999), manufacturers who demonstrate the safety and efficacy of their fibrin sealant preparations in a variety of clinical settings that include several types of surgery reflecting the range of hemostatic difficulties encountered in surgery may, upon FDA licensure, label and promote their products as general adjuncts to hemostasis. For original licensure of VISTASEAL in 2017, studies in vascular surgery, parenchymal surgery, and soft tissue surgery supported the general surgery indication in adults. Studies to support this pediatric efficacy supplement enrolled pediatric subjects who had only parenchymal or soft tissue bleeding sites. Due to the limited need for a fibrin sealant hemostatic adjunct in pediatric vascular surgery, pediatric studies did not enroll subjects with a vascular bleeding site. After discussion with the review teams, it is this reviewer's opinion that if the data from the pediatric PMR support safety and efficacy of VISTASEAL in parenchymal and soft tissue surgery, the general surgery indication in pediatrics is appropriate. The package insert should reflect that no studies were completed that evaluated VISTASEAL in vascular surgery in children.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Alternative methods for hemostasis when common measures such as suture, ligature, and cautery are ineffective or impractical depend on the bleeding site, the severity of bleeding, and the experience of the surgeon. Options may include repeating measures already tried, MC, porcine gelatin, bovine collagen, oxidized regenerated cellulose mesh

or powder, polysaccharide hemospheres, or sealants such as polyethylene glycol polymer or albumin with glutaraldehyde (Guzzetta et al. 2023; Nellenbach et al. 2024).

2.3 Safety and Efficacy of Pharmacologically Related Products

Pharmacologically related products include alternative fibrin sealants and fibrin sealant patches that have been found to be effective in mild and moderated surgical bleeding. Benefits generally outweigh risks that include thromboembolism, hypersensitivity reactions, air or gas embolism when spray application is too close to the tissue surface, infection from donor human plasma (e.g., viruses, Creutzfeldt-Jakob agent), and impaired wound healing.

2.4 Previous Human Experience With the Product (Including Foreign Experience)

In addition to human exposure in the clinical studies reviewed for this submission, VISTASEAL (also marketed outside the United States as VERASEAL) has been administered after approval in 11 countries: Australia, Canada, Europe, United Kingdom, United States, Switzerland, Singapore, Taiwan, India, South Korea, and Brazil. The total amount of Fibrin Sealant distributed by the manufacturer from first sales data available (August 1, 2019) to data lock point (November 30, 2022) of the May 18, 2023 report was (b) (4) vials, corresponding to (b) (4) estimated number of estimated doses.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 5. Clinical Regulatory Interactions Pertaining to This Efficacy Supplement

Date	Regulatory Activity
August 10, 2016	Pediatric Review Committee reviewed iPSP submitted to IND 14986/0.
August 11, 2016	FDA emailed Applicant recommending changes to iPSP primary endpoint, number of subjects per target bleeding site, and an earlier target study start date.
November 1, 2016	FDA issued letter indicating agreement with final agreed iPSP that the Applicant submitted to IND 14986 on October 4, 2016
November 1, 2017	FDA issued approval letter for original biologics license for treatment in adults. Approval letter includes a postmarketing requirement (PREA PMR) for pediatric Study IG1405.
November 30, 2018	Applicant submitted HF study to BLA 125640/8 as part of an efficacy supplement to approve a new applicator tip. During the current pediatric efficacy supplement, FDA assessed this HF study as adequate to fulfill the HF study that was required as part of the PREA PMR.
November 24, 2021	Applicant submitted updated Agreed iPSP with revised IG1405 protocol to include nonelective (emergency surgery) in neonates aged <28 days to increase study enrollment in this age group, as advised by FDA PeRC in response to Applicant's request for a waiver in this age group.
July 4, 2023	Applicant submitted Complete Study Report for PREA PMR study IG1405 with request for a BLA efficacy supplement to add the pediatric population to the approved indication. FDA staff were not alerted to the submission until January 29, 2024.

Date	Regulatory Activity
January 29, 2024	FDA CBER/OTP established this create date when staff were notified of the July efficacy supplement request. Due to the delay, OTP and the Applicant agreed to an 8-month review clock.
February 28, 2024	First clinical information request (IR) sent to the Applicant to request completed FDA forms 3674 and 3455 with financial disclosure information. Response received March 5, 2024
April 22, 2024	Second clinical IR sent to the Applicant to • Confirm low numbers of AEs reported at specific study sites • Clarify reasons for screen failures • Request case report forms Response received: April 29, 2024
May 6, 2024	Third clinical IR sent to Applicant to request additional information regarding observed differences in adverse events per study subjects across study sites. An informal teleconference to discuss Response received: May 9, 2024
May 7, 2024	Informal teleconference with Applicant to clarify reason for substantially different quantity of AE reporting among study sites
July 30, 2024	Efficacy supplement presented to FDA Pediatric Review Committee (PeRC)
August 27, 2024	Labeling change suggestions sent to the Applicant

Source: Original Table Created by Clinical Reviewer
Abbreviations: AE, adverse event; HF, human factors; iPSP, initial pediatric study plan; IR, information request; OTP, Office of Therapeutic Products; PeRC, Pediatric Review Committee; PMR, postmarketing requirement; PREA, Pediatric Research Equity Act

Reviewer comment: The submitted pediatric Study IG1405 differs from the agreed initial pediatric study plan (iPSP) and the PREA PMR in that a human factors (HF) study was not completed as part of pediatric Study IG1405 and in the numbers of pediatric participants per age group. The following summary includes the rationale for why both changes to the PREA PMR are acceptable.

Human Factors Study

The original BLA approval in 2017 included a PMR to study the use of VISTASEAL in pediatric subjects. During review of the original BLA the HF review team identified deficiencies regarding packaging and the Instruction for Use in the initial HF study conducted in February 2017. To address the deficiencies, the PMR specifies that the required pediatric study was to include an HF study. In April 2019 FDA approved a supplement submitted to BLA 125640, Submission Tracking Number (STN) 8 that included a change in the device applicator tip and packaging. With the change in device, the HF study that was planned for the pediatric study was no longer relevant because the device and instructions for how to use the device changed. The Applicant asked FDA if the HF study that was submitted with the 2019 supplement could fulfill the HF study that was specified in the PMR. FDA communicated to the Applicant that the change in PMR to no longer include an HF study would be determined during review of the pediatric efficacy supplement.

In 2022 the Applicant submitted a BLA supplement that addressed some changes to the product that included the thawing and the shelf life after the produce is thawed. FDA

issued a complete response letter that included a request to perform additional product testing (after the new thawing procedure and during the proposed extended shelf life after thaw) and an HF study to assess the impact of the changes. The Applicant submitted a complete response to clinical hold on May 23, 2024, during the review of this pediatric efficacy supplement.

2019 Change in Applicator Tip Packaging

Change in Applicator Tip

During pediatric Study IG1405, the VISTASEAL container and packaging was modified and communicated to study sites through protocol amendment 1 version 2.0, dated May 21, 2019.

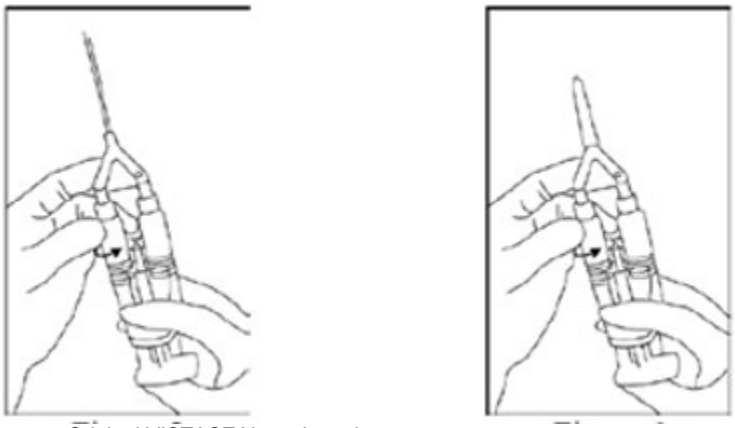
The modified VISTASEAL kit contains two separate packages; one package contains one syringe holder, and the other package contains the Dual Applicator device for both drip and spray application. The applicator tip was a Dual Applicator device intended for use in open surgical procedures, allowing both drip application and spray application without gas assistance. The drip and spray tip was a trilumen-malleable cannula ending in a threaded connector, which allowed attachment of a removable airless spray tip. The fibrinogen and thrombin travel through the cannula without making contact until they reach the tip. To drip, the spray tip was unscrewed from the threaded connector at the distal end of the device. As the plungers of the syringe holder were depressed, the fibrinogen and thrombin solutions travel through the device in separate lumens and do not mix until after they exit the threaded connector. In spray mode, the Dual Applicator mixes the fibrinogen and thrombin in the airless spray tip prior to atomization. If the expression was stopped, the airless spray tip was clogged and was to be replaced with one of the two spare airless spray tips provided.

Since November 30, 2019, the Applicant has provided the VISTASEAL kit in two separate packages; one package contains one syringe each of human fibrinogen and human thrombin sterile frozen solutions assembled in a syringe holder and another package contains the Dual Applicator device for both drip and spray application.

Approved Change in Applicator Tip

The following is a drawing of the Fibrijet applicator that was used in the studies to support original BLA and used in the pediatric study through November 30, 2019:

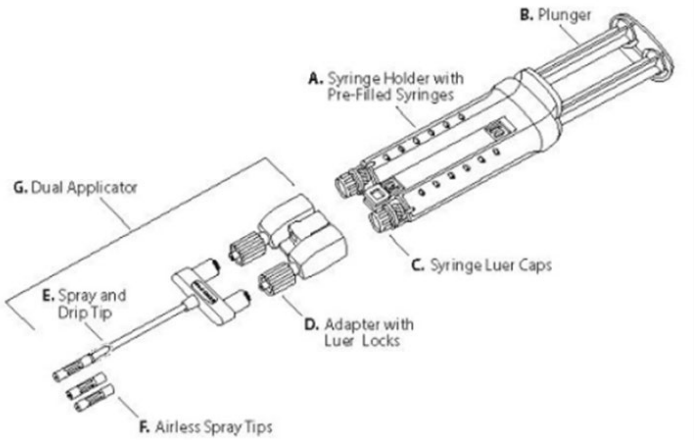
Figure 1. Drawing of Fibrijet Tip, Original BLA and Pediatric Study Through November 30, 2019



Source: Original VISTASEAL package insert

The following is a drawing of the current applicator tip that was approved in the April 2019 supplement and used in the pediatric study after November 30, 2019:

Figure 2. Drawing of Current Applicator, Approved April 2019, Used in Pediatric Study After November 30, 2019



Source: Currently approved package insert submitted to this efficacy supplement.

Reviewer comment: I agree with the FDA HF review team that the HF study that the Applicant submitted to support the change in applicator tip and packaging that was approved in April 2019 is adequate to support application to pediatric patients and to fulfill the HF study that was required as part of the PMR.

Protocol Revision With New Planned Numbers Per Age Group

The PMR specified the number of pediatric subjects per age group to be enrolled in pediatric Study IG1405. Table 6 compares the original number of subjects planned per age group to the number of subjects ultimately enrolled in the study.

Table 6. Planned vs. Actual Pediatric Subjects by Age Group

Age Category	Agreed Number of Subjects	Number of Subjects Enrolled N=186 n (%)	VISTASEAL (n=95)	EVICEL (n=91)
≤27 days	6	6 (3.2)	4 (4.2)	2 (2.2)
≤28 days to ≤23 months	16	37 (19.9)	19 (20.0)	18 (19.8)
≤2 to ≤11 years	50	67 (36.0)	34 (35.8)	33 (36.3)
≥12 to ≤17 years	100	76 (40.9)	38 (40.0)	38 (41.8)

Source: Original table assembled by reviewer from information included in this supplement.
Abbreviations: n, sample size

Reviewer comment: The changes in numbers of pediatric subjects per age group do not decrease the ability of pediatric Study IG1405 to assess the safety and efficacy of use of VISTASEAL in pediatric patients for the proposed indication. The changes are acceptable.

2.6 Other Relevant Background Information

No additional relevant background information was identified.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

STN 125640/220 is of acceptable quality and is complete in the clinical studies sections.

3.2 Compliance With Good Clinical Practices and Submission Integrity

Clinical studies in STN 125640/0 conform to Good Clinical Practice with good integrity.

Reviewer comment: Bioresearch Monitoring communicated to the clinical review team on July 18, 2024 that schedule for the planned inspection of study site 614 would be delayed due to power outages caused by a recent hurricane in Houston, Texas. The clinical team determined it was not necessary to delay the projected review timeline due to delay in receiving the inspection report.

3.3 Financial Disclosures

The financial disclosure statements for pediatric Study IG1405 were provided to BLA 125640/220 and financial disclosure statements for Studies IG1101, IG1102, and IG1103 were provided in the BLA 125640/0. Each of the statements contained a list of clinical investigators and sites: total of 20 investigators for IG1405, 50 investigators for IG1101, 46 investigators for IG1102, and 44 investigators for IG1103. For all four studies, no investigator was identified to be an Applicant employee and no investigator had disclosable financial interests/arrangements.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

No new chemistry, manufacturing, and controls (CMC) information was included in the supplement.

VISTASEAL is a frozen, sterile, two-component fibrin sealant solution obtained from human plasma pools. VISTASEAL consists of human fibrinogen (component 1) and human thrombin with calcium chloride (component 2) solutions filled in syringes and assembled on a syringe holder. VISTASEAL is being submitted as a combination product and is packaged with a spray device.

The human fibrinogen solution contains:

- Human fibrinogen: 80 mg/ml solution
- Other ingredients: sodium citrate, sodium chloride, arginine, L-isoleucine, L-glutamic acid monosodium, and water for injection.

The human thrombin solution contains:

- Human thrombin: 500 IU/ml solution
- Other ingredients: calcium chloride, human albumin, sodium chloride, glycine, and water for injection.

4.2 Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data were submitted to this sBLA. Please refer to the review of the original BLA.

4.3 Clinical Pharmacology

No new clinical pharmacology information was submitted to this sBLA. Please see clinical pharmacology review memo from the original BLA submission for additional information.

4.3.1 Mechanism of Action

VISTASEAL comprises human fibrinogen (component 1) and human thrombin with calcium chloride (component 2) frozen solutions, which, when mixed, generate a cross-

linked fibrin clot in a process that mimics the last stage of the human coagulation system. The fibrin adhesion system initiates the last phase of physiological blood coagulation. Fibrinogen is converted into fibrin monomers and fibrinopeptides by thrombin. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is activated from factor XIII by thrombin, crosslinks fibrin. Calcium ions are required for both the conversion of fibrinogen and the crosslinking of fibrin. As wound healing progresses increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated.

4.4 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the Applicant were supported by the submitted data. See statistical review of STN 125640/220.

4.5 Pharmacovigilance

Table 7 from the VISTASEAL periodic safety update report summarizes AEs reported as of June 2022:

Table 7. Adverse Events as of June 2022

System Organ Class Preferred Term	Spontaneous Sources Serious Interval	Spontaneous Sources Serious Cumulative	Spontaneous Sources Nonserious Interval	Spontaneous Sources Nonserious Cumulative	Spontaneous Sources Total Spontaneous Cumulative All	Noninterventional Postmarketing Study and Reports From Other Solicited Sources Serious Interval	Noninterventional Postmarketing Study and Reports From Other Solicited Sources Cumulative
Product issues	-	-	-	-	-	-	-
Product adhesion issue	1	1	0	0	1	0	0
Subtotal	1	1	0	0	1	0	0
Infections and infestations	-	-	-	-	-	-	-
Postprocedural infection	0	0	8	8	8	0	0
Subtotal	0	0	8	8	8	0	0
Gastrointestinal disorders	-	-	-	-	-	-	-
Fistula of small intestine	1	1	0	0	1	0	0
Large intestinal obstruction	1	1	0	0	1	0	0
Subtotal	2	2	0	0	2	0	0

System Organ Class Preferred Term	Spontaneous Sources Serious Interval	Spontaneous Sources Serious Cumulative	Spontaneous Sources Nonserious Interval	Spontaneous Sources Nonserious Cumulative	Spontaneous Sources Total Spontaneous Cumulative All	Noninterventional Postmarketing Study and Reports From Other Solicited Sources Serious Interval	Noninterventional Postmarketing Study and Reports From Other Solicited Sources Cumulative
Reproductive system and breast disorders	-	-	-	-	-	-	-
Vaginal discharge	0	0	4	4	4	0	0
Vaginal fistula	0	0	1	1	1	0	0
Subtotal	0	0	5	5	5	0	0

Source: VISTASEAL Periodic Safety Update Report June 2022

FDA Adverse Event Reporting System included two postmarketing reports of intestinal adhesions occurred 9 days and 4 to 5 weeks after VISTASEAL application. The cases are summarized below:

- An 80-year-old subject underwent laparoscopic subtotal gastrectomy that included VISTASEAL application along the staple line. Nine days later the subject presented with large bowel obstruction and blown duodenal stump secondary to sigmoid colon adherent to gastric remnant.
- A 54-year-old female received VISTASEAL during sleeve gastrectomy and developed hiatal hernia 4 to 5 weeks post-op. During the subject's repair procedure, thick adhesions were found where VISTASEAL was sprayed, including at the esophageal junction.

Reviewer comment: Tissue adhesion is a theoretical risk of fibrin sealants. Because tissue adhesion is known to occur after surgery, accurate attribution to surgery versus VISTASEAL is challenging. Although no AEs of tissue adhesion in the pivotal studies were attributed to VISTASEAL, it is possible that the above postmarketing reports of adhesions and adhesion-related AEs from clinical studies were due to VISTASEAL. In pediatric Study IG1405, one subject in the VISTASEAL group and one subject in the EVICEL group experienced intussusception, and one subject in the EVICEL group experienced paralytic ileus. The investigators assessed these events as unrelated to the fibrin sealants but did not determine the underlying cause of the events. It is possible that these events were caused by adhesions that developed due to the use of VISTASEAL or EVICEL. It is also possible that the events occurred due to underlying disease in these subjects who are at high risk of adhesions because they underwent surgery. Available evidence is not sufficient to support either fibrin sealant as the cause of these AEs. I agree with the pharmacovigilance team that a pharmacovigilance plan designed to detect adhesion-related AEs after VISTASEAL administration is appropriate. Please refer to the pharmacovigilance review memo for additional information.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

Pediatric Study IG1405 was the main study reviewed for approval of this pediatric efficacy supplement. The clinical reviewer:

- Reviewed documents submitted to BLA 125640/220 (listed in Section 5.2 of this memo),
- Received dataset format validation from the Clinical Data Interchange Standards Consortium validation team,
- Requested additional information from the Applicant regarding screen failures,
- Verified analyses included in the study report for IG1405 using data sets,
- With a clinical analyst combined similar AE terms, then used the combined terms to reanalyze relative frequency of AEs,

- Compared AE nature and frequency across pediatric age groups,
- Reviewed relevant Case Report Forms and Patient Narratives,
- Compared AEs that occurred during use of the original Fibrijet applicator tip to AEs that occurred during use of the new Dual Applicator tip,
- Sent two information requests (IRs) and held an informal teleconference with the Applicant to request additional information regarding differences in AE reporting across study sites,
- Requested consultative advice from the following FDA review teams from other centers:
  - Center for Devices and Radiological Health
  - Office of Device Evaluation Office of Health Technology Division of Surgical and Infection Control Devices.
  - Office of Product Evaluation and Quality/Office of Health Technology/Division of Health Technology (HF Study review team)
- Reviewed documents previously submitted to BLA 125640, including HF, use-related risk analyses, and relevant correspondence to assess whether pediatric Study IG1405 fulfills the PREA PMR, especially regarding the changes in numbers of pediatric subjects per age group and the omission of a HF evaluation as part of the study,
- With the clinical analyst combined safety data from all clinical studies that included children (IG1102, IG1103, and IG1104) to assess safety in pediatric subjects compared to adult subjects, and
- Reviewed proposed changes to the labeling and communicated recommended changes to the Applicant through interactive review.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Submitted to BLA 125640/220:

- Cover Letter
- Clinical Overview
- Summary of Clinical Efficacy
- Summary of Clinical Safety
- Complete Study Report and data sets for pediatric Study IG1405
- Draft package insert and revisions
- Protocol and Protocol Amendments for pediatric Study IG1405 – Appendix 16.1.1
- Case report forms for pediatric Study IG1405
- Financial disclosures

Submitted to Earlier Sequences and/or IND 14986:

- Original BLA approval letter dated November 1, 2017

- Agreed iPSP submitted to IND 14986
- Study reports and datasets for Studies IG1101, IG1102, and IG1103 (BLA 125640/0
- Integrated Summary of Safety for Studies IG1101, IG1102, and IG1103, dated September 16, 2016
- BLA 125640/8 Supplement Approval Letter dated April 12, 2019 (regarding modification of the co-packaged application device (VISTASEAL Dual Applicator)
- Various correspondence regarding Applicant's request for waiver for the age group of ≤27 days and protocol revision to include emergency surgeries in this neonatal age group
- Various correspondence between FDA and the Applicant regarding removing the HF study requirement from the PREA PMR including:
  - FDA email dated May 13, 2019 (regarding need for formal PREA PMR change request to remove requirement for HF study)
  - PREA PMR Change Request - BL 125640: Applicant response to FDA correspondence received May 13, 2019
  - Protocol version 3 dated June 4, 2019, proposing to remove the HF study requirement
  - PREA PMR change request dated July 23, 2019
  - FDA email dated Friday, May 22, 2020 in response to May 13, 2019 PREA PMR change request IR response, with notification that "in a forthcoming efficacy supplement application for a pediatric indication in order to fulfill your outstanding PREA PMR, you should include adequate safety and efficacy data, along with sensitivity analyses, for any applicator being used with the Fibrin Sealant (Human) final drug product in order to support the indication. An FDA Pediatric Review Committee review will be scheduled during that review cycle."
  - Risk Analysis REGD-0019886, version 8 dated September 5, 2022
  - 100997851 VISTASEAL™ Fibrin Sealant (Human) - HF Supplemental Usability Study Completion Report dated September 19, 2022
- Periodic Safety Update Report, covering June 9, 2020 – June 8, 2023 (BLA125640/214)

Other

- Review memo from original BLA 125640/0, Author Agnes Lim, M.D.
- Literature

5.3 Table of Clinical Pivotal Studies to Support the Proposed Indication

Table 8. Clinical Pivotal Studies Supporting the Proposed Indication

Study No.	Surgery Type	Active Control	Hypothesis Testing	Number of Adults Enrolled	Number of Children Enrolled	Number of Children Who Received VISTASEAL
IG1405	Parenchymous (hepatic) and soft tissue	EVICEL	Noninferiority	0	186	91
IG1101	Vascular	Manual compression	Superiority	225	0	0
IG1102	Parenchymous (hepatic)	SURGICEL	Noninferiority	320	5	0
IG1103	Soft tissue	SURGICEL	Noninferiority	309	18	1

Source: Original table by clinical reviewer, adapted from Clinical Overview Table 1,page 11 of 68.

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

No Advisory Committee Meeting occurred for this efficacy supplement.

5.4.2 External Consults/Collaborations

There were no external consults.

5.5 Literature Reviewed (if applicable)

2014, Sprayable fibrin sealants (Evicel, Tisseel and Artiss): updated guidance, accessed August 15, 2024, https://www.gov.uk/drug-safety-update/sprayable-fibrin-sealants-evicel-tisseel-and-artiss-updated-guidance.

Andrade-Barazarte, H, Z Chen, C Feng, VM Srinivasan, CG Furey, MT Lawton, and J Hernesniemi, 2021, Case report: Internal carotid artery thrombosis: A rare complication after fibrin glue injection for cavernous sinus hemostasis, Frontiers in Surgery, 8:730408.

Guzzetta, NA, D Faraoni, and CD Josephson, 2023, Hemostasis Management of the Pediatric Surgical Patient: Elsevier.

Lewis, KM, Q Li, DS Jones, JD Corrales, H Du, PE Spiess, EL Menzo, and A DeAnda Jr, 2017, Development and validation of an intraoperative bleeding severity scale for use in clinical studies of hemostatic agents, Surgery, 161(3):771-781.

Guidance for industry *Efficacy Studies to Support Marketing of Fibrin Sealant Products Manufactured for Commercial Use* (May 1999)

Moro, PL and DN Reddy, 2024, Echinococcosis: Clinical manifestations and diagnosis, accessed August 15, 2024, 2024, https://medilib.ir/uptodate/show/5669.

Nellenbach, K, MM John, S Shashidharan, and AC Brown, 2024, Biomaterials and other adjuncts for pediatric hemostasis, Hemostasis Management of the Pediatric Surgical Patient: Elsevier, 289-303.

Orihara, M, T Takazawa, T Horiuchi, S Sakamoto, M Uchiyama, and S Saito, 2021, Intraoperative anaphylaxis due to aprotinin after local application of fibrin sealant diagnosed by skin tests and basophil activation tests: a case report, JA Clinical Reports, 7:1-5.

Saffarzadeh, M, A Mulpuri, and JS Arneja, 2021, Recalcitrant anaphylaxis associated with fibrin sealant: treatment with “TISSEEL-ectomy”, Plastic and Reconstructive Surgery–Global Open, 9(1):e3382.

Schievink, W, S Georganos, M Maya, F Moser, and M Bladyka, 2008, Anaphylactic reactions to fibrin sealant injection for spontaneous spinal CSF leaks, Neurology, 70(11):885-887.

Singh, S, SK Dube, BR Jena, and MP Pandia, 2018, Pulmonary Embolism following Fibrin Glue Application. Can It Be?, Journal of Neuroanaesthesiology and Critical Care, 5(02):125-126.

Tonner, P and J Scholz, 1994, Possible lung embolism following embolization of a hemangioma with fibrin glue, Der Anaesthesist, 43(9):614-617.

6. Discussion of Individual Studies/Clinical Studies

Four Phase 3 multicenter, prospective, randomized, subject-blind active-controlled clinical studies were conducted to evaluate the safety and efficacy of VISTASEAL when applied as an adjunct to hemostasis when control of mild to moderate bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. Each study enrolled subjects with a specific TBS, including vascular, parenchymous (liver), or soft tissue, as listed in Table 9.

Table 9. Summary of Phase 3 Randomized, Controlled Studies

Study Number	Study ID	Surgery Type	Comparator	Number of Adult Subjects	Number of Pediatric Subjects
1	IG1405	Parenchymous and soft tissue	EVICEL (fibrin sealant, human)	0	186
2	IG1101	Vascular	Manual Compression	225	0
3	IG1102	Parenchymous (hepatic)	SURGICEL	320	5
4	IG1103	Soft tissue	SURGICEL	309	18

Source: sBLA clinical reviewer, adapted from sBLA submission.

6.1 Study #1 IG1405

6.1.1 Objectives

The objectives of this study were to evaluate the efficacy and safety of VISTASEAL as an adjunct to achieve hemostasis during surgery in pediatric subjects.

Primary Efficacy Objective

- To evaluate VISTASEAL as noninferior to EVICEL by proportion of subjects achieving hemostasis at the TBS by 4 minutes (T4) from the start of treatment application (T_{Start}) with no occurrence of rebleeding until the completion of the surgical closure by layers of the exposed surgical field containing the TBS ($T_{Closure}$).

Secondary Efficacy Objectives

- To determine the cumulative proportion of subjects achieving hemostasis at the TBS by the defined observation time points of 7 minutes (T7) and 10 minutes (T10) from T_{Start}
- To determine prevalence of treatment failures

Exploratory Efficacy Objectives

- To determine the proportion of subjects achieving at least one point decrease in bleeding intensity according to the 5-point validated bleeding severity scale by the defined observation time points of T4, T7, and T10
- To determine the mean change from baseline in bleeding intensity according to the 5-point validated bleeding severity scale at the defined observation time points of T4, T7, and T10

Safety Objective

- To evaluate the safety and tolerability of VISTASEAL in pediatric subjects undergoing surgery

6.1.2 Design Overview

This was a prospective, randomized, active-controlled, single-blind, parallel group clinical study to evaluate the safety and efficacy of VISTASEAL as an adjunct to hemostasis during surgery in pediatric subjects.

Pediatric subjects (<18 years of age) requiring an elective (nonemergent), open (non-laparoscopic), pelvic, abdominal, or thoracic (noncardiac) surgical procedure, wherein a TBS was identified, and a topical hemostatic agent is indicated, were eligible to participate in the clinical study.

Preterm (up to gestational age <37 weeks) and term newborn infants (0 to 27 days) requiring either an elective (nonemergent) or an emergency, open (non-laparoscopic) pelvic, abdominal, or thoracic (noncardiac) surgical procedure wherein a TBS was identified, and a topical hemostatic agent was indicated, were eligible to participate in the clinical study.

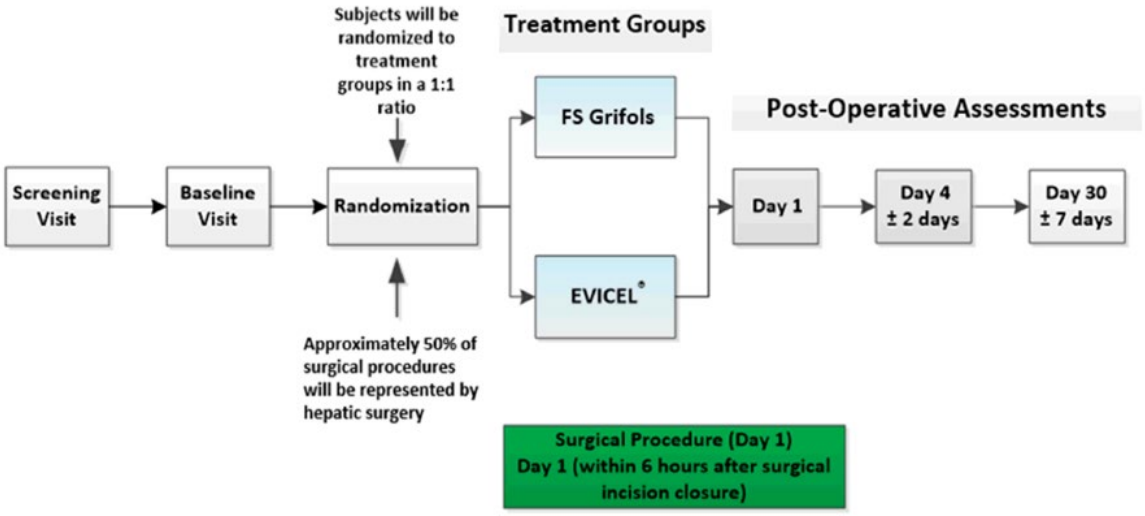
The study treatments were applied on the cut parenchymous surface of a solid organ (i.e., liver) and in soft tissue (i.e., fat, muscle, or connective tissue). Emergency surgery was included in the last phases of the study to increase the chance for enrolling subjects in the newborn age subgroup, by allowing enrollment of subjects undergoing emergency (nonelective) surgeries in this specific age subgroup only.

A specific bleeding site was defined as the TBS when the investigator (the surgeon) determined that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) was ineffective or impractical and required an adjunct treatment to achieve hemostasis.

When the TBS was identified, the investigator recorded the precise anatomical location of the TBS, rated the intensity of the bleeding at the TBS (Grade 1 to 4 according to the 5-point validated bleeding severity scale), and the size of the approximate bleeding surface, (small, medium, and large). For soft tissue surgery the investigator also recorded the type of soft tissue (i.e., fat, muscle, or connective tissue). In this clinical study, only subjects with a TBS with bleeding of Grade 1 (mild) or Grade 2 (moderate) intensity were enrolled.

Subjects were randomly allocated in a 1:1 ratio into one of two treatment groups: VISTASEAL or EVICEL. The first 24 subjects enrolled in the study were adolescents (range: 12 to 17 years). Enrollment was monitored by surgery type to ensure approximately 50% of the surgical procedures were parenchymous.

Figure 3. Study Schema, IG1405



Source: CSR IG1405 in Module 5.3.5.1

6.1.3 Population

One hundred eighty-six pediatric subjects (95 subjects in the VISTASEAL treatment group and 91 subjects in the EVICEL treatment group) were randomized. Enrollment by age group is depicted in Table 10.

Table 10. Enrollment by Age Group, IG1405

Age Category	# Subjects N =186 n (%)	VISTASEAL n=95	EVICEL n=91
≤27 days	6 (3.2)	4 (4.2)	2 (2.2)
≤28 days to ≤23 months	37 (19.9)	19 (20.0)	18 (19.8)
≤2 years to ≤11 years	67 (36.0)	34 (35.8)	33 (36.3)
≤12 to ≤17 years	76 (40.9)	38 (40.0)	38 (41.8)

Source: Reviewer table based on information in the Complete Study Report from pediatric study IG1405
Abbreviations: N, study population; n, sample size

Reviewer comment: In the agreed iPSP, the Applicant planned the following number of subjects per age group:

- *Adolescents (12 to <18 years): 100*
- *Children (2 to 11 years): 50*
- *Infants and toddlers (28 days to 23 months): 16*
- *Preterm (up to gestational age less of 37 weeks) and term newborn infants (0 to 27 days): 6*

In 2019 the Applicant submitted a protocol amendment to allow flexibility in the number of subjects per age group. After interactive review of the submission, FDA did not bring the changes to the Pediatric Review Committee for approval but informed the Applicant that the acceptability of the amended plan will be reviewed at the time of submission of this efficacy supplement. The numbers of subjects in the younger age groups are equal

to or greater than the number of subjects planned for that age group. Only the adolescent age group enrolled fewer than the planned number of subjects. Adolescents are more like adults than younger children; three other Phase 3 randomized controlled studies evaluate VISTASEAL in adults. Therefore, it is this reviewer's opinion that the modification of the numbers of subjects per age group does not significantly impact the acceptability of the safety and efficacy database for each age group.

Of the 186 subjects who were randomized (intent-to-treat [ITT] group), 178 subjects received VISTASEAL or EVICEL (mITT group). Eight subjects who were randomized did not have an intraoperative bleeding site that fulfilled intraoperative application criteria and thus did not receive VISTASEAL or EVICEL. Subjects who did not receive product were evenly distributed among treatment group for sex, age, study site, and country as shown in Table 11.

Table 11. Demographics of Subjects Who Were Randomized Preoperatively but Did Not Receive Either Study Treatment, IG1405

SUBJID	Age (Years)	Sex	Race	Arm	Country
(b) (6)	13.9	M	White	VISTASEAL	SRB
	14.6	F	White	EVICEL	SRB
	4.3	F	White	VISTASEAL	HUN
	2.6	F	White	EVICEL	GBR
	4.8	M	White	VISTASEAL	GBR
	16.8	M	Black or African American	VISTASEAL	USA
	15.1	F	White	EVICEL	USA
	3.3	M	White	EVICEL	USA

Source: Clinical reviewer generated table based on information included in the Complete Study Report for pediatric Study IG1405
Abbreviations: F, female; GBR, Great Britain; HUN, Hungary; M, male; SRB, Serbia; USA, United States of America

Inclusion Criteria

For inclusion in the study, subjects were required to meet all the following criteria:

Preoperative

1. Less than 18 years of age.
2. Required an elective (nonemergent), open (non-laparoscopic), pelvic, abdominal, or thoracic (noncardiac) surgical procedure. Or was a preterm (up to gestational age <37 weeks) or term newborn infant (0 to 27 days) requiring either an elective (nonemergent) or an emergency, open (non-laparoscopic) pelvic, abdominal, or thoracic (noncardiac) surgical procedure.
3. Subject and/or subject's legal guardian was willing to give permission for the subject to participate in the clinical study and provide written informed assent for the subject. In addition, consent was obtained from pediatric subjects who possessed the intellectual and emotional ability to comprehend the concepts involved in the clinical study.

Intraoperative

4. Presence of an appropriate parenchymous or soft tissue TBS (as defined in inclusion criterion 5) identified intraoperatively by the investigator (the surgeon).
5. TBS had Grade 1 (mild) or Grade 2 (moderate) bleeding according to the investigator's (the surgeon's) judgment. The intensity of the bleeding at the TBS was rated by the investigator using a 5-point validated bleeding severity scale (Table 14).

Exclusion Criteria

A subject with any of the following exclusion criteria was NOT eligible for participation in the study:

Preoperative

1. Subjects admitted for trauma surgery.
2. Subjects unwilling to receive blood products.
3. Subjects with known history of severe (e.g., anaphylactic) reaction to blood products.
4. Subjects with known history of intolerance to any of the components of the investigational product (IP).
5. Female subjects who were pregnant, breastfeeding or, if of child-bearing potential (i.e., adolescent), unwilling to practice a highly effective method of contraception.
6. Subjects previously enrolled in clinical studies with VISTASEAL.
7. Subjects concurrently participating, or during the study had planned to participate, in any other investigational device or medicinal product study.

Intraoperative

1. An appropriate parenchymous or soft tissue TBS (as defined in exclusion criteria 9 and 10) could not be identified intraoperatively by the investigator (the surgeon).
2. The TBS had Grade 3 (severe) bleeding according to the investigator's (the surgeon's) judgment that could not be controlled with conventional surgical techniques to Grade 1 or Grade 2 bleeding. The intensity of the bleeding at the TBS was rated by the investigator using the 5-point validated bleeding severity scale (Table 14).
3. The TBS was in an actively infected surgical field.
4. Occurrence of major intraoperative complications that required resuscitation or deviation from the planned surgical procedure.
5. Application of any topical hemostatic agent on the resection surface of parenchyma or soft tissue prior to application of the IP.

6.1.4 Study Treatments or Agents Mandated by the Protocol

VISTASEAL

Subjects randomized to receive VISTASEAL were administered the fibrin sealant intraoperatively. An initial volume of fibrin sealant was applied to the TBS in an amount sufficient to entirely cover the area with a thin, even layer by dripping or spraying (depending on tissue type) onto the TBS surface according to the investigator's judgement. If the hemostatic effect was considered incomplete, additional amounts of fibrin sealant could be applied at the TBS up to the maximum allowed volume 12 mL for subjects >2 years of age and 6 mL for subjects <2 years of age.

EVICEL

Subjects randomized to receive EVICEL were administered the fibrin sealant intraoperatively. An initial volume of fibrin sealant was applied to the TBS in an amount sufficient to entirely cover the area with a thin, even layer by dripping or spraying (depending on tissue type) onto the TBS surface according to the investigator's judgement. If the hemostatic effect was considered incomplete, additional amounts of fibrin sealant could be applied at the TBS up to the maximum allowed volume 12 mL for subjects >2 years of age and 6 mL for subjects <2 years of age.

6.1.5 Directions for Use

VISTASEAL solution is applied topically via drip or spray application.

Apply VISTASEAL fibrin sealant (human) using the syringe holder, plunger, and Dual Applicator provided with the product. When using the provided Dual Applicator, follow the connection instructions in the package insert section for Preparation.

Before administration of VISTASEAL fibrin sealant (human):

- To prevent tissue adhesion at undesired sites, protect (cover) parts of the body outside the intended application area.
- Use standard techniques (e.g., intermittent application of compresses, swabs, use of suction devices) to dry the surface area of the TBS.

Application by Spraying

1. Grasp and bend the Dual Applicator to the desired position. Tip will retain its shape.
2. Position the Airless Spray Tip at least 2 cm away from the target tissue. Apply firm even pressure to the plunger to spray the fibrin sealant. Increase distance accordingly to achieve desired coverage of the target area.
3. If expression is stopped for any reason, change the Airless Spray Tip. To change the Airless Spray Tip, remove the device from the patient and unscrew the used Airless Spray Tip. See Figure 7. Place the used Airless Spray Tip away from the spare Airless Spray Tips. Wipe the end of the applicator using dry or moist sterile surgical

gauze. Then, connect a new Airless Spray Tip provided in the package and ensure it is firmly connected before use.

- NOTE: Red indicator will not be visible if Airless Spray Tip is properly connected. See Figure 8.
- NOTE: Do not continue pushing the plunger in an attempt to clear the fibrin clot within the Airless Spray Tip; otherwise the applicator may become unusable.
- NOTE: Do not trim the Dual Applicator to avoid exposing internal wire.

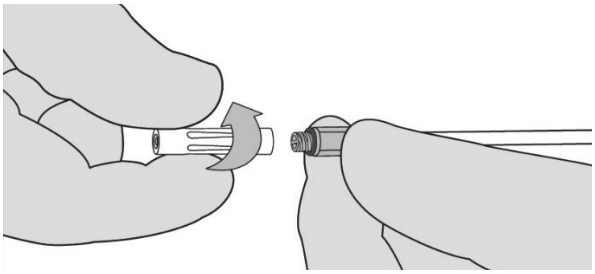


Figure 7

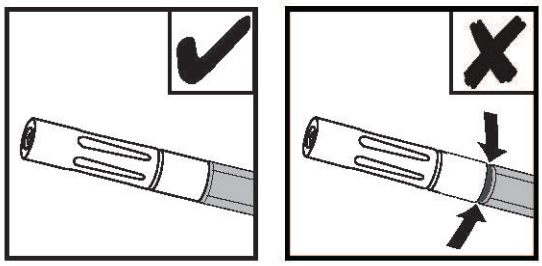


Figure 8

Application by Dripping

1. Remove the Airless Spray Tip portion of the spray and drip tip by unscrewing the Airless Spray Tip. See Figure 7.
2. Grasp and bend the drip tip to the desired position. Tip will retain its shape.
3. During dripping, keep the end of the drip tip as close to the tissue surface as possible without touching the tissue during application.
4. Apply individual drops to the surface area to be treated. To prevent uncontrolled clotting, allow the drops to separate from each other and from the end of the drip tip.

NOTE: Do not reconnect a used drip tip after it has been removed from the adapter; otherwise a clot may form inside the drip tip and the applicator may become unusable.

Application Precautions

- Apply VISTASEAL as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

- Only spray VISTASEAL if it is possible to accurately judge the distance from the spray tip to the tissue surface.

6.1.6 Sites and Centers

Table 12. Sites and Investigators, Pediatric Study IG1405

Site Number/Country	Investigators	Site Address and Telephone Number
102/Bulgaria	Krasimira Kalinova	2, General Stoletov, Str., 6000 Stara Zagora, Bulgaria
103/Bulgaria	Borislav Ninov	8A, Georgi Kochev, Str., 5800 Pleven, Bulgaria
104/Bulgaria	Simeon Simeonov	2, Nezavisimost Str., 7002 Ruse, Bulgaria
105/Bulgaria	Krasimir Kamenov	92, Aleksandar Stamboliiski Bul., 3400 Montana, Bulgaria
153/Romania	Laura Balanescu	Bd. Iancu de Hunedoara Nr. 30-32, Sector 1, 010623 Bucuresti, Romania
200/Serbia	PI#1 Zoran Radojicic PI#2Aleksandar Sretenovic	Tiršova 10, Beograd 11000, Serbia
201/Serbia	Djordje Gajdobranski	Hajduk Veljkova 10, Novi Sad 21000, Serbia
202/Serbia	Andjelka Slavkovic	Bulevar Dr Zorana Đinđića 48, Niš 18000, Serbia
203/Serbia	Maja Milickovic	Radoja Dakića 6-8, Beograd, Serbia
251/Hungary	Laszlo Sasi-Szabo	Nagyerdei krt. 98., 4032 Debrecen, Hungary
254/Hungary	Peter Vajda	József Attila u. 7., 7623 Pécs, Hungary
255/Hungary	Zoltan Jenovari	Tűzoltó u. 7-9., 1094 Budapest. Hungary
300/France	Sabine Irtan	Service de Chirurgie Pédiatrique Viscérale et Néonatale, 26, avenue du Dr Arnold Netter. Paris. France
550/United Kingdom	Khalid Sharif	Birmingham Children's Hospital, Birmingham, West Midlands, United Kingdom, B4 6NH
602/United States	PI#1 Ankush Gosain PI#2 Max Langham	Le Bonheur Children's Hospital, Faculty Office Building, 49 N Dunlap St, 2nd Floor, Memphis, Tennessee, United States
604/United States	Tomoaki Kato	622 W 168th St #PH1291 New York, New York. United States
610/United States	Dev Desai	1935 Medical District Dr Dallas, Texas, United States
614/United States	Isidoro Wiener	Memorial Hermann Memorial City, 921 Gessner Road, Houston, Texas, United States

Source: Clinical study report for pediatric Study IG1405, Section 16.1.4

6.1.7 Surveillance/Monitoring

The phases of this study included (see Table 13):

- Screening Visit (within 21 days prior to surgical procedure): Eligibility criteria were reviewed and required screening assessments and procedure were performed.
- Baseline Assessment Visit (within 24 hours prior to surgical procedure): Any new events, changes in the medical and surgical history, and medications since the Screening Visit were recorded. Required baseline assessments and procedures were performed.

- Surgical Procedure Day: Required assessments and procedures were performed prior to surgery, during the surgery, and during the observational period following completion of the surgery.
- Postoperative Visits (Day 4 and Day 30): Required assessments and procedures to assess postsurgical outcomes were performed.

The Schedule of Study Procedures and Events is provided in Table 13. The Validated Bleeding Severity Scale is provided in Table 14.

Table 13. Schedule of Study Procedures and Events

Procedures and Tests	Screening Visit[1] Visit 1 Day -21 to -1	Baseline Visit[1] Visit 2 Day 0	Day of Surgery Visit 3 Day 1 Preoperative	Day of Surgery Visit 3 Day 1 Observational Period	Day of Surgery Visit 3 Day 1 Intraoperative	Day of Surgery Visit 3 Day 1 Postoperative	Postoperative Visits Visit 4 Day 4±2	Postoperative Visits Visit 5 Final Study Visit Day 30±7
Informed consent	X	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	X	-	-	-	-	-	-
Medical/surgical history	X	X	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-
Bleeding history	X	-	-	-	-	-	-	-
Topical hemostat history	X	-	-	-	-	-	-	-
Height and weight	-	X	-	-	-	-	-	-
Physical examination	-	X	-	-	-	-	X	X
Vital signs	-	X[2]	X	X[3]	X[4]	-	X[2]	-
Pregnancy test[5]	-	X	-	-	-	-	-	-
Randomization	-	X	-	-	-	-	-	-
TBS identification	-	-	-	-	X	-	-	-
Rate bleeding at TBS[6]	-	-	-	-	X	-	-	-
Rate size of TBS	-	-	-	-	X	-	-	-
Record anatomical location of TBS	-	-	-	-	X	-	-	-
Record type of TBS[7]	-	-	-	-	X	-	-	-
Intraoperative inclusion/exclusion criteria	-	-	-	-	X	-	-	-
IP preparation	-		X	-	-	-	-	-
VISTASEAL or EVICEL application	-	-	-	-	X	-	-	-
Record T_{Start}	-				X	-	-	-
Hemostatic assessment[8]	-	-	-	X	-	-	-	-
Record $T_{Closure}$	-	-	-	-	X	-	-	-

Procedures and Tests	Screening Visit[1] Visit 1 Day -21 to -1	Baseline Visit[1] Visit 2 Day 0	Day of Surgery Visit 3 Day 1 Preoperative	Day of Surgery Visit 3 Day 1 Observational Period	Day of Surgery Visit 3 Day 1 Intraoperative	Day of Surgery Visit 3 Day 1 Postoperative	Postoperative Visits Visit 4 Day 4±2	Postoperative Visits Visit 5 Final Study Visit Day 30±7
Record $T_{Completion}$	-	-	-	-	X	-	-	-
Coagulation[9]	-	X	-	-	-	-	X	-
Hematology[8]	-	X	-	-	-	-	X	-
Clinical chemistry[10]	-	X	-	-	-	-	X	-
Prior/concomitant medications[11]	X	X	X	-	X	X	X	X
Adverse events	-	X	X	X	X	X	X	X

Source: Final Study report

[1] Procedures scheduled at the Screening Visit could be done during the Baseline Assessments Visit (i.e., within 24 hours prior to the surgical procedure). Assessments required during both visits (Screening and Baseline) were performed.

[2] Vital signs included heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, and body temperature.

c Vital signs included heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, and body temperature immediately prior to skin incision to expose the surgery field and at 5 minutes after T_{Start}.

[3] Vital signs included heart rate, respiratory rate, systolic blood pressure, and diastolic blood pressure recorded at 30 minutes after T_{Start}, every 30 minutes until $T_{Closure}$, and at $T_{Completion}$.

[4] Human chorionic gonadotropin-based blood or urine assay for subjects of childbearing potential was performed locally at the investigative site within 24 hours prior to the surgical procedure. See Section 9.3.2 in the final study report.

[5] 5-point validated bleeding severity scale: Grade 0 (No bleeding), Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (severe), or Grade 4 (life-threatening). Only subjects with Grade 1 (mild) or Grade 2 (moderate) bleeding were eligible for participation. Any subject with Grade 3 (severe) bleeding that could not be controlled with standard conventional surgical techniques (e.g., cautery, sutures, clips, or ligation) to Grade 1 or 2 or subjects with Grade 4 (life-threatening) bleeding were withdrawn from the study. See Table 14.

[6] Type of soft tissue TBS (i.e., fat, muscle, or connective tissue).

[7] Hemostatic assessment of the TBS at 4, 7, and 10 minutes following T_{Start}.

[8] Hematology assessments included hemoglobin, hematocrit, platelets, red blood cell, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration , mean corpuscular volume, whole blood cell, and differential.

[9] Coagulation assessments included prothrombin time and activated partial thromboplastin time

[10] Clinical chemistry assessments included creatinine, blood urea nitrogen, tuberculosis, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, glucose, sodium, potassium, chloride, and calcium

[11] Prior medications for the last 3 months and concomitant medication during study participation

Abbreviations: IP, investigational product; TBS, target bleeding site; $T_{Closure}$, time of completion of the surgical closure by layers of the exposed surgical field containing the TBS; $T_{Completion}$, time of completion of surgical incision closure – when the last skin closure stitch is put in – of the last exposed file, regardless of if it was the field containing the TBS; T_{Start}, time of the start of initial investigational medicinal product (VISTASEAL or EVICEL) application

Table 14. Validated Bleeding Severity Scale, Pediatric Study IG1405

Grade	Visual Presentation	Anatomic Appearance	Qualitative Description	Visually Estimated Rate of Blood Loss (mL/min)
0	No bleeding	No bleeding	No bleeding	≤1.0
1	Ooze or intermittent flow	Capillary-like bleeding	Mild	>1.0-5.0
2	Continuous flow	Venule and arteriolar-like bleeding	Moderate	>5.0-10.0
3	Controllable spurting and/or overwhelming flow	Noncentral venous- and arterial-like bleeding	Severe	>10.0-50.0
4	Unidentified or inaccessible spurting or gush	Central arterial- or venous-like bleeding	Life threatening[1]	>50.0

Source: Final clinical study report (Lewis et al. 2017)
[1] Systemic resuscitation is required (e.g., volume expanders, vasopressors, blood products, etc.).

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint in this clinical study is the proportion of subjects achieving hemostasis at the TBS by T4, with no occurrence of rebleeding until the completion of the surgical closure by layers of the exposed surgical field containing the TBS ($T_{Closure}$).

Hemostasis is defined as Grade 0 bleeding at the TBS according to the investigator's (the surgeon's) judgment, so that the surgical closure of the exposed field could be started. Rebleeding is defined as Grade ≥1 bleeding from the TBS requiring further hemostatic intervention.

Secondary efficacy endpoints include the following:

- Cumulative proportion of subjects achieving hemostasis at the TBS by the defined observation time points of T7 and T10
- Prevalence of treatment failures, defined as:
  - Persistent bleeding at the TBS beyond T4
  - Grade 3 or 4 breakthrough bleeding at the TBS that jeopardizes subject safety, according to the investigator's (the surgeon's) judgment, at any moment during the 10-minute observation period and until $T_{Closure}$
  - Use of alternative topical hemostatic agents or maneuvers (other than the study treatment) at the TBS during the 10-minute observation period until $T_{Closure}$ or use of study treatment at the TBS beyond the assessment of the primary efficacy endpoint at T4 until $T_{Closure}$
  - Rebleeding (Grade ≥1) at the TBS after the assessment of the primary efficacy endpoint at T4 until $T_{Closure}$

6.1.9 Statistical Considerations & Statistical Analysis Plan

Four analysis populations were defined for efficacy and safety analyses as follows:

1. The ITT population includes all subjects who were randomized, regardless of meeting intraoperative enrollment criteria and regardless of whether VISTASEAL or the comparator EVICEL were administered to the subject.
2. The mITT population includes all subjects in the ITT population who meet the intraoperative enrollment criteria, and thus treated with any amount of VISTASEAL or EVICEL. Note that the mITT population is equal to the safety population.
3. The Per Protocol (PP) population includes all subjects in the mITT population who did not have any major protocol deviations which could impact the primary efficacy endpoint.
4. The safety population includes all subjects who receive any amount of VISTASEAL or EVICEL and is therefore equal to the mITT population.

Primary Efficacy Analyses

As prespecified in the protocol, the primary efficacy analyses were performed using the mITT population (all subjects who received any amount of VISTASEAL or EVICEL).

The primary efficacy endpoint of hemostasis at TBS by T4 was analyzed using the Cochran-Mantel-Haenszel test stratified by type of surgery (i.e., parenchymous versus soft tissue surgery).The ratio of the proportion of subjects meeting the primary efficacy endpoint in the two treatment groups (VISTASEAL relative to EVICEL) and its 2-sided asymptotic 95% CI was be provided. The noninferiority was to have been demonstrated if the lower limit of the 95% CI exceeds 0.8. After the noninferiority of VISTASEAL to EVICEL is established, its superiority may be additionally claimed if the 95% CI for the ratio is entirely above one.

Secondary Efficacy Analyses

Secondary efficacy endpoints were analyzed by similar methods at other individual assessment time points (i.e., T7 and T10 minutes).

Exploratory Efficacy Analyses

Exploratory efficacy endpoints were descriptively summarized by treatment group. The proportion of subjects achieving at least 1 point decrease in bleeding intensity according to the 5-point validated bleeding severity scale (Table 14) by each of the defined observation time points (i.e., T4, T7, and T10) was analyzed using Cochran-Mantel-Haenszel test stratified by type of surgery (i.e., hepatic versus soft tissue surgery).

Safety Analysis

The safety analyses are based on the safety population. The safety analyses were addressed by listing and tabulation of AEs and include suspected ADRs, vital signs,

physical assessments, and clinical laboratory tests. Data are described using descriptive analyses.

Determination of Sample Size

The sample size of the study was estimated to provide sufficient power (at least 80%) to demonstrate the hemostatic efficacy of VISTASEAL in parenchymous and soft tissue surgery.

Assuming that the true response rate is 80% for the VISTASEAL group, and 80% for the EVICEL group, it can be shown that a sample size of 172 subjects (86 subjects in the VISTASEAL group and 86 subjects in the EVICEL group, with a 1:1 assignment ratio) would give a power of at least 80% to establish noninferiority, with lower 95% CI for the ratio of the proportion of subjects with hemostasis success by 4 minutes in the 2 treatment groups (VISTASEAL relative to EVICEL) above 0.80.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

6.1.10.1.1 Demographics

Table 15 summarizes the demographic characteristics of the ITT population. Overall, subjects had a median age of 9.80 years (range: 0.0 to 17.9 years) at randomization and the ages were well-balanced in both the treatment groups. Overall, 62.4% of the subjects were male.

Subjects in the ITT population were primarily White (94.1%). Demographic characteristics were balanced in both the groups. At randomization, the overall median weight was 35.00 kg (range: 2.2 to 110.0 kg) and the overall median body mass index was 18.45 kg/m^2 (range: 8.0 to 61.2 kg/m^2).

Table 15. Summary of Demographics, Intent-to-Treat Population

Variable	VISTASEAL n=95	EVICEL n=91	Total N=186
Age (years) at randomization (n)	-	-	-
Mean (SD)	8.43 (6.108)	8.84 (6.320)	8.63 (6.199)
Median	9.40	10.30	9.80
Min – max	0.0-17.9	0.0-17.9	0.0-17.9
Age category – n (%)	-	-	-
≤27 days	4 (4.2%)	2 (2.2%)	6 (3.2%)
≥28 days - ≤23 months	19 (20.0%)	18 (19.8%)	37 (19.9%)
≥2 years - ≤11 years	34 (35.8%)	33 (36.3%)	67 (36.0%)
≥12 years - ≤17 years	38 (40.0%)	38 (41.8%)	76 (40.9%)

Variable	VISTASEAL n=95	EVICEL n=91	Total N=186
Sex – n (%)	-	-	-
Male	55 (57.9%)	61 (67.0%)	116 (62.4%)
Female	40 (42.1%)	30 (33.0%)	70 (37.6%)
If female[1]	-	-	-
Pre-Menarche	22 (55.0%)	17 (56.7%)	39 (55.7%)
Childbearing potential	18 (45.0%)	13 (43.3%)	31 (44.3%)
Pregnancy test - n (%)[2]	18	13	31
Positive	0 (0.0%)	0 (0.0%)	0 (0.0%)
Negative	18 (100%)	13 (100%)	31 (100%)
Ethnicity - n (%)	-	-	-
Hispanic or Latino	13 (13.7%)	11 (12.1%)	24 (12.9%)
Not Hispanic or Latino	82 (86.3%)	80 (87.9%)	162 (87.1%)
Race - n (%)	-	-	-
White	86 (90.5%)	89 (97.8%)	175 (94.1%)
Black or African American	6 (6.3%)	2 (2.2%)	8 (4.3%)
Asian	1 (1.1%)	0 (0.0%)	1 (0.5%)
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
Multiple	1 (1.1%)	0 (0.0%)	1 (0.5%)
Other	1 (1.1%)	0 (0.0%)	1 (0.5%)
Height (cm)	-	-	-
n	94	90	184
Mean (SD)	123.96 (43.332)	125.16 (44.389)	124.54 (43.736)
Median	133.25	141.00	139.85
Min – max	45.0-196.0	35.0-195.0	35.0-196.0
Weight (kg)	-	-	-
n	93	90	183
Mean (SD)	35.78 (26.241)	37.87 (27.719)	36.81 (26.924)
Median	30.40	36.50	35.00
Min – max	2.4-110.0	2.2-106.0	2.2-110.0
BMI (kg/m²)	-	-	-
n	93	90	183
Mean (SD)	19.37 (5.929)	20.59 (7.458)	19.97 (6.734)
Median	18.07	18.69	18.45
Min – max	8.0-41.9	8.8-61.2	8.0-61.2

Source: Final study report, Table 14.1.2.1; Listing 16.2.4.1
[1] The percentages are based on the number of female subjects.
[2] The percentages are based on the number of female subjects with childbearing potential.
The percentages are based on the number of female subjects.
The percentages are based on the number of female subjects with childbearing potential.
Abbreviations: BMI, body mass index; ITT, intent-to-treat; max, maximum; min, minimum; N, study population; n, sample size

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 16 summarizes the baseline characteristics of the ITT population. Overall, 53.3% subjects had mild baseline intensity of bleeding at the TBS and the size of bleeding was mainly ≤10 cm^2 (86.1%). Subjects were well-balanced at randomization in both parenchymous and soft tissue surgeries (51.1% and 48.9%, respectively).

Table 16. Summary of Baseline Characteristics, Intent-to-Treat Population

Characteristic	VISTASEAL (n =95)	EVICEL (n =91)	Total (N=186)
Baseline intensity of bleeding at TBS - n (%)[1]	92	88	180
Grade 1: Mild	45 (48.9%)	51 (58.0%)	96 (53.3%)
Grade 2: Moderate	47 (51.1%)	37 (42.0%)	84 (46.7%)
Size of bleeding surface at TBS - n (%)[1]	92	88	180
Small: TBS ≤10 cm^2	77 (83.7%)	78 (88.6%)	155 (86.1%)
Medium: 10 cm^2<TBS ≤100 cm^2	15 (16.3%)	10 (11.4%)	25 (13.9%)
Large: TBS >100 cm^2	0 (0.0%)	0 (0.0%)	0 (0.0%)
Type of surgery - n (%)	95	91	186
Parenchymous	50 (52.6%)	45 (49.5%)	95 (51.1%)
Soft tissue	45 (47.4%)	46 (50.5%)	91 (48.9%)

Source: Table 14.1.2.1; Listing 16.2.4.1
[1] The percentages are based on the number of subjects with available size of approximate bleeding surface at TBS.
Abbreviations: ITT, intent-to-treat; N, study population; n, sample size; TBS, target bleeding site

Medical History

The most common disorders/conditions (≥5 subjects overall) observed in the study population are presented in Table 17.

Table 17. Most Common Medical History Disorders/Conditions (Preferred Terms With ≥5 Subjects in Either Treatment Group), Intent-to-Treat Population

System Organ Class Preferred Term	VISTASEAL (n=95) n (%)	EVICEL (n=91) n (%)	Total (N=186) n (%)
Number of subjects with at least one medical history	94 (98.9%)	91 (100.0%)	185 (99.5%)
Blood and lymphatic system disorders	-	-	-
Anemia	4 (4.2%)	5 (5.5%)	9 (4.8%)
Congenital, familial, and genetic disorders	-	-	-
Cryptorchism	4 (4.2%)	6 (6.6%)	10 (5.4%)
Hydrocele	7 (7.4%)	0 (0.0%)	7 (3.8%)
Hypospadias	4 (4.2%)	5 (5.5%)	9 (4.8%)
Gastrointestinal disorders	-	-	-
Abdominal pain	2 (2.1%)	5 (5.5%)	7 (3.8%)
Inguinal hernia	3 (3.2%)	13 (14.3%)	16 (8.6%)
Hepatobiliary disorders	-	-	-
Cholelithiasis	8 (8.4%)	6 (6.6%)	14 (7.5%)
Jaundice	4 (4.2%)	7 (7.7%)	11 (5.9%)
Infections and infestations	-	-	-
Hepatic echinococciasis	8 (8.4%)	10 (11.0%)	18 (9.7%)
Metabolism and nutrition disorders	-	-	-
Obesity	4 (4.2%)	5 (5.5%)	9 (4.8%)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	-	-	-
Hepatic neoplasm	9 (9.5%)	2 (2.2%)	11 (5.9%)

System Organ Class Preferred Term	VISTASEAL (n=95) n (%)	EVICEL (n=91) n (%)	Total (N=186) n (%)
Reproductive system and breast disorders	-	-	-
Varicocele	3 (3.2%)	6 (6.6%)	9 (4.8%)
Respiratory, thoracic, and mediastinal disorders	-	-	-
Asthma	6 (6.3%)	0 (0.0%)	6 (3.2%)

Source: Table 14.1.3.1; Listing 16.2.4.2.1
Percentages were based on the total number of ITT subjects in each treatment group (n). Surgical History
Abbreviations: ITT, intent-to-treat; N, study population; n, sample size; PT, preferred term

The most common surgical history in ≥5 subjects was biopsy liver which was reported in 6.3% and 6.6% of subjects in VISTASEAL and EVICEL groups, respectively. Surgical history observed in the study population are presented in Table 18.

Table 18. Most Common Medical History Disorders/Conditions (Preferred Terms With ≥5 Subjects Overall), Intent-to-Treat Population

System Organ Class Preferred Term	VISTASEAL (n =95) n (%)	EVICEL (n =91) n (%)	Total (N=186) n (%)
Number of subjects with at least one surgical history	12 (12.6%)	15 (16.5%)	27 (14.5%)
Investigations	-	-	-
Biopsy liver	6 (6.3%)	6 (6.6%)	12 (6.5%)

Source: Table 14.1.3.2; Listing 16.2.4.2.2
Percentages were based on the total number of ITT subjects in each treatment group (n). Prior and Concomitant Medications
Abbreviations: ITT, intent-to-treat; N, study population; n, sample size; PT, preferred term

Blood products and concomitant medications more commonly used during the study are consistent with the medical history reported and the current medical condition.

6.1.10.1.3 Subject Disposition

Subject disposition is summarized in Table 19. A total of 197 subjects were screened, 186 subjects were randomized, and 178 subjects were dosed in the study. A total of 171 (91.9%) subjects completed the study. Seven (3.8%) subjects were discontinued prematurely from the study: three (1.6%) subjects were lost to follow-up; three (1.6%) subjects died; and one (0.5%) subject discontinued for other reasons. For the subjects who did not complete the study after receiving product, four (4.2%) subjects were in the VISTASEAL group and three (3.3%) subjects were in the EVICEL group.

Table 19. Subject Disposition, All Screened Subjects

Characteristic	VISTASEAL n (%)	EVICEL n (%)	Total N (%)
Screened	-	-	197
Subjects randomized/in the ITT population	95	91	186
Subjects dosed in the study (mITT population)	91 (95.8%)	87 (95.6%)	178 (95.7%)

Characteristic	VISTASEAL n (%)	EVICEL n (%)	Total N (%)
Subjects completed the study (after being dosed)	87 (91.6%)	84 (92.3%)	171 (91.9%)
Subjects discontinued prematurely (after being dosed)	4 (4.2%)	3 (3.3%)	7 (3.8%)
Reasons for premature discontinuation (after being dosed)	-	-	-
Adverse event	0 (0.0%)	0 (0.0%)	0 (0.0%)
Subject withdrew consent	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lost to follow-up	3 (3.2%)	0 (0.0%)	3 (1.6%)
Death	1 (1.1%)	2 (2.2%)	3 (1.6%)
Investigator's discretion (does not include AEs)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Applicant's termination of the study	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol violation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	1 (1.1%)	1 (0.5%)

Source: Table 14.1.1.1; Listing 16.2.1.1; from final study report
Percentages are based on the number of subjects randomized (ITT).
Abbreviations: AE, adverse event; ITT, intent-to-treat; mITT, modified intent-to-treat; N, study population; n, sample size

Eleven subjects failed screening. Reasons for screen failure included:

- Three subjects did not fulfill inclusion criterion 3 (no consent signed),
- Six subjects did not have enough IP at the study site or the kit was expired, and
- Two subjects lacked an appropriate bleeding site or did not need surgery.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Primary Efficacy Analyses

The primary efficacy assessment in this study was the proportion of subjects in the VISTASEAL and EVICEL treatment groups achieving hemostasis at the TBS by T4, with no occurrence of rebleeding until the completion of the surgical closure by layers of the exposed surgical field containing the TBS ($T_{Closure}$). The rate of hemostasis by T4 was 96.7% in VISTASEAL treatment group and 95.4% in the EVICEL treatment group. The estimated ratio of proportion achieving hemostasis by T4 in subjects receiving VISTASEAL relative to EVICEL was 1.01 (0.96 to 1.07), demonstrating that VISTASEAL is noninferior to EVICEL at the primary efficacy endpoint. The rate of hemostasis by T4 was numerically higher in VISTASEAL treatment group compared to the EVICEL treatment group.

There was no single occurrence of persistent bleeding, breakthrough bleeding, rebleeding, use of additional/alternative hemostatic treatment, or reapplication of fibrin sealant beyond T4 to closure for either of the two treatment arms, resulting in 0%

incidence of treatment failure in pediatric subjects receiving either VISTASEAL or EVICEL for parenchymous or soft tissue surgery.

Table 20. Summary and Analysis of Primary Efficacy Endpoint, Modified Intent-to-Treat Population

Efficacy Endpoint	VISTASEAL N=91 n (%)	EVICEL N=87 n (%)	RR (95% CI)[2, 4]	*p*-Value[3]
Number (%) subjects achieving hemostasis at the TBS by T4[1]	88 (96.7%)	83 (95.4%)	1.01 (0.96-1.07)	<0.001
Type of Surgery	-	-	-	-
Parenchymous	46/46 (100.0%)	43/43 (100.0%)	1.00 (0.92-1.09)	<0.001
Soft Tissue	42/45 (93.3%)	40/44 (90.9%)	1.03 (0.91-1.16)	<0.001

Source: Table 14.2.1.2.1; Listing 16.2.6
[1] If the intensity of bleeding at the TBS was Grade 0, hemostasis was considered achieved. If the intensity was Grade 1 or above, hemostasis was considered not achieved.
[2] Relative risk (RR) is the ratio of proportions of subjects meeting the efficacy endpoint in VISTASEAL versus EVICEL. For the overall category, RR is the common relative risk, stratified by type of surgery.
[3] In general, the CI and p-value were calculated by the Cochran–Mantel–Haenszel method, and it was adjusted for the type of surgery for the overall category. When all subjects were responders in both groups, the CI and p-value were computed by the Miettinen-Nurminen score method and Farrington-Manning test, respectively.
[4] If the lower limit of the 95% CI was above the noninferiority margin 0.8, it could be claimed that VISTASEAL was not inferior to EVICEL.
Abbreviations: mITT, modified intent-to-treat; N, study population; n, sample size; RR, relative risk; TBS, target bleeding site

6.1.11.2 Analyses of Secondary Endpoints

Cumulative Proportion of Subjects Achieving Hemostasis at TBS by Defined Observation Time Points of T7

The secondary efficacy variable was cumulative proportion of subjects achieving hemostasis at the TBS by T7, defined as an absence/cessation of bleeding (Grade 0) at the TBS by T7 without occurrence of rebleeding, Grade 3 or 4 bleeding, use of alternative hemostatic treatment, and reapplication of study treatment after T4 and until $T_{Closure}$. All 91 (100.0%) subjects from the VISTASEAL group (46 subjects in parenchymous surgery and 43 subjects in soft tissue surgery), and all 87 (100.0%) subjects from the EVICEL group (43 subjects in parenchymous surgery and 44 subjects in soft tissue surgery) met the secondary efficacy endpoint and achieved hemostasis at the TBS by T7. (Table 21).

Table 21. Summary and Analysis of Subjects Achieving Hemostasis at Target Bleeding Site by T7, Modified Intent-to-Treat Population

Efficacy Endpoint	VISTASEAL N=91 n (%)	EVICEL N=87 n (%)	RR (95% CI)[2, 4]	*p*-value[3]
Number (%) subjects achieving hemostasis at the TBS by T7[1]	91 (100.0%)	87 (100.0%)	1.00 (0.96-1.04)	<0.001

Efficacy Endpoint	VISTASEAL N=91 n (%)	EVICEL N=87 n (%)	RR (95% CI)[2, 4]	*p*-value[3]
Type of Surgery	-	-	-	-
Parenchymous	46/46 (100.0%)	43/43 (100.0%)	1.00 (0.92-1.09)	<0.001
Soft Tissue	45/45 (100.0%)	44/44 (100.0%)	1.00 (0.92-1.09)	<0.001

Source: Table 14.2.1.2.1; Listing 16.2.6
[1] If the intensity of bleeding at the TBS was Grade 0, hemostasis was considered achieved. If the intensity was Grade 1 or above, hemostasis was considered not achieved.
[2] Relative risk (RR) is the ratio of proportions of subjects meeting the efficacy endpoint in VISTASEAL versus EVICEL. For the overall category, RR is the common relative risk, stratified by type of surgery.
[3] In general, the CI and p-value were calculated by the Cochran–Mantel–Haenszel method, and it was adjusted for the type of surgery for the overall category. When all subjects were responders in both groups, the CI and p-value were computed by the Miettinen-Nurminen score method and Farrington-Manning test, respectively.
[4] If the lower limit of the 95% CI was above the noninferiority margin 0.8, it could be claimed that VISTASEAL was not inferior to EVICEL.
Abbreviations: mITT, modified intent-to-treat; N, study population; n, sample size; RR, relative risk; TBS, target bleeding site

Similar observations were made in the PP population and ITT population.

Cumulative Proportion of Subjects Achieving Hemostasis at Target Bleeding Site by Defined Observation Time Points of T10

An additional secondary efficacy variable was cumulative proportion of subjects achieving hemostasis at the TBS by T10, defined as an absence/cessation of bleeding (Grade 0) at the TBS by T10 without occurrence of rebleeding, Grade 3 or 4 bleeding, use of alternative hemostatic treatment, and reapplication of study treatment after T4 and until $T_{Closure}$. A total of 90/91 (98.9%) subjects from the VISTASEAL group and all 87 (100.0%) subjects from the EVICEL group met the secondary efficacy endpoint and achieved hemostasis at the TBS by T10. In parenchymous surgery, 45/46 (97.8%) subjects in VISTASEAL group and all 43 (100.0%) subjects in EVICEL group achieved hemostasis. In soft tissue surgery, all 45 (100.0%) subjects in VISTASEAL group and all 44 (100%) subjects in EVICEL group achieved hemostasis. The only subject who did not achieve hemostasis at T10 was Subject (b) (6) in VISTASEAL group. This subject missed hemostasis assessment at T10, hence the missing assessment was considered not to have achieved hemostasis. However, this subject achieved hemostasis at T4 and T7 (Table 22).

Table 22. Summary and Analysis of Subjects Achieving Hemostasis at Target Bleeding Site by T10, Modified Intent-to-Treat Population

Efficacy Endpoint	VISTASEAL N=91 n (%)	EVICEL N=87 n (%)	RR (95% CI)[2, 4]	*p*-Value[3]
Number (%) subjects achieving hemostasis at the TBS by T10[1]	90* (98.9%)	87 (100.0%)	0.99 (0.97-1.01)	<0.001

Efficacy Endpoint	VISTASEAL N=91 n (%)	EVICEL N=87 n (%)	RR (95% CI)[2, 4]	*p*-Value[3]
Type of surgery	-	-	-	-
Parenchymous	45/46 (97.8%)	43/43 (100.0%)	0.98 (0.94-1.02)	<0.001
Soft tissue	45/45 (100.0%)	44/44 (100.0%)	1.00 (0.92-1.09)	<0.001

Source: Table 14.2.1.2.1; Listing 16.2.6
[1] If the intensity of bleeding at the TBS was Grade 0, hemostasis was considered achieved. If the intensity was Grade 1 or above, hemostasis was considered not achieved.
[2] Relative risk (RR) is the ratio of proportions of subjects meeting the efficacy endpoint in VISTASEAL versus EVICEL. For the overall category, RR is the common relative risk, stratified by type of surgery.
[3] In general, the CI and p-value were calculated by the Cochran–Mantel–Haenszel method, and it was adjusted for the type of surgery for the overall category. When all subjects were responders in both groups, the CI and p-value were computed by the Miettinen-Nurminen score method and Farrington-Manning test, respectively.
[4] If the lower limit of the 95% CI was above the noninferiority margin 0.8, it could be claimed that VISTASEAL was not inferior to EVICEL.
*A missing hemostasis assessment at a time point was considered not to have achieved hemostasis at that specific time point. Subject (b) (6) who achieved hemostasis at T4 and T7 had a missing assessment at T10.
Abbreviations: mITT, modified intent-to-treat; N, study population; n, sample size; RR, relative risk; TBS, target bleeding site

Similar observations were made in the PP population and ITT population.

Prevalence of Treatment Failures

There was no single occurrence of persistent bleeding, breakthrough bleeding, rebleeding, use of additional/alternative hemostatic treatment, or reapplication of IP beyond T4 to $T_{Closure}$. All 91 (100.0%) subjects in the VISTASEAL group and all 87 (100.0%) subjects in EVICEL group met this secondary efficacy endpoint, with no treatment failures identified in either arm.

6.1.11.3 Subpopulation Analyses

Subgroup analyses by age, sex, race, bleeding intensity at baseline, and TBS size at baseline were also performed for primary efficacy endpoint; analyses demonstrated that VISTASEAL is noninferior to EVICEL.

- In subgroup analysis by age group:
  - The rates of hemostasis at the TBS by T4 in subjects aged ≤27 days and ≥28 days to ≤23 months old in the VISTASEAL and EVICEL treatment groups were 100.0%.
  - The rates of hemostasis at the TBS by T4 for subjects aged ≥2 to ≤11 years were 90.6% in VISTASEAL group and 93.5% in EVICEL group.
  - The rates of hemostasis at the TBS by T4 for subjects aged ≥12 to ≤17 years were 100.0% in VISTASEAL group and 94.4% in EVICEL group.
- In subgroup analysis by sex group, the rates of hemostasis at the TBS by T4 for male subjects were 96.2% in VISTASEAL group and 96.7% in EVICEL group, and 97.4% in VISTASEAL group and 92.6% in EVICEL group for female subjects.

- The majority of subjects were White in both the treatment groups, 91.2% in VISTASEAL group and 97.7% in EVICEL group, of which 97.6% subjects in VISTASEAL group and 95.3% in EVICEL group achieved hemostasis by T4.
- In subgroup analysis by bleeding intensity at baseline, the rates of hemostasis at the TBS by T4 for subjects with mild intensity were 97.8% in VISTASEAL group and 100.0% in EVICEL group, and 95.7% in VISTASEAL group and 88.9% in EVICEL group for subjects with moderate intensity.
- In subgroup analysis by TBS size, the rate of hemostasis at the TBS by T4 in subjects with a small bleeding surface at the TBS was higher in the VISTASEAL group (96.1%) compared to the EVICEL group (94.8%). The rates of hemostasis by T4 in subjects with medium bleeding surfaces at the TBS were 100% in both treatment groups.

Table 23. Subgroup Analysis, Primary Endpoint, Modified Intent-to-Treat Population

Subgroup Category	VISTASEAL N=91	EVICEL N=87	RR (95% CI)[1, 3]	*p*-value[2]
Hemostasis by 4 minutes	88/91 (96.7%)	83/87 (95.4%)	1.01 (0.95-1.07)	<0.001
Age	-	-	-	-
≤27 days	4/4 (100.0%)	2/2 (100.0%)	Not Calculable	-
≥28 days to ≤23 months	19/19 (100.0%)	18/18 (100.0%)	1.00 (0.83-1.22)	0.015
≥2 to ≤11 years	29/32 (90. 6%)	29/31 (93.5%)	0.97 (0.84-1.12)	0.005
≥12 to ≤17 years	36/36 (100. 0%)	34/36 (94.4%)	1.06 (0.98-1.15)	<0.001
Sex	-	-	-	-
Male	50/52 (96.2%)	58/60 (96.7%)	0.99 (0.93-1.07)	<0.001
Female	38/39 (97.4%)	25/27 (92.6%)	1.05 (0.93-1.18)	<0.001
Race	-	-	-	-
White	81/83 (97.6%)	81/85 (95.3%)	1.02 (0.97-1.09)	<0.001
Black or African American	4/5 (80.0%)	2/2 (100.0%)	Not Calculable	-
Asian	1/1 (100.0%)	0/0 (0.0%)	Not Calculable	-
American Indian or Alaskan Native	0/0 (0.0%)	0/0 (0.0%)	Not Calculable	-
Native Hawaiian or other Pacific Islander	0/0 (0.0%)	0/0 (0.0%)	Not Calculable	-
Multiple	1/1 (100.0%)	0/0 (0.0%)	Not Calculable	-
Other	1/1 (100.0%)	0/0 (0.0%)	Not Calculable	-
Bleeding intensity at baseline	-	-	-	-
Grade 1: Mild	44/45 (97.8%)	51/51 (100.0%)	0.98 (0.94-1.02)	<0.001
Grade 2: Moderate	44/46 (95.7%)	32/36 (88.9%)	1.08 (0.94-1.23)	<0.001

Subgroup Category	VISTASEAL N=91	EVICEL N=87	RR (95% CI)[1, 3]	*p*-value[2]
TBS size at baseline	-	-	-	-
Small: TBS ≤10 cm^2	73/76 (96.1%)	73/77 (94.8%)	1.01 (0.95-1.09)	<0.001
Medium: 10 cm^2<TBS ≤100 cm^2	15/15 (100.0%)	10/10 (100.0%)	1.00 (0.79-1.40)	0.026
Large: TBS >100 cm^2_	0/0 (0.0%)	0/0 (0.0%)	Not Calculable	-

Source: Table 14.2.1.5

[1] The CI and *p*-value were reported only when there were at least five subjects in both the treatment groups. Relative risk (RR) is the ratio of proportions of subjects meeting the efficacy endpoint in VISTASEAL versus EVICEL. For the overall category, RR is the common relative risk, stratified by type of surgery.

[2] In general, the CI and p-value were calculated by the Cochran–Mantel–Haenszel method, and it was adjusted for the type of surgery for the overall category. When all subjects were responders in both groups, the CI and p-value were computed by the Miettinen-Nurminen score method and Farrington-Manning test, respectively.

[3] If the lower limit of the 95% CI was above the noninferiority margin 0.8, it could be claimed that VISTASEAL was not inferior to EVICEL.

Abbreviations: mITT, modified intent-to-treat; N, study population; RR, relative risk; TBS, target bleeding site

6.1.11.4 Dropouts and/or Discontinuations

See Section 6.1.10.1.3 Subject Disposition.

6.1.11.5 Exploratory and Post Hoc Analyses

The exploratory efficacy endpoint of proportion of subjects achieving at least 1 point decrease in bleeding intensity from baseline met with a total of 97.8% subjects from the VISTASEAL group and 100.0% subjects from the EVICEL group achieving at least a 1 point decrease in bleeding intensity by T4, and 100.0% subjects in both the treatment groups achieving this decrease in bleeding intensity by T7 and T10. Bleeding intensity decreased from baseline to T4 and no bleeding was observed at time points T7 and T10.

6.1.12 Safety Analyses

6.1.12.1 Methods

AEs were recorded through 30 +/- 7 days after VISTASEAL or EVICEL was applied and reported in the complete study report and data sets. The clinical reviewer and the clinical data analyst combined like terms to determine the most frequent AEs as follows:

Table 24. Combined Like-Terms for Adverse Event Analysis, IG1405

Grouped Term (Revised)	Terms Reported in CSR
Anemia	anemia anemia postoperative hemoglobin decreased
Upper respiratory infection	respiratory syncytial virus infection respiratory tract infection rhinovirus infection upper respiratory tract infection viral upper respiratory tract infection

Grouped Term (Revised)	Terms Reported in CSR
Wound complication	wound complication wound infection wound dehiscence postoperative wound infection
Bleeding	post procedural hemorrhage procedural hemorrhage
Low platelets	thrombocytosis platelet count increased
Ileus	Ileus paralytic ileus
Vomiting	vomiting procedural vomiting

Source: Original table by clinical reviewer based on information extracted from the complete study report.
Abbreviations: CSR, complete study report

6.1.12.2 Overview of Adverse Events

Table 25. Overall Summary of Treatment-Emergent Adverse Events, Safety Population

Variable	VISTASEAL N=91 Number of Subjects[1] n (%)	VISTASEAL N=91 Number of Events[2]	EVICEL N=87 Number of Subjects[1] n (%)	EVICEL N=87 Number of Events[2]
Subjects with any TEAE	24 (26.4%)	46	16 (18.4%)	38
Relationship to IP	-	-	-	-
Unrelated	23 (25.3%)	45	16 (18.4%)	38
Possibly related	1 (1.1%)	1	0 (0%)	0
Definitely related	0 (0.0%)	0	0 (0.0%)	0
Severity	-	-	-	-
Mild	13 (14.3%)	29	6 (6.9%)	17
Moderate	8 (8.8%)	13	5 (5.7%)	13
Severe	3 (3.3%)	4	5 (5.7%)	8
Subjects with any suspected ADRs[3]	1 (1.1%)	1	0 (0.0%)	0
Subjects with any ARs[4]	0	0	0	0
Subjects with any treatment-emergent SAE[5]	8 (8.8%)	12	9 (10.3%)	11
Subjects with any TEAEs with outcome of death	1 (1.1%)	1	2 (2.3%)	2

Variable	VISTASEAL N=91 Number of Subjects[1] n (%)	VISTASEAL N=91 Number of Events[2]	EVICEL N=87 Number of Subjects[1] n (%)	EVICEL N=87 Number of Events[2]
Subjects with any nonfatal TEAEs leading to study discontinuation	0 (0.0%)	0	1 (1.1%)	1

Source: Table 14.3.1.2, Table 14.3.1.4.1, Table 14.3.1.5, Table 14.3.2.3, Listing 16.2.1.1, and Listing 16.2.7
[1] At each level of summation (overall, relationship, severity), subjects reporting more than one AE were counted only once using the strongest relationship to IP and maximum severity.
[2] Number of events included all occurrences of AEs.
[3] Suspected ADRs are adverse events with a definite or possible causal relationship to study treatment.
[4] ARs are AEs with a definite causal relationship to study treatment.
[5] Subject (b) (6) experienced SAE anaphylactic shock due to Echinococcus granulosus cyst spillage on Day 1. Because the time of onset was not documented in the electronic data capture database, this event was conservatively attributed as treatment-emergent SAE. However, source data residing in the study database indicate onset prior to administration of the IP, hence this SAE is not treatment-emergent.
There are other AEs where no onset time is documented on Day 1, and they are also represented conservatively as treatment-emergent events. This SAE case was handled in the same manner for consistency.
Note: TEAEs are AEs that occurred on or after the date/time of IP administration. Percentages were based on the total number of safety subjects in each treatment group (N).
Abbreviations: ADR, adverse drug reaction; AE, adverse event; AR, adverse reaction; IP, investigational product; N, study population; n, sample size; SAE, serious adverse event; TEAE, treatment-emergent adverse event

No substantial differences in safety were identified when comparing the frequency and nature of AEs that occurred after VISTASEAL application using the original Fibrijet applicator to VISTASEAL application using the Dual Applicator as seen in Table 26:

Table 26. Adverse Events After VISTASEAL With Original Applicator Versus Dual Applicator

Preferred Term	Fibrijet Applicator N=55 n (%)	Dual Applicator N=36 n (%)
Abdominal distension	2 (3.6)	0 (0.0)
Anemia[1]	3 (5.5)	1 (2.8)
Anemia	2 (3.6)	0 (0.0)
Anemia postoperative	1 (1.8)	0 (0.0)
Hemoglobin decreased	0 (0.0)	1 (2.8)
Anaphylactic shock (not related)	0 (0.0)	2 (5.6)
Atelectasis	0 (0.0)	1 (2.8)
Bacteremia	1 (1.8)	0 (0.0)
Blood magnesium decreased	0 (0.0)	1 (2.8)
Bronchospasm	1 (1.8)	0 (0.0)
Cardiac arrest	0 (0.0)	1 (2.8)
Decreased appetite	0 (0.0)	1 (2.8)
Diarrhea	0 (0.0)	1 (2.8)
Epistaxis	1 (1.8)	0 (0.0)
Hypertension	1 (1.8)	1 (2.8)
Ileus[1]	1 (1.8)	0 (0.0)
Intra-abdominal fluid collection	1 (1.8)	0 (0.0)
Intussusception	1 (1.8)	0 (0.0)
Low platelets[1]	0 (0.0)	1 (2.8)
Melena	1 (1.8)	0 (0.0)
Nausea	0 (0.0)	1 (2.8)

Preferred Term	Fibrijet Applicator N=55 n (%)	Dual Applicator N=36 n (%)
Oxygen saturation decreased	1 (1.8)	0 (0.0)
Pleural effusion	1 (1.8)	0 (0.0)
Pneumothorax	0 (0.0)	1 (2.8)
Procedural pain	1 (1.8)	0 (0.0)
Pyrexia	0 (0.0)	1 (2.8)
Rash	1 (1.8)	0 (0.0)
Staphylococcal infection	0 (0.0)	1 (2.8)

Source: sBLA Clinical Data Analyst generated table based on adverse event data set submitted with pediatric study IG1405.
[1] Custom groupings of preferred terms: Anemia includes (Anemia, Anemia postoperative, Hemoglobin decreased), Ileus includes (Ileus, Ileus paralytic), Low platelets includes (Thrombocytosis, Platelet count increased)
Abbreviations: N, study population; n, sample size

Summary of Most Common Adverse Events

Table 27 includes the most common AEs:

Table 27. Most Common Adverse Events

Preferred Term	VISTASEAL N=91 n (%)	EVICEL N=87 n (%)
Abdominal distension	2 (2.2)	0 (0.0)
Anemia[1]	4 (4.4)	4 (4.6)
Anemia	2 (2.2)	3 (3.4)
Anemia postoperative	1 (1.1)	0 (0.0)
Hemoglobin decreased	1 (1.1)	1 (1.1)
Anaphylactic shock	2 (2.2)	0 (0.0)
Hypertension	2 (2.2)	0 (0.0)
Nausea	1 (1.1)	2 (2.3)
Pyrexia	1 (1.1)	5 (5.7)
Upper respiratory infection[1]	1 (1.1)	2 (2.3)
Respiratory syncytial virus infection	0 (0.0)	1 (1.1)
Respiratory tract infection	0 (0.0)	1 (1.1)
Upper respiratory tract infection	1 (1.1)	0 (0.0)
Vomiting[1]	7 (7.7)	3 (3.4)
Procedural vomiting	1 (1.1)	0 (0.0)
Vomiting	6 (6.6)	3 (3.4)

Preferred Term	VISTASEAL N=91 n (%)	EVICEL N=87 n (%)
Wound complication[1]	5 (5.5)	0 (0.0)
Postoperative wound infection	1 (1.1)	0 (0.0)
Wound complication	1 (1.1)	0 (0.0)
Wound dehiscence	2 (2.2)	0 (0.0)
Wound infection	2 (2.2)	0 (0.0)

Source: sBLA Clinical Data Analyst generated table based on adverse event data set submitted with pediatric Study IG1405.
Source datasets: adsl.xpt, adae.xpt.
ADSL filters: SAFFL = Y.
ADAE filters: TRTEMFL = Y.
Column grouping variable: TRT01A.
[1] Custom groupings of preferred terms: Anemia includes (Anemia, Anemia postoperative, Hemoglobin decreased), Ileus includes (Ileus, Ileus paralytic), Bleeding includes (Post procedural hemorrhage, Procedural hemorrhage), Wound complication includes (Postoperative wound complication, Postoperative wound infection, Wound complication, Wound dehiscence, Wound infection), Low platelets includes (Thrombocytosis, Platelet count increased), Vomiting includes (Procedural vomiting, Vomiting), Upper respiratory infection includes (Respiratory syncytial virus infection, Respiratory tract infection, Rhinovirus infection,
Upper respiratory tract infection, Viral upper respiratory tract infection)
Abbreviations: N, study population; n, sample size

The most common TEAEs that occurred in >1 subject in the VISTASEAL group are in Table 28:

Table 28. Most Common Treatment-Emergent Adverse Events in >1 Subject, VISTASEAL Group (N=91)

Preferred Term	n (%)
Abdominal distension	2 (2.2)
Anemia[1]	4 (4.4)
Hypertension	2 (2.2)
Vomiting[1]	7 (7.7)
Wound dehiscence	2 (2.2)
Wound infection	2 (2.2)

Source: sBLA Clinical Data Analyst generated table based on adverse event data set submitted with pediatric Study IG1405
[1] Custom groupings of preferred terms: Anemia includes (Anemia, Anemia postoperative, Hemoglobin decreased), Vomiting includes (Procedural vomiting, Vomiting)
Abbreviations: N, study population; n, sample size; TEAE, treatment-emergent adverse event

The most common TEAEs that occurred in >1 subject in the EVICEL group follow.

Table 29. Most Common Treatment-Emergent Adverse Events in >1 Subject, EVICEL Group (N=87)

Preferred Term	n (%)
Anemia[1]	4 (4.6)
Nausea	2 (2.3)
Pyrexia	5 (5.7)
Upper respiratory infection[1]	2 (2.3)
Vomiting[1]	3 (3.4)

Source: sBLA Clinical Data Analyst generated table based on adverse event data set submitted with pediatric Study IG1405
[1] Custom groupings of preferred terms: Anemia includes (Anemia, Anemia postoperative, Hemoglobin decreased), Upper respiratory infection includes (Respiratory syncytial virus infection, Respiratory tract infection, Rhinovirus infection, Upper respiratory tract infection, Viral upper respiratory tract infection), Vomiting includes (Procedural vomiting, Vomiting)
Abbreviations: N, study population; n, sample size; TEAE, treatment-emergent adverse event

Reviewer comment: The nature and severity of AEs are consistent with AEs that were likely to occur after the types of surgeries that were performed in subjects with the underlying disease that required surgery.

Table 30. Adverse Events Reported Per Study Site

Site ID	102	103	104	105	153	200	201	202	203	254	255	300	550	602	604	610	614
# Subjects	11	4	5	6	63	13	22	3	10	12	11	1	4	1	1	1	28
# All AEs	0	0	1	1	33	18	7	1	1	4	16	0	11	0	0	1	2
# AE/subj	0	0	0.2	0.2	0.5	1.4	0.3	0.3	0.1	0.3	1.5	0	2.8	0	0	1	0.1
Mild	0	0	1	0	19	10	6	1	0	3	8	0	8	0	0	1	0
Moderate	0	0	0	1	8	6	1	0	0	1	6	0	3	0	0	0	0
Severe	0	0	0	0	6	2	0	0	1	0	2	0	0	0	0	0	2

Source: Reviewer generated table based on Complete Study Report for pediatric Study IG1405
Abbreviations: AE, adverse event; subj, subject

Reviewer comment: The number of AEs reported was noted to be substantially lower at study sites 102, 103, 104, 105, 201, 203, 254, and 614 compared to other study sites. To ascertain whether there were differences in safety reporting procedures/documentation at these sites, the clinical team held an informal teleconference with the Applicant who clarified that the investigators at study sites 102, 103, 104, 105, 201, 203, 254, and 614 did not report AEs that they assessed as expected to occur due to underlying illness or after the surgeries that were performed. The Applicant's rationale that some investigator's did not report AEs that were more likely due to underlying disease or surgery is reasonable. Despite differences in AE reporting across study sites, it is this reviewer's opinion that pediatric Study IG1405 is adequate to assess the safety of VISTASEAL use in the pediatric population as an adjunct to hemostasis in surgery.

6.1.12.3 Deaths

A total of three deaths occurred in the study, one (1/91 [1.1%]) in VISTASEAL group and two (2/87 [2.3%]) in the EVICEL group. All deaths were considered by the investigator and Applicant as unrelated to study treatment (Table 31).

Table 31. Deaths by Subject

Treatment Group	Type of Surgery	Subject	SAE Preferred Term	Start Day of SAE[1]	Causality
VISTASEAL	Parenchymous	(b) (6)	Cardiac arrest	Day 10	Unrelated
EVICEL	Parenchymous	(b) (6)	Cardiac arrest	Day 2	Unrelated
EVICEL	Soft Tissue	(b) (6)	Pulmonary hypertension	Day 10	Unrelated

Source: CSR Table 14.3.2.1 and Listing 16.2.7
[1] Beginning on the surgery day, day corresponds to the protocol-defined visit day.
Abbreviations: SAE, serious adverse event

Reviewer comment: Cardiac arrest may be a result of air or thrombotic embolism. Air embolism has been reported after spray of other marketed fibrin sealants (2014) when administered closer than recommended to the application site. Thrombosis has been reported after intravascular administration of fibrin sealants (Tonner and Scholz 1994; Singh et al. 2018; Andrade-Barazarte et al. 2021); however, this reviewer was unable to identify cases of thrombosis that occurred after topical administration of fibrin sealant. To assess for relatedness of the cardiac arrest that occurred in Subject (b) (6) 10 days after exposure to VISTASEAL, the case narrative was reviewed. The narrative report is summarized below.

> *"Patient (b) (6) (randomized to VISTASEAL) was a 9-month-old white female infant in Romania with a medical history that included abdominal neoplasm diagnosed during fetal development with previous tumor resection in the newborn period and pancreatic hamartoma. After initial surgery in the newborn period, the subject presented with growth of the tumor mass, growth of hepatic masses, and significant dilation of the inferior vena cava with tumor thrombi. She had clotting problems, anemia, and thrombocytopenia. At screening/baseline she had dyspnea and a distended abdomen which was hard on palpation due to tumor. Surgery was*

performed in order to have a new tumor mass biopsy as there was suspicion of malignancy (which biopsy excluded). Anesthesia commenced at 12:01 on December 4, 2020 (Day 1). The TBS was identified with Grade 2 moderate bleeding on the liver surface with a small bleeding area ≤10 cm^2. No bleeding was observed at any of the post application scheduled time points (4, 7, or 10 minutes from application [T4, T7, or T10]). Time of operative closure was 40 minutes later. Due to medical complications listed above, the patient was considered inoperable. So she was placed under palliative care. The patient's condition worsened progressively. She developed cardiac arrest and died on (b) (6) *(Day 10) at 02:00 hours. An autopsy was performed. The autopsy showed intra-abdominal tumor and vena cava embolism and thrombosis. The Death Certificate indicated acute cardiorespiratory failure secondary to intra-abdominal tumor as the primary cause of death. The investigator considered the causal relationship of the SAE of cardiac arrest as not related to the IP. The Sponsor also considers this SAE as not related to IP."*

This case narrative describes underlying medical issues, (e.g., vena cava dilatation with tumor thrombi), that are substantially more likely than VISTASEAL to have caused cardiac arrest in this subject. I agree with the investigator and the Applicant that this cardiac arrest was unrelated to VISTASEAL.

6.1.12.4 Nonfatal Serious Adverse Events

As shown in the following table, the number and nature of nonfatal TESAEs were similar in the VISTASEAL and EVICEL groups. Fifteen subjects experienced TESAEs: seven (7.7%) subjects in VISTASEAL group and eight (9.2%) subjects in EVICEL group. All TESAEs were considered unrelated to the study treatment by the investigator and the Applicant.

Table 32. Treatment-Emergent Serious Adverse Events, Pediatric Study IG1405

ID Age Sex	Product Received	Surgery/ Indication for Surgery	SAE	Time Since Product Applied	Causality Applicant	Applicant Rationale for Relatedness	Causality Reviewer	Reviewer Analysis
(b) (6) 14 years Female	VISTASEAL	Hydatid hepatic cyst evacuation	Anaphylactic shock	Minus 2 hours	Not related	Occurred prior to application	Not related	Occurred prior to application
(b) (6) 9 years Male	VISTASEAL	Hepatic and pulmonary hydatid cyst evacuation	Anaphylactic shock	1.5 hours	Not related	Due to spillage of cyst contents	Unlikely related	Likely due to spillage of cyst contents (Echinococcus)
(b) (6) 8 months Male	VISTASEAL	Intraabdominal cystic mass excision	Ileoileal intussusception	2 days	Not related	Not related	Possibly related	No Meckel's or lymph nodes to predispose to intussusception ; plausible mechanism from fibrin sealant
(b) (6) 20 months Female	VISTASEAL	Choledochal cystectomy	Transaminitis	6-21 days	Not related	Not specified	Not related	May be expected from underling surgery
(b) (6) 13 years Female	VISTASEAL	Psoas abscess drainage	Postop wound infection	14-20 days	Not related	Not specified	Not related	More likely due to underlying condition
(b) (6) 4 Years Male	VISTASEAL	Right Hepatectomy Rhabdomyosarcoma	Diarrhea, wound infection, vomiting	10 days	Not related	Not specified	Not related	Multiple other sources of infection more likely
(b) (6) 3 years Female	VISTASEAL	Hepatectomy Hepatoblastoma	Pyrexia staph liver abscess	0-3 days	Not related	Not specified	Not related	Other sites of infection more likely than product

ID Age Sex	Product Received	Surgery/ Indication for Surgery	SAE	Time Since Product Applied	Causality Applicant	Applicant Rationale for Relatedness	Causality Reviewer	Reviewer Analysis
(b) (6) 6 years Female	EVICEL	Congenital choledochal cystectomy	Ascites	7 days	Not related	Not Specified	Not likely related	Could be reaction to product; more likely underlying disease
(b) (6) 3 years Female	EVICEL	Liver biopsy Suspected biliary atresia	Postoperative bleeding	5.5 hours	Not related	Bleeding from site where product was not applied	Not related	Bleeding was from site where product was not applied
(b) (6) 11 years Female	EVICEL	Central liver resection Metastatic liver sarcoma	Pancytopenia	20-25 days	Not related	Related to chemo	Not related	Expected after chemotherapy for underlying disease
(b) (6) 1 year Female	EVICEL	Partial hepatectomy of Hepatoblastoma	Pulmonary embolism	7 days	Not related	Due to port-a-cath	Unlikely related	Possibly due to port-a-cath; may be related to product
(b) (6) 4 years Female	EVICEL	Removal of liver metastases Neuroblastoma	Sepsis paralytic ileus	2-3 days	Not related	Not specified	Not related	Ileus may be due to fibrin sealant
(b) (6) 8 years Female	EVICEL	Surgery not specified Wilms Tumor with Liver metastases	Anaphylactic reaction	Neg 2 days	Not related	Occurred prior to application	Not related	Occurred prior to application
(b) (6) 8 years Female	EVICEL	Surgery not specified. Benign liver tumor	Respiratory tract Infection	11 days	Not related	Not specified	Not related	Unlikely mechanism

ID Age Sex	Product Received	Surgery/ Indication for Surgery	SAE	Time Since Product Applied	Causality Applicant	Applicant Rationale for Relatedness	Causality Reviewer	Reviewer Analysis
(b) (6) 24-week gestation premature infant Male	EVICEL	Circumcision	Acute respiratory failure due to RSV	34-41 days	Not Related	Due to RSV	Not related	No logical mechanism; consistent with underlying prematurity

Source: Reviewer generated table using data included in pediatric Study IG1405 complete study report (CSR).
Abbreviations: RSV, respiratory syncytial virus; SAE, serious adverse event; TESAE, treatment-emergent serious adverse event

Reviewer comment: Fibrin sealants have been associated with anaphylaxis and inflammation and/or adhesions that lead to bowel obstruction. Therefore, SAEs of anaphylaxis, bowel obstruction and infection in subjects who received VISTASEAL were reviewed for possible relatedness.

Anaphylaxis

Anaphylaxis has been reported after topical administration or injection of fibrin sealants (Schievink et al. 2008; Orihara et al. 2021; Saffarzadeh et al. 2021). To assess for possible relatedness to VISTASEAL or EVICEL, case narratives were reviewed in subjects who experienced anaphylactic reactions during the study.

Two subjects in the VISTASEAL group and one subject in the EVICEL group experienced SAEs of anaphylaxis. The first subject in the VISTASEAL group and the one subject in the EVICEL group experienced anaphylaxis prior to administration of the fibrin sealant study medication. Therefore, this reviewer agrees with the investigator and Applicant that the anaphylaxis was not related to VISTASEAL. (Note: These instances of anaphylaxis were considered SAEs because they occurred after enrollment that occurred prior to start of surgery.) The second subject in the VISTASEAL group experienced anaphylaxis during drainage of a hydatid cyst that contains echinococcus. Anaphylactic reaction is a known complication of hydatid cyst/echinococcus (Moro and Reddy 2024), which is an alternative and more likely cause of the anaphylaxis than that the fibrin sealant. Therefore, this reviewer assesses the anaphylaxis as unlikely related to VISTASEAL.

Bowel Obstruction

Section 4.5 includes postmarketing reports of bowel obstruction and hiatal hernia that occurred due to adhesions in the area of VISTASEAL application 9 days and 4 to 5 weeks respectively after VISTASEAL administration, raising concern for VISTASEAL as a possible cause of the adhesion. To assess for possible relatedness of VISTASEAL to cases of bowel obstruction in pediatric Study IG1405, the case narratives of Subjects (b) (6) *who experienced Ileoileal intussusception 2 days after VISTASEAL administration and Subject* (b) (6) *who experienced paralytic ileus 2 days after EVICEL were reviewed:*

> *"Subject* (b) (6) *was an 8-month-old patient who received VISTASEAL during an intraabdominal cystic mass excision. Two days after product administration the subject experienced an ileoileal intussusception that was assessed as not related by both the investigator and the Sponsor. When the subject was taken back to the operating room to treat the intussusception the surgeon noted there were no Meckel's diverticulum or lymph nodes that might predispose the subject to intussusception. Because there was no clear predisposition or alternative cause, it is possible that the event was related to VISTASEAL. It is not clear whether the intraabdominal cystic mass was in the vicinity of the intussusception. Therefore, this reviewer assesses the TESAE of Ileoileal intussusception as possibly related to VISTASEAL.*

Subject (b) (6) was a 4-month-old patient who developed paralytic ileus 2 days after EVICEL application, after a second-look surgery done to assess neuroblastoma and liver metastasis removal. The patient deteriorated postoperatively and had a distended abdomen with no bowel sounds. Abdominal ultrasound and X-ray were consistent with paralytic ileus. Treatment of the ileus included nasogastric (NG) tube insertion and rectal tube. Hypokalemia was observed and assessed to be a consequence of paralytic ileus. Bowel motility improved after the potassium was corrected. Seventy-two hours postoperatively bowel sounds returned. The NG fluid output was clear. The ileus resolved on Day 4 of the study. In this reviewer's assessment, the case report supports postoperative paralytic ileus as an accurate diagnosis. Therefore, I agree with the investigator and the Applicant that this case of ileus is unrelated to EVICEL administration."

6.1.12.5 Adverse Events of Special Interest

Thrombotic Events

Injection and intravascular administration of marketed fibrin sealants have been associated with thrombotic events. This reviewer was unable to identify any cases of thrombotic events that were determined to be caused by topical administration of fibrin sealants. To assess for relatedness, case reports of TEAEs in pediatric Study IG1405 that may have been caused by thrombosis were reviewed. One subject in the VISTASEAL group (cardiac arrest), and two subjects in the EVICEL group (pulmonary embolism, cardiac arrest) experienced TEAEs that may have been due to thrombosis. All three events were considered unrelated to the administered fibrin sealant by the investigator and the Applicant.

Reviewer comment: This reviewer agrees that the cardiac arrests were unrelated to the fibrin sealants. Please see reviewer comment in Section 6.1.12.3 (Deaths). The subject in the EVICEL group who experienced a pulmonary embolism had a central line that may predispose the patient to pulmonary embolism. However, a thrombus was not identified in the central line. Due to lack of an alternative explanation and the association of fibrin sealants with thrombotic events after intravenous administration, this reviewer assesses the pulmonary embolism that occurred in the EVICEL group as possibly related to the EVICEL.

Please see reviewer comment in Section 6.1.12.4 regarding the adverse event of special interest of anaphylaxis.

6.1.12.6 Clinical Test Results

When comparing the VISTASEAL treatment group with the EVICEL group, no apparent clinically relevant differences in the treatment-emergent pattern of changes in laboratory parameters at postoperative Day 4 were observed.

6.1.12.7 Dropouts and/or Discontinuations

One subject (1.1%) in EVICEL group reported a nonfatal TEAE (acute respiratory failure, from which the subject recovered) leading to study discontinuation.

No subjects were discontinued from the study due to nonfatal TEAEs in VISTASEAL group. One (1.1%) subject treated with VISTASEAL died (cardiac arrest) and did not complete the study. One subject (1.1%) from EVICEL group experienced a nonfatal TEAE (acute respiratory failure) resulting in discontinuation from which the subject recovered. Two subjects (2.3%) in the EVICEL group died (cardiac arrest, and pulmonary hypertension) and did not complete study. All of these events were considered unrelated to study treatment.

6.1.12.8 Comparison of Safety Between Fibrijet and Dual Applicator Tips

Post hoc clinical reviewer analysis comparing safety in subjects who received VISTASEAL using the Fibrijet applicator tip (supplied as part of the kit prior to November 30, 2019) versus the Dual Applicator tip (supplied with the kit after November 30, 2019 through present) revealed similar number and nature of AEs in both groups as seen in Table 33.

Table 33. Treatment-Emergent Adverse Events by Applicator, VISTASEAL-Treated Only, Safety Population, IG1405

Preferred Term	Fibrijet Applicator N=55 n (%)	Dual Applicator N=36 n (%)
Abdominal distension	2 (3.6)	0 (0.0)
Anemia[1]	3 (5.5)	1 (2.8)
Anemia	2 (3.6)	0 (0.0)
Anemia postoperative	1 (1.8)	0 (0.0)
Hemoglobin decreased	0 (0.0)	1 (2.8)
Anaphylactic shock	0 (0.0)	2 (5.6)
Atelectasis	0 (0.0)	1 (2.8)
Bacteremia	1 (1.8)	0 (0.0)
Blood magnesium decreased	0 (0.0)	1 (2.8)
Bronchospasm	1 (1.8)	0 (0.0)
Cardiac arrest	0 (0.0)	1 (2.8)
Decreased appetite	0 (0.0)	1 (2.8)
Diarrhea	0 (0.0)	1 (2.8)
Epistaxis	1 (1.8)	0 (0.0)
Hypertension	1 (1.8)	1 (2.8)
Ileus[1]	1 (1.8)	0 (0.0)
Ileus	1 (1.8)	0 (0.0)
Intra-abdominal fluid collection	1 (1.8)	0 (0.0)
Intussusception	1 (1.8)	0 (0.0)
Low platelets[1]	0 (0.0)	1 (2.8)
Platelet count increased	0 (0.0)	1 (2.8)
Melaena	1 (1.8)	0 (0.0)
Nausea	0 (0.0)	1 (2.8)
Oxygen saturation decreased	1 (1.8)	0 (0.0)

Preferred Term	Fibrijet Applicator N=55 n (%)	Dual Applicator N=36 n (%)
Pleural effusion	1 (1.8)	0 (0.0)
Pneumothorax	0 (0.0)	1 (2.8)
Procedural pain	1 (1.8)	0 (0.0)
Pyrexia	0 (0.0)	1 (2.8)
Rash	1 (1.8)	0 (0.0)
Staphylococcal infection	0 (0.0)	1 (2.8)

Source: sBLA Clinical Data Analyst generated table based on adverse event data set submitted with pediatric Study IG1405[1]
Custom groupings of preferred terms: Anemia includes (Anemia, Anemia postoperative, Hemoglobin decreased), Ileus includes (Ileus, Ileus paralytic), Low platelets includes (Thrombocytosis, Platelet count increased)
Abbreviations: N, study population; n, sample size

Table 34. Treatment-Emergent Adverse Events by Applicator, VISTASEAL-Treatment Only, Safety Population, IG1405

Preferred Term	Fibrijet Applicator N=55 n (%)	Dual Applicator N=36 n (%)
Transaminases increased	1 (1.8)	0 (0.0)
Upper respiratory infection[1]	1 (1.8)	0 (0.0)
Upper respiratory tract infection	1 (1.8)	0 (0.0)
Vomiting[1]	4 (7.3)	3 (8.3)
Procedural vomiting	1 (1.8)	0 (0.0)
Vomiting	3 (5.5)	3 (8.3)
Wound complication[1]	3 (5.5)	2 (5.6)
Postoperative wound infection	1 (1.8)	0 (0.0)
Wound complication	0 (0.0)	1 (2.8)
Wound dehiscence	2 (3.6)	0 (0.0)
Wound infection	1 (1.8)	1 (2.8)

Source: sBLA Clinical Data Analyst generated table based on adverse event data set submitted with pediatric Study IG1405
Source datasets: adsl.xpt, adae.xpt.
ADSL filters: SAFFL = Y, TRT01A = VISTASEAL.
ADAE filters: TRTEMFL = Y.
Column grouping variable: APLCTR (Custom variable, Fibrijet Applicator as TRTSDT ≤30Nov2019 versus Dual Applicator as TRTSDT >30Nov2019).
[1] Custom groupings of preferred terms: Upper respiratory infection includes (Respiratory syncytial virus infection, Respiratory tract infection, Rhinovirus infection, Upper respiratory tract infection, Viral upper respiratory tract infection), Vomiting includes (Procedural vomiting, Vomiting), Wound complication includes (Postoperative wound complication, Postoperative wound infection, Wound complication, Wound dehiscence, Wound infection)
Abbreviations: N, study population; n, sample size

6.1.13 Study Summary and Conclusions

Overall, data from pediatric Study IG1405 demonstrate the safety and hemostatic efficacy of VISTASEAL and support the use of VISTASEAL as an effective local hemostatic agent in parenchymal and soft tissue surgeries in pediatric subjects. Primary efficacy analysis of hemostasis rate by T4 demonstrated that VISTASEAL is noninferior to EVICEL and that the rate of hemostasis by T4 in the VISTASEAL treatment group was higher, but not statistically superior to the EVICEL treatment group.

The results of all secondary efficacy endpoints provided additional support for VISTASEAL as an effective local hemostatic agent in soft tissue surgery.

6.2 Summary of Studies #2, #3, and #4 (IG1101, IG1102, and IG1103)

The following sections 6.3, 6.4, and 6.5 summarize individual Studies IG1101, IG1102, and IG1103 that the Applicant submitted to support the original BLA that was approved November 1, 2017. Much of the information included in this section was extracted from the clinical review memo for the original BLA, written by Dr. Agnes Lim. Dr. Lim's review memo contains a detailed review of these studies and can be downloaded online.

Section 8 of this memo summarizes available integrated demographic, efficacy, and safety data from these studies, and included a comparison of safety in adults compared to pediatric subjects.

All three clinical studies were conducted using the same general study design with each study consisting of a Preliminary Part I followed by a Primary Part II. Part I was used to train the surgeons on proper application of VISTASEAL. In Part 2 of each study, subjects were randomized to receive VISTASEAL or control (MC or SURGICEL). The same subject monitoring and follow-up periods were used in the three studies. The inclusion and exclusion criteria were generally the same for all clinical studies except for the types of surgeries included in each study: vascular surgery in IG1101, parenchymous surgery in IG1102, and soft tissue surgery in IG1103.

6.3 Study #2 IG1101

Design

Study IG1101 was a multicenter Phase 3, prospective, subject-blinded, randomized, controlled study to compare the safety and efficacy of VISTASEAL to MC as an adjunct to hemostasis during peripheral vascular surgery. The study enrolled 225 adults undergoing an elective, open peripheral vascular surgical procedure. The TBS was identified when the investigator (surgeon) determined that control of moderate bleeding by conventional surgical techniques (including suture, ligature, and cautery) was ineffective or impractical and required an adjunct treatment to achieve hemostasis. No pediatric subjects enrolled in the study, although eligibility criteria included children. The absence of pediatric enrollment was attributed to the low prevalence of children who undergo peripheral vascular surgery. Subjects were randomized 1:1 to receive VISTASEAL or MC.

Primary Endpoint

The primary efficacy endpoint, comparing VISTASEAL to MC using the ITT population, was the proportion of subjects achieving hemostasis at the TBS by 4 minutes after application (T4) without occurrence of rebleeding or reapplication of study treatment after T4 until the time of completion of closure by layers of the exposed surgical field containing the TBS ($T_{Closure}$) without brisk bleeding or use of alternative hemostatic treatment after time of start of initial study treatment (T_{Start}) and until $T_{Closure}$.

Primary Efficacy Analysis

For primary efficacy analysis, only the data from Part II of the study (the randomized controlled part of the study) were used. VISTASEAL would be deemed superior to MC if the 2-sided test was statistically significant at the 5% level and VISTASEAL had a greater proportion of subjects with achievement of hemostasis by T4 than MC.

Secondary Endpoints

Secondary endpoints included achieving hemostasis at TBS by time points T2, T3, T5, T7, and T10; and TTH from ≤2 minutes to ≤10 minutes; and treatment failures, defined as:

- Persistent bleeding at the TBS beyond T4
- Breakthrough bleeding from the TBS that jeopardized subject safety according to the investigator's judgment at any moment during the 10-minute observational period and until $T_{Closure}$.
- Rebleeding at the TBS after the assessment of the primary efficacy endpoint at T4 and until closure
- Use of alternative hemostatic treatments or maneuvers (other than the study treatment) at the TBS during the 10-minute observational period and until $T_{Closure}$ or use of study treatment at the TBS beyond T4 and until $T_{Closure}$.

Secondary Efficacy Analysis

For secondary efficacy analysis, the TTH was measured from T_{Start} to the achievement of hemostasis at the TBS, or to the end of the 10-minute observation period when hemostasis had not yet been achieved; in latter case, the TTH was considered as censored at the end of the 10-minute observation period. The TTH was quantified in minutes according to its nominal time point.

If the TBS rebled but cessation of bleeding was again achieved at a later time point, then the effective hemostatic time point would be the last one where the cessation of bleeding happened. The TTH would be the time passed from T_{Start} to that last effective hemostatic time point.

Demographic Summary of IG1101

Table 35 in Section 7 includes a summary of demographics from Studies IG1101, IG1102, and IG1103. No difference in efficacy was identified among demographic groups. No pediatric subjects enrolled in this study.

Summary of Efficacy Results From IG1101

The results of the primary efficacy analysis of hemostasis at the TBS by T4 was performed using the ITT population in Part II of the study. The rate of hemostasis by T4 was statistically and significantly higher in the VISTASEAL group compared to the MC group (p-value<0.001) in each study center, indicating that VISTASEAL is superior to

MC and that the primary efficacy objective was met in the ITT population. Please see summary table of primary efficacy results in Section 7, Integrated Efficacy.

The results of secondary efficacy endpoints provided additional support for VISTASEAL as an effective local hemostatic agent in vascular surgery, with an acceptable safety profile.

Safety Summary of Study IG1101

Deaths

Deaths were reported in 4/168 (2.4%) of subjects who received VISTASEAL, the cause of death included myocardial infarction, gastrointestinal hemorrhage, and multiorgan failure. All deaths were considered unrelated to study treatment by investigators. No death occurred in the MC group. Deaths are further discussed in Section 8.4.1.

Nonfatal Serious Adverse Events

Thirty-four of 168 (20.2%) subjects in the VISTASEAL group (pooled safety population) experienced 60 SAEs versus 11 of 57 (19.3%) subjects in the MC group experienced 14 SAEs. In both the VISTASEAL group and the MC group, many of the SAEs were reported in a single subject.

In this study, all except five SAEs were considered by investigators not related to study treatment: four SAEs in the VISTASEAL group and one SAE in the MC treatment group. Three SAEs (two VISTASEAL subjects and one MC subject) were considered unlikely related to study treatment, and two SAEs from the VISTASEAL group were considered possibly related.

Adverse Events of Special Interest

Two subjects in the VISTASEAL group (2/168; 1.2%) and three subjects in the MC group (3/57; 5.3%) each experienced a vascular graft thrombosis event.

Adverse Drug Reactions

Section 8 includes a discussion of ADRs from all studies.

Study IG1101 Summary and Conclusions

Overall, data demonstrate the hemostatic efficacy of VISTASEAL and support the use of VISTASEAL as an effective local hemostatic agent in vascular surgery. Primary efficacy analysis of hemostasis at the TBS by T4 demonstrated that the rate of hemostasis at the TBS by T4 was statistically and significantly higher in the VISTASEAL treatment group (76.1%) as compared to the MC treatment group (22.8%; p-value <0.001) and that VISTASEAL was superior to MC. The results of secondary efficacy endpoints provided additional support for VISTASEAL as an effective local hemostatic agent in vascular surgery, with an acceptable safety profile.

Reviewer comment:

- *Please see the clinical review memo for the original BLA for details and in-depth discussion regarding the attribution of deaths and other AEs. Overall, the clinical reviewer assessed the clinical studies as not identifying new safety concerns, and assessed that evidence from all three clinical studies to support the benefit outweighs risk for the intended indication. I agree with the clinical reviewer's assessment in the original BLA review.*
- *Please see Section 8 for a summary and discussion of pooled safety information.*

6.4 Study #3 IG1102

Design

Study IG1102 was a Phase 3, multicenter, subject-blinded prospective randomized, controlled study to evaluate the safety and efficacy of VISTASEAL compared to SURGICEL as an adjunct to hemostasis during parenchymous tissue open surgeries. The secondary objectives evaluate hemostasis at other various time points. Subjects were randomized 1:1 to receive VISTASEAL or SURGICEL. SURGICEL is a sterile, absorbable, knitted fabric prepared by the controlled oxidation of regenerated cellulose that contains no biologic/fibrin sealant.

Primary Endpoint

The primary endpoint was the proportion of subjects achieving hemostasis at the TBS by T4 without occurrence of rebleeding and reapplication of study treatment after T4 and until $T_{Closure}$.

Primary Efficacy Analysis

For primary efficacy analysis, only the data from Part II of the study (the randomized controlled part of the study) were used.

The efficacy endpoint was analyzed by providing the ratio of hemostasis rates by T4 in the two treatment groups (VISTASEAL relative to SURGICEL). VISTASEAL would be considered noninferior to SURGICEL if the lower limit of the 95% CI exceeded 0.8.

Secondary Endpoints From Study IG1102

- Time to hemostasis, which was measured from T_{Start} to the achievement of hemostasis at the TBS, or to the end of the 10-minute observational period when hemostasis had not yet been achieved.
- Cumulative proportion of subjects achieving hemostasis at the TBS by each of the following time points: T2, T3, T5, T7, and T10.

Secondary Efficacy Analysis

For secondary efficacy analysis, the TTH was measured from T_{Start} to the achievement of hemostasis at the TBS, or to the end of the 10-minute observation period when hemostasis had not yet been achieved; in the latter case, the TTH was considered as censored at the end of the 10-minute observation period. The TTH was quantified in minutes according to its nominal time point.

If the TBS rebled but cessation of bleeding was again achieved at a later time point, then the effective hemostatic time point would be the last one where the cessation of bleeding happened. The TTH would be the time passed from T_{Start} to that last effective hemostatic time point.

Demographic Summary of IG1102

The study enrolled 320 adult and 5 pediatric subjects. Two pediatric subjects received VISATSEAL and three received SURGICEL. No pediatric subjects enrolled in Part II of the study. Table 35 in Section 7 includes a summary of demographics from Studies IG1101, IG1102, and IG1103. No difference in efficacy was identified among demographic groups.

Summary of Efficacy Results From Study IG1102

Primary Endpoint

The rate of hemostasis by T4 was 92.8% (103/111 subjects) in the VISTASEAL treatment group and was 80.5% (91/113 subjects) in the SURGICEL treatment group. The 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving VISTASEAL relative to SURGICEL was 1.152 (1.038, 1.279), indicating that VISTASEAL is noninferior to SURGICEL (i.e., the lower limit of the 95% CI. 0.8). Additionally, the lower limit of the 95% CI above 1 indicates that VISTASEAL is superior to SURGICEL. The rate of hemostasis by T4 was significantly higher in the VISTASEAL group compared to the SURGICEL group (p-value=0.010). Tabular results of primary endpoints from four clinical studies are included in Table 13.

Secondary Endpoints

Secondary endpoints supported the results of the primary analysis. In the ITT population, the rate of hemostasis by T3 was 85.6% (95/111 subjects) in the VISTASEAL group and was 62.8% (71/113 subjects) in the SURGICEL group. The 95% CI of proportion of subjects achieving hemostasis by T3 in subjects receiving VISTASEAL relative to SURGICEL was 1.362 (1.160, 1.600), indicating that VISTASEAL is superior to SURGICEL at T3. The rate of hemostasis by T3 was superior in the VISTASEAL group compared to the SURGICEL group (p-value<0.001). The median TTH was significantly shorter (p-value<0.001) in the VISTASEAL treatment group (2.0 minutes) compared to the SURGICEL treatment group (3.0 minutes), indicating that VISTASEAL is superior to SURGICEL. The results for cumulative

proportion of subjects achieving hemostasis at the TBS by T2, T5, T7, and T10 show a similar pattern as the primary efficacy analysis in favor of VISTASEAL.

Reviewer comment: Because no pediatric subjects enrolled in Part II (the randomized control part) of the study, they were not included in the ITT population or included in the efficacy evaluation of this study. Therefore, this study does not provide data to compare efficacy of VISTASEAL to SURGICEL in parenchymous surgery in pediatric subjects. VISTASEAL is not expected to work differently in children than in adults. Data from this study support efficacy of VISTASEAL in adults undergoing parenchymous surgery. Therefore, combined with pediatric Study 1405, efficacy data from this study in adults support efficacy in children.

Summary of Safety From Study IG1102

Deaths

A total of 10 deaths occurred in this Study IG1102. AEs with the outcome of death were more frequently reported in VISTASEAL group than the SURGICEL the group. There were seven (4.3%) deaths in the VISTASEAL group versus three (1.9%) in the SURGICEL group. All death outcomes were considered not related to study treatment by investigators and the Applicant. Death AEs are further discussed in Section 8.4.1.

Nonfatal Serious Adverse Events

Thirty out of 163 (18.4%) subjects in the VISTASEAL group experienced 78 SAEs, and 23 out of 162 (14.2%) subjects in the SURGICEL group experienced 38 SAEs. In the VISTASEAL group, 38/78 SAEs (48.7%) occurred in only single subjects. In the SURGICEL group, 30/38 SAEs (78.9%) were reported in only single subjects. Of the total 78 SAEs occurring in 30 VISTASEAL subjects in this study, the SAEs were considered not related to study treatment in all except 4 subjects in which the SAEs were considered unlikely related to study treatment; this included SAEs of pulmonary embolism and deep vein thrombosis considered as unlikely related to study treatment. All of the 38 SAEs occurring in 23 SURGICEL subjects were considered not related to study treatment.

Adverse Events of Special Interest

Three subjects in the VISTASEAL group (3/163; 1.8%) experienced a deep vein thrombosis. Of these, one of the thrombotic events was considered unrelated, and two were considered unlikely related to study treatment by investigators and the Applicant. One subject in the SURGICEL group (1/162; 0.6%) experienced a deep vein thrombosis that was considered unrelated to study treatment by the investigator.

Study IG1102 Summary and Conclusions

Overall, efficacy data are positive for VISTASEAL and support the use of VISTASEAL as an effective local hemostatic agent in parenchymous tissue (liver) surgery. Primary efficacy analysis of hemostasis at the TBS by T4 demonstrated that the rate of

hemostasis by T4 was statistically and significantly higher (p-value=0.010) in the VISTASEAL treatment group (92.8%), compared to the SURGICEL treatment group (80.5%). Additionally, data shows VISTASEAL is superior to SURGICEL.

The results of all secondary efficacy endpoints provided additional support for VISTASEAL as an effective local hemostatic agent in parenchymous tissue surgery.

6.5 Study #4 IG1103

Design

Study IG1103 was a Phase 3, multicenter, subject-blinded, prospective, randomized, controlled study to evaluate the hemostatic efficacy and safety of VISTASEAL compared to SURGICEL as an adjunct to hemostasis during open soft tissue surgery. The secondary objectives evaluate hemostasis at other various time points. Subjects were randomized 1:1 to receive VISTASEAL or SURGICEL.

Primary Endpoint in Study IG1103

The primary efficacy endpoint was the proportion of subjects achieving hemostasis at the TBS by T4 without occurrence of rebleeding and reapplication of study treatment after T4 and until $T_{Closure}$ without brisk bleeding and use of alternative hemostatic treatment after T_{Start} and until $T_{Closure}$.

Secondary Endpoints From Study IG1102

- Time to hemostasis, which was measured from T_{Start} to the achievement of hemostasis at the TBS, or to the end of the 10-minute observational period when hemostasis had not yet been achieved.
- Cumulative proportion of subjects achieving hemostasis at the TBS by each of the following time points: T2, T3, T5, T7, and T10.

Primary Efficacy Analysis

The primary efficacy endpoint was analyzed by providing the ratio of hemostasis rates by T4 in the two treatment groups (VISTASEAL relative to SURGICEL). VISTASEAL would be considered noninferior to SURGICEL if the lower limit of the 95% CI exceeded 0.8.

Secondary Efficacy Analysis

For secondary efficacy analysis, the TTH was measured from T_{Start} to the achievement of hemostasis at the TBS, or to the end of the 10-minute observation period when hemostasis had not yet been achieved; in latter case, the TTH was considered as censored at the end of the 10-minute observation period. The TTH was quantified in minutes according to its nominal time point.

If the TBS rebled but cessation of bleeding was again achieved at a later time point, then the effective hemostatic time point would be the last one where the cessation of

bleeding happened. The TTH would be the time passed from T_{Start} to that last effective hemostatic time point.

Demographic Summary of IG110

Eighteen pediatric subjects enrolled in this study: nine subjects in the VISTASEAL cohort and nine in the SURGICEL control. All pediatric subjects were enrolled in Part I other than one 15-year-old subject who received VISTASEAL in Part II of the study.

Table 35 in Section 7 includes a summary of demographics from Studies IG1101, IG1102, and IG1103. No difference in efficacy was identified among demographic groups.

Summary of Efficacy Results for Study IG1103

Primary Endpoint Results

The rate of hemostasis by T4 was 92.8% (103/111 subjects) in the VISTASEAL treatment group and 80.5% (91/113 subjects) in the SURGICEL treatment group. The 95% CI of proportion of subjects meeting the primary efficacy endpoint in subjects receiving VISTASEAL relative to SURGICEL was 1.152 (1.038, 1.279), indicating that VISTASEAL is noninferior to SURGICEL. Additionally, the lower limit of the 95% CI above 1 indicates that VISTASEAL is superior to SURGICEL. The rate of hemostasis by T4 was significantly higher in the VISTASEAL group compared to the SURGICEL group (p-value=0.010).

Secondary Endpoint Results

To control for multiple comparison/multiplicity, the superiority for the secondary endpoints were tested after the noninferiority for the primary efficacy endpoint was demonstrated. Secondary endpoints were analyzed according to the sequence described in Section 6.2.9 in the final study report. In the ITT population, the rate of hemostasis by T3 was 85.6% (95/111 subjects) in the VISTASEAL group and was 62.8% (71/113 subjects) in the SURGICEL group. The 95% CI of proportion of subjects achieving hemostasis by T3 in subjects receiving VISTASEAL relative to SURGICEL was 1.362 (1.160, 1.600), indicating that VISTASEAL is superior to SURGICEL at T3. The rate of hemostasis by T3 was superior in the VISTASEAL group compared to the SURGICEL group (p-value<0.001). The median TTH was significantly shorter (p-value <0.001) in the VISTASEAL treatment group (2.0 minutes) compared to the SURGICEL treatment group (3.0 minutes), indicating that VISTASEAL is superior to SURGICEL. The results for cumulative proportion of subjects achieving hemostasis at the TBS by T2, T5, T7, and T10 show a similar pattern as the primary efficacy analysis in favor of VISTASEAL.

Summary of Safety From Study IG1103

Deaths

A total of three deaths occurred in two (1.2%) VISTASEAL subjects and one (0.6%) SURGICEL subjects during the study. All death outcomes were considered not related to study treatment. See Section 8.4.1 for further details.

Nonfatal Serious Adverse Events

Seventeen out of 169 (10.1%) subjects in the VISTASEAL treatment group experienced 29 SAEs, and 18 out of 158 (11.4%) subjects in the SURGICEL treatment group experienced 27 SAEs. In the VISTASEAL treatment group, 19/29 (65.5%) SAEs were reported in only single subjects, while 20/27 (74.0%) SAEs were reported in only single subjects in the SURGICEL treatment group,

A total of 29 SAEs occurred in 17 subjects in the VISTASEAL treatment group in this study. Of these, all were considered not related by investigators, except for two SAEs (abdominal wound dehiscence and peritonitis) that were considered possibly related, and attributable to application technique. All of the 27 SAEs occurring in 18 SURGICEL-treated subjects were considered not related to study treatment.

Adverse Events of Special Interest

One subject in the VISTASEAL group (1/169; 0.6%) and one subject in the SURGICEL group (1/158; 0.6%) each experienced a deep vein thrombosis event.

Most Common Adverse Events in Study IG1103

Most common AEs were evaluated in an integrated summary of safety, included in Table 39 in Section 8.

Study IG1103 Summary and Conclusions

Overall, data demonstrate the hemostatic efficacy of VISTASEAL and support the use of VISTASEAL as an effective local hemostatic agent in soft tissue surgeries. Primary efficacy analysis of hemostasis rate by T4 demonstrated that VISTASEAL is noninferior to SURGICEL and that the rate of hemostasis by T4 in the VISTASEAL treatment group (82.8%) was higher, but not statistically superior (p-value=0.401) to the SURGICEL treatment group (77.8%). The results of all secondary efficacy endpoints provided additional support for VISTASEAL as an effective local hemostatic agent in soft tissue surgery.

Reviewer comment: Because only one pediatric subject enrolled in Part II of the study (the ITT population included in the efficacy analysis), this study alone does not provide adequate data to compare efficacy of VISTASEAL to SURGICEL in parenchymous surgery in pediatric subjects. VISTASEAL is not expected to work differently in children than in adults. Data from this study support efficacy of VISTASEAL in adults undergoing

soft tissue surgery. Therefore, combined with pediatric Study 1405, efficacy data from this study in adults supports efficacy in children.

7. INTEGRATED OVERVIEW INCLUDING EFFICACY

7.1 Integrated Tabular Overview of Demographics

Table 35. Subject Demographics in Primary Part II, ITT Population, IG1101, IG1102, and IG1103

ATC Level 4[a]	IG1101 VISTASEAL N=109 n (%)	IG1101 MC N=57 n (%)	IG1102 VISTASEAL N=111 n (%)	IG1102 SURGICEL N=113 n (%)	IG1103 VISTASEAL N=116 n (%)	IG1103 SURGICEL N=108 n (%)	Integrated (IG1102 + IG1103) VISTASEAL N=227 n (%)	Integrated (IG1102 + IG1103) SURGICEL N=221 n (%)
Sex – n (%)	-	-	-	-	-	-	-	-
Male	76 (69.7)	31 (54.4)	59 (53.2)	63 (55.8)	29 (25.0)	22 (20.4)	88 (38.8)	85 (38.5)
Female	33 (30.3)	26 (45.6)	52 (46.8)	50 (44.2)	87 (75.0)	86 (79.6)	139 (61.2)	136 (61.5)
Age (years)	-	-	-	-	-	-	-	-
Mean (SD)	63.72 (8.908)	62.04 (10.734)	59.87 (12.222)	57.71 (13.595)	48.51 (14.369)	46.72 (14.330)	54.07 (14.497)	52.34 (14.975)
Median	64.00	61.00	61.00	61.00	46.00	45.00	56.00	52.00
Min, max	44.0, 84.0	22.0, 82.0	25.0, 82.0	19.0, 84.0	15.0, 85.0	21.0, 84.0	15.0, 85.0	19.0, 84.0
Age category (years) - n (%)	-	-	-	-	-	-	-	-
≤11	0	0	0	0	0	0	0	0
12-17	0	0	0	0	1 (0.9)	0	1 (0.4)	0
18-64	58 (53.2)	32 (56.1)	70 (63.1)	76 (67.3)	98 (84.5)	90 (83.3)	168 (74.0)	166 (75.1)
≥65	51 (46.8)	25 (43.9)	41 (36.9)	37 (32.7)	17 (14.7)	18 (16.7)	58 (25.6)	55 (24.9)
65-84	51 (46.8)	25 (43.9)	41 (36.9)	37 (32.7)	16 (13.8)	18 (16.7)	57 (25.1)	55 (24.9)
≥85	0	0	0	0	1 (0.9)	0	1 (0.4)	0

ATC Level 4[a]	**IG1101 VISTASEAL N=109 n (%)**	**IG1101 MC N=57 n (%)**	**IG1102 VISTASEAL N=111 n (%)**	**IG1102 SURGICEL N=113 n (%)**	**IG1103 VISTASEAL N=116 n (%)**	**IG1103 SURGICEL N=108 n (%)**	**Integrated (IG1102 + IG1103) VISTASEAL N=227 n (%)**	**Integrated (IG1102 + IG1103) SURGICEL N=221 n (%)**
Ethnicity – n (%)	-	-	-	-	-	-	-	-
Hispanic or Latino	3 (2.8)	2 (3.5)	5 (4.5)	7 (6.2)	20 (17.2)	12 (11.1)	25 (11.0)	19 (8.6)
Not Hispanic or Latino	106 (97.2)	55 (96.5)	106 (95.5)	105 (92.9)	96 (82.8)	96 (88.9)	202 (89.0)	201 (91.0)
Not specified	0	0	0	1 (0.9)	0	0	0	1 (0.5)
Race – n (%)	-	-	-	-	-	-	-	-
White (Caucasian)	101 (92.7)	49 (86.0)	106 (95.5)	103 (91.2)	93 (80.2)	81 (75.0)	199 (87.7)	184 (83.3)
Black or African American	6 (5.5)	8 (14.0)	1 (0.9)	2 (1.8)	22 (19.0)	25 (23.1)	23 (10.1)	27 (12.2)
Asian	2 (1.8)	0	4 (3.6)	6 (5.3)	1 (0.9)	1 (0.9)	5 (2.2)	7 (3.2)
American Indian or Alaskan Native	0	0	0	1 (0.9)	0	1 (0.9)	0	2 (0.9)
Multiracial (no primary race)	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0
Not specified	0	0	0	1 (0.9)	0	0	0	1 (0.5)

Source: Table 5.1/2a of ISE in Module 5.3.5.3 and Table 14.1.2 of CSR IG1101, CSR IG1102, and CSR IG1103 in Module 5.3.5.1.
Abbreviations: ATC, Anatomical Therapeutic Chemical; MC, manual compression; N, study population; n, sample size

Table 36. Subject Demographics, Pediatric Study IG1405

Characteristic	VISTASEAL (n =95)	EVICEL (n =91)	Total (N=186)
Age (years) at randomization (n)	95	91	186
Mean (SD)	8.43 (6.108)	8.84 (6.320)	8.63 (6.199)
Median	9.40	10.30	9.80
Min – max	0.0-17.9	0.0-17.9	0.0-17.9
Age category – n (%)	-	-	-
≤27 days	4 (4.2%)	2 (2.2%)	6 (3.2%)
≥28 days - ≤23 months	19 (20.0%)	18 (19.8%)	37 (19.9%)
≥2 years - ≤11 years	34 (35.8%)	33 (36.3%)	67 (36.0%)
≥12 years - ≤17 years	38 (40.0%)	38 (41.8%)	76 (40.9%)
Sex – n (%)	-	-	-
Male	55 (57.9%)	61 (67.0%)	116 (62.4%)
Female[1]	40 (42.1%)	30 (33.0%)	70 (37.6%)
Pre-menarche	22 (55.0%)	17 (56.7%)	39 (55.7%)
Childbearing potential	18 (45.0%)	13 (43.3%)	31 (44.3%)
Pregnancy test - n (%)[2]	18	13	31
Positive	0 (0.0%)	0 (0.0%)	0 (0.0%)
Negative	18 (100%)	13 (100%)	31 (100%)
Ethnicity - n (%)	-	-	-
Hispanic or Latino	13 (13.7%)	11 (12.1%)	24 (12.9%)
Not Hispanic or Latino	82 (86.3%)	80 (87.9%)	162 (87.1%)
Race - n (%)	-	-	-
White	86 (90.5%)	89 (97.8%)	175 (94.1%)
Black or African American	6 (6.3%)	2 (2.2%)	8 (4.3%)
Asian	1 (1.1%)	0 (0.0%)	1 (0.5%)
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)
Multiple	1 (1.1%)	0 (0.0%)	1 (0.5%)
Other	1 (1.1%)	0 (0.0%)	1 (0.5%)

Characteristic	VISTASEAL (n =95)	EVICEL (n =91)	Total (N=186)
Height (cm)	-	-	-
n	94	90	184
Mean (SD)	123.96 (43.332)	125.16 (44.389)	124.54 (43.736)
Median	133.25	141.00	139.85
Min-max	45.0-196.0	35.0-195.0	35.0-196.0
Weight (kg)	-	-	-
N	93	90	183
Mean (SD)	35.78 (26.241)	37.87 (27.719)	36.81 (26.924)
Median	30.40	36.50	35.00
Min-max	2.4-110.0	2.2-106.0	2.2-110.0
BMI (kg/m²)	-	-	-
N	93	90	183
Mean (SD)	19.37 (5.929)	20.59 (7.458)	19.97 (6.734)
Median	18.07	18.69	18.45
Min-max	8.0-41.9	8.8-61.2	8.0-61.2

Source: Table 14.1.2.1 and Listing 16.2.4.1 of CSR IG1405
1 The percentages are based on the number of female subjects.
2 The percentages are based on the number of female subjects with childbearing potential.
Abbreviations: BMI, body mass index; max, maximum; min, minimum; N, study population; n, sample size

7.2 Dose

The concentration of VISTASEAL administered to all subjects in the three studies was the same; however, the volume of VISTASEAL administered was up to 6 mL in Study IG1101 (vascular surgery) and up to 12 mL in Studies IG1102 (parenchymous surgery) and IG1103 (soft tissue surgery). The actual volume of VISTASEAL applied varied for each individual subject and was based on the investigator's determination of the volume needed to achieve hemostasis at the TBS. The mean volume of VISTASEAL applied among all studies was 6.78 mL, with a median of 6.00 mL and a range of 0.3 to 18.0 mL.

7.3 Integrated Efficacy Results

Efficacy results were not pooled. VISTASEAL met its primary efficacy endpoint in each study, showing superior efficacy to MC in vascular surgery in adults in Study IG1101, noninferiority to SURGICEL in parenchyma and soft tissue surgery in Studies IG102 and IG1103, and noninferiority to EVICEL in pediatric Study IG1405. Section 6 includes a written summary of efficacy for each individual study.

Table 37 summarizes the primary efficacy endpoint results in each individual study:

Table 37. Summary of Primary Efficacy Endpoint Results, Intent-to-Treat Population, All Four Clinical Studies

Study ID	Study Treatment	Primary Endpoint Hemostasis at the TBS by T4 n/N (%)	Primary Endpoint Hemostasis at the TBS by T4 RR (95% CI)	Primary Endpoint Hemostasis at the TBS by T4 P-value	Primary Endpoint Hemostasis at the TBS by T4 Efficacy Result
IG1101	VISTASEAL	83/109 (76.1)	3.339 (2.047, 5.445)[1]	<0.001[2]	VISTASEAL is superior to MC
IG1101	MC	13/57 (22.8)	3.339 (2.047, 5.445)[1]	<0.001[2]	VISTASEAL is superior to MC
IG1102	VISTASEAL	103/111 (92.8)	1.152 (1.038, 1.279)[3]	0.010[2]	VISTASEAL is noninferior to SURGICEL. Additionally, the lower limit of the 95% CI above 1 indicates that VISTASEAL is superior to SURGICEL.

Study ID	Study Treatment	Primary Endpoint Hemostasis at the TBS by T4 n/N (%)	Primary Endpoint Hemostasis at the TBS by T4 RR (95% CI)	Primary Endpoint Hemostasis at the TBS by T4 P-value	Primary Endpoint Hemostasis at the TBS by T4 Efficacy Result
IG1102	SURGICEL	91/113 (80.5)	1.152 (1.038, 1.279)[3]	0.010[2]	VISTASEAL is noninferior to SURGICEL. Additionally, the lower limit of the 95% CI above 1 indicates that VISTASEAL is superior to SURGICEL.
IG1103	VISTASEAL	96/116 (82.8)	1.064 (0.934, 1.213)[3]	0.401[2]	VISTASEAL is noninferior to SURGICEL
IG1103	SURGICEL	84/108 (77.8)	1.064 (0.934, 1.213)[3]	0.401[2]	VISTASEAL is noninferior to SURGICEL
Integrated analysis (IG1102 + IG1103)	VISTASEAL	199/227 (87.7)	1.109 (1.021, 1.205)[3]	0.014[2]	VISTASEAL is noninferior to SURGICEL. Additionally, the lower limit of the 95% CI above 1 indicates that VISTASEAL is superior to SURGICEL.
Integrated analysis (IG1102 + IG1103)	SURGICEL	175/221 (79.2)	1.109 (1.021, 1.205)[3]	0.014[2]	VISTASEAL is noninferior to SURGICEL. Additionally, the lower limit of the 95% CI above 1 indicates that VISTASEAL is superior to SURGICEL.

Study ID	Study Treatment	Primary Endpoint Hemostasis at the TBS by T4 n/N (%)	Primary Endpoint Hemostasis at the TBS by T4 RR (95% CI)	Primary Endpoint Hemostasis at the TBS by T4 P-value	Primary Endpoint Hemostasis at the TBS by T4 Efficacy Result
IG1405	VISTASEAL	88/91 (96.7)	1.01 (0.96-1.07)[5]	<0.001[4]	VISTASEAL is noninferior to EVICEL
IG1405	EVICEL	83/87 (95.4)	1.01 (0.96-1.07)[5]	<0.0014	VISTASEAL is noninferior to EVICEL

Reviewer source: Summary of clinical efficacy document, page 37 of 59
Applicant source: Table 5.2/1.1 of ISE in Module 5.3.5.3 and Table 14.2.1/1 of CSR IG1101, CSR IG1102, and CSR IG1103 in Module 5.3.5.1, and Table 14.2.1.2.1 and Listing 16.2.6 of CSR IG1405
Note: Data for studies IG1101, IG1102, and IG1103 apply to Primary Part II of each study
[1] RR (Relative risk) was the ratio of proportion of subjects meeting the efficacy endpoint in the two treatment groups in the Primary Part (II) (VISTASEAL relative to MC)
[2] P-value was tested for superiority and was calculated from Fisher Exact Test.
[3] RR was the ratio of the proportion of subjects meeting the efficacy endpoint in the two treatment groups in the Primary Part (II) (VISTASEAL relative to SURGICEL)
[4] P-value was tested for noninferiority and was calculated from Cochran-Mantel-Haenszel Test stratified by study/surgery type
[5] Relative risk (RR) is the ratio of proportions of subjects meeting the efficacy endpoint in VISTASEAL versus EVICEL. For the overall category, RR is the common relative risk, stratified by type of surgery
Abbreviations: ITT, intent-to-treat; MC, manual compression; N, study population; n, sample size; RR, relative risk; TBS, target bleeding site

7.4 Subpopulations

No differences in efficacy were detected in subpopulations analyzed.

7.5 Efficacy Conclusions

Overall, data from clinical Studies IG1101, IG1102, IG1103, and pediatric Study IG1405 demonstrate the hemostatic efficacy of VISTASEAL in surgery types (parenchymous and soft tissue) that are most likely to be performed in children and support the application of VISTASEAL as an adjunct to hemostasis in pediatric subjects undergoing surgery.

8. Integrated Overview of Safety

8.1 Safety Assessment Methods

The Applicant included an integrated summary of safety in the original BLA submission that included Studies IG1101, IG1102, and IG1103 but did not integrate safety data from pediatric Study IG1405. The clinical reviewer and clinical analyst pooled AE data from datasets from all four Phase 3 clinical studies to compare safety in pediatric subjects to safety in adult subjects. AEs with similar terms were grouped together.

8.2 Safety Database

8.2.1 Studies/Clinical Studies Used to Evaluate Safety

Study IG1101 evaluated safety in adult subjects undergoing vascular surgery.

Studies IG1102, IG1103, and IG1405 evaluated safety in adult and pediatric subjects undergoing parenchyma and soft tissue surgery.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Among the 4 clinical studies, 1,063 subjects were assigned or randomized to specific study treatment. Among those, 593 subjects were assigned or randomized to receive VISTASEAL (ITT Population), 322 subjects were randomized to receive SURGICEL (ITT Population), 57 subjects were randomized to receive MC (ITT Population), and 91 subjects were randomized to receive EVICEL (ITT Population).

Due to two subjects who were initially randomized to SUGICEL in Study IG1103 but actually received VISTASEAL and eight subjects in pediatric Study IG1405 that did not receive either VISTASEAL or EVICEL, the safety population included 591 subjects treated with VISTASEAL, 320 subjects treated with SURGICEL, 57 subjects treated with MC, and 87 subjects treated with EVICEL. All subjects received treatment and are included in the safety population based on actual treatment received and used for safety analysis.

8.4 Safety Results

8.4.1 Deaths

A list of deaths among Studies IG1101, IG1102, and IG1103 is shown in Table 38. Thirteen of 500 (2.6%) subjects in the VISTASEAL treatment group, 4/320 (1.3%) subjects from the SURGICEL treatment group, and 0 subjects from the MC treatment group died. All the SAEs with a fatal outcome were considered unrelated to study treatment by the investigator and Applicant. The clinical review memo from the original BLA review includes details and an in-depth discussion regarding the deaths that occurred in Studies IG1101, IG1102, and IG1103.

Table 38. List of Death Reports, All Three Studies; N=500

Subject	Study	Hemostatic Agent	MedDRA Preferred Term	Days After Exposure
(b) (6)	IG1101	VISTASEAL	Myocardial infarction	41
(b) (6)	IG1101	VISTASEAL	Death (not otherwise specified)	10
(b) (6)	IG1101	VISTASEAL	Gastrointestinal hemorrhage	34
(b) (6)	IG1101	VISTASEAL	Multi-organ failure	2
(b) (6)	IG1101	VISTASEAL	Respiratory failure	3
(b) (6)	IG1102	VISTASEAL	Vena cava thrombosis	3
(b) (6)	IG1102	VISTASEAL	Cardiac arrest	5

Subject	Study	Hemostatic Agent	MedDRA Preferred Term	Days After Exposure
(b) (6)	IG1102	VISTASEAL	Hypotension	0
(b) (6)	IG1102	VISTASEAL	Respiratory failure	3
(b) (6)	IG1102	VISTASEAL	Hepatic failure	3
(b) (6)	IG1102	VISTASEAL	Septic shock	8
(b) (6)	IG1102	VISTASEAL	Brain injury	17
(b) (6)	IG1102	VISTASEAL	Hepatic necrosis	28
(b) (6)	IG1102	VISTASEAL	Liver abscess	28
(b) (6)	IG1102	VISTASEAL	Abdominal wound dehiscence	9
(b) (6)	IG1102	VISTASEAL	Intestinal perforation	9
(b) (6)	IG1102	VISTASEAL	Wound evisceration	9
[redacted]	IG1102	VISTASEAL	Sepsis syndrome	33
(b) (6)	IG1102	VISTASEAL	Deep vein thrombosis	40
(b) (6)	IG1103	VISTASEAL	Cardiac arrest	26
(b) (6)	IG1103	VISTASEAL	Respiratory failure	4
(b) (6)	IG1102	SURGICEL	Multi-organ failure	13
(b) (6)	IG1102	SURGICEL	Hemorrhage	0
(b) (6)	IG1102	SURGICEL	Venous injury	0
(b) (6)	IG1102	SURGICEL	Disseminated intravascular coagulation	0
(b) (6)	IG1102	SURGICEL	Cardiac arrest	0
(b) (6)	IG1102	SURGICEL	Hepatic failure	29
(b) (6)	IG1103	SURGICEL	Death (cause unknown)	44

Source: Clinical reviewer table with data extracted from Table 7-8 from ISS in Module 5.3.5.3
Abbreviations: ISS, integrated summary of safety; MedDRA, Medical Dictionary for Regulatory Activities. Note that days after exposure correlate to one day earlier than the study day because the product/surgery was considered Day 1.

Reviewer comment: Please refer to the original BLA memo for the clinical reviewer's discussion regarding the deaths that occurred in Studies IG1101, IG1102, and IG1103

and relatedness to VISTASEAL. I agree with the following summary written by the author of that memo:

> *"Although there were more deaths reported with [VISTASEAL] subjects than with the comparator SURGICEL, many of the deaths occurred more than 1 week from the time of exposure, and no discernable pattern was detected from review of the death narratives. Therefore, except for Subject* (b) (6) *(Vena Cava thrombosis occurring 5 days postexposure), which may be possibly related, the deaths are considered unrelated to the study drug."*

8.4.2 Nonfatal Treatment-Emergent Serious Adverse Events

Eight (8.8%) subjects in the VISTASEAL group reported 12 TESAEs and 9 (10.3%) subjects in the EVICEL group reported 11 TESAEs. All TESAEs were considered unrelated to IP/fibrin sealant.

Of the TESAEs in the VISTASEAL group (72/81 subjects), all were considered unrelated to study treatment by investigators except in 9 subjects (9/81 subjects). In the VISTASEAL group, five subjects had TESAEs that were considered unlikely related; these included postoperative wound infection, wound infection, abdominal abscess, deep vein thromboses, pulmonary embolism, postprocedural bile leak, and liver abscess. In the VISTASEAL group, four subjects had TESAEs that were considered possibly related to the study treatment: cellulitis, parvovirus B19 (B19V) positive test, abdominal wound dehiscence, and peritonitis. All TESAEs in the SURGICEL and all TESAEs in the MC treatment groups were considered unrelated to study treatment. Overall, there were no substantial differences in SAE incidences noted among treatment groups.

Reviewer comment: I agree with the following comment by Agnes Lim from the original BLA memo:

> *"In Study IG1102, the Sponsor considered SAEs of pulmonary embolism and deep vein thrombosis as unlikely to be related to study treatment. The pharmacovigilance reviewer disagrees and considers these SAEs as possibly related in the context of fibrin sealant use, which is well known to be thrombogenic. I agree that the SAEs of pulmonary embolism and deep vein thrombosis could be related."*

8.4.3 Common Adverse Events

The Applicant included Table 39 comparing the safety of pediatric subjects enrolled in studies that supported the original BLA (IG1101, IG1102, and IG1103) to adults in those studies.

Table 39. Treatment-Emergent Adverse Events Reported in ≥5% of Subjects Within a Treatment Group in Adult (>16 Years) Versus Pediatric (≤16 Years) Subjects, Safety Population

Preferred Term	VISTASEAL Adult N=489 n (%)	VISTASEAL Pediatric N=11 n (%)	SURGICEL Adult N=308 n (%)	SURGICEL Pediatric N=12 n (%)
Incision site pain	28 (5.7)	0	18 (5.8)	0
Procedural nausea	24 (4.9)	0	32 (10.4)	0
Tachycardia	23 (4.7)	0	31 (10.1)	0
Pruritus	23 (4.7)	0	21 (6.8)	1 (8.3)
Diarrhea	15 (3.1)	1 (9.1)	12 (3.9)	0
Procedural hemorrhage	12 (2.5)	1 (9.1)	6 (1.9)	0
Body temperature increased	11 (2.2)	0	1 (0.3)	1 (8.3)
Hyperglycemia	9 (1.8)	0	18 (5.8)	0
Hypophosphatemia	9 (1.8)	0	16 (5.2)	0
Upper respiratory tract infection	5 (1.0)	0	4 (1.3)	1 (8.3)
Urinary tract infection	3 (0.6)	0	13 (4.2)	1 (8.3)
Hypoalbuminemia	3 (0.6)	0	1 (0.3)	1 (8.3)
Electrolyte imbalance	3 (0.6)	0	0	1 (8.3)
Thrombocytosis	2 (0.4)	0	0	1 (8.3)
Vascular graft thrombosis	2 (0.4)	0	0	0
Clostridium difficile colitis	1 (0.2)	1 (9.1)	1 (0.3)	0
Procedural vomiting	0	1 (9.1)	2 (0.6)	0
Activated partial thromboplastin time prolonged	0	1 (9.1)	1 (0.3)	0
Productive cough	1 (0.2)	0	0	1 (8.3)
Influenza	1 (0.2)	0	0	1 (8.3)
Febrile neutropenia	0	1 (9.1)	0	1 (8.3)
International normalized ratio increased	0	1 (9.1)	0	0
Hepatic cyst	0	1 (9.1)	0	0
Bronchopneumonia	0	1 (9.1)	0	0
Erythema infectiosum	0	1 (9.1)	0	0
Urine abnormality	0	1 (9.1)	0	0
Laryngospasm	0	1 (9.1)	0	0
Adverse drug reaction	0	0	0	1 (8.3)
Teething	0	0	0	1 (8.3)
Bronchitis	0	0	0	1 (8.3)
Enterovirus infection	0	0	0	1 (8.3)
Rhinovirus infection	0	0	0	1 (8.3)
Viral upper respiratory tract infection	0	0	0	1 (8.3)
Lymphocyte count increased	0	0	0	1 (8.3)
Neuralgia	0	0	0	1 (8.3)
Hypoventilation	0	0	0	1 (8.3)
Pharyngeal erythema	0	0	0	1 (8.3)
Sneezing	0	0	0	1 (8.3)

Source: Post-text Table 5.3/1.22
Note: For each preferred term, subjects are counted only once. The incidence of a TEAE is presented for all treatment groups if the TEAE was reported in 5% or more of subjects within any treatment group.
Abbreviations: N, study population; n, sample size; TEAE, treatment-emergent adverse event

Reviewer comment: TEAEs that occurred more frequently in pediatric subjects occurred in only one pediatric subject each and included: procedural vomiting, prolonged

activated partial thromboplastin time febrile neutropenia, international normalized ratio increased, hepatic cyst, bronchopneumonia, erythema infectiosum, urine abnormality, and laryngospasm. Because only 10 pediatric subjects in these 3 studies combined received VISTASEAL, and because these TEAEs occurred in only 1 subject each, the data are not adequate to identify these TEAEs as additional risks in pediatric subjects compared to adults. Overall, more TEAEs occurred in the adult population. This data suggests that in the pediatric population VISTASEAL may be at least as safe as in adults. Additional data in children was obtained in the PREA PMR Study IG1405.

Comparison of Treatment-Emergent Adverse Events in Different Age Groups Among Patients Who Received VISTASEAL

Overall, most TEAEs occurred substantially more frequently in adults than in children. Table 40 lists all TEAES that occurred in children in all four studies that did not occur in adults.

Table 40. TEAES Occurring in Children but Not Adults, All Four Studies

Preferred Term	Preterm/ Newborn[1] N=4 n (%)	Preterm/ Newborn[1] N=4	Infants/ Toddlers[2] N=24 n (%)	Infants/ Toddlers[2] N=24	Children[3] N=37 n (%)	Children[3] N=37	Adolescents[4] N=37 n (%)	Adolescents[4] N=37	Adults[5] N=489 n (%)	Adults[5] N=489
Activated partial thromboplastin time prolonged	0 (0.0)	0	1 (4.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Blood magnesium decreased	0 (0.0)	0	0 (0.0)	0	1 (2.7)	1	0 (0.0)	0	0 (0.0)	0
Bronchopneumonia	0 (0.0)	0	1 (4.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Erythema infectiosum	0 (0.0)	0	0 (0.0)	0	1 (2.7)	1	0 (0.0)	0	0 (0.0)	0
Febrile neutropenia	0 (0.0)	0	0 (0.0)	0	1 (2.7)	1	0 (0.0)	0	0 (0.0)	0
Hemoglobin decreased	0 (0.0)	0	0 (0.0)	0	1 (2.7)	1	0 (0.0)	0	0 (0.0)	0
Hepatic cyst	0 (0.0)	0	0 (0.0)	0	1 (2.7)	1	0 (0.0)	0	0 (0.0)	0
International normalized ratio increased	0 (0.0)	0	1 (4.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Intra-abdominal fluid collection	0 (0.0)	0	1 (4.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Intussusception	0 (0.0)	0	1 (4.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Laryngospasm	0 (0.0)	0	1 (4.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Melaena	0 (0.0)	0	1 (4.2)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Procedural vomiting	0 (0.0)	0	0 (0.0)	0	2 (2.7)	2	0 (0.0)	0	0 (0.0)	0
Rash	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	1 (2.7)	1	0 (0.0)	0
Urine abnormality	0 (0.0)	0	0 (0.0)	0	1 (2.7)	1	0 (0.0)	0	0 (0.0)	0

Source: Original Table by Clinical Reviewer, adapted from original table made by FDA Clinical Analyst
[1] <28 dys
[2] 28 dys to <2 yrs
[3] 2 yrs - <12 yrs
[4] 12 yrs - <18 yrs
[5] ≥18 yrs
Abbreviations: dy, day; N, study population; n, sample size; TEAE, treatment-emergent adverse event; yr, year

Reviewer comment: As shown in the table, only one TEAE (procedural vomiting) occurred in two or more children that did not occur in adults. Based on this data, no new safety concerns were identified in children from pediatric Study IG1405.

8.4.4 Adverse Drug Reactions

The definition of ADR differed among the initial three studies that supported the original BLA and the pediatric Study IG1405. Studies IG1101, IG1102, and IG1103 defined ADR as an AE assessed by the investigator as definitely related, probably related, possibly related, or unlikely related. Pediatric Study IG1405 defined ADR as any AE that the investigator assessed as related.

Table 41 summarizes all ADRs that occurred in ≥1% in the safety population of the VISTASEAL treatment group in Studies 1101, 1102, and 1103. The majority of individual ADRs (preferred terms) in the VISTASEAL and SURGICEL treatment groups occurred in ≤2 subjects, and all the individual ADRs in the MC treatment group occurred in single subjects. Of the 64 subjects with any ADR reported in the VISTASEAL group, 1 subject had 1 event (preferred term: procedural pain) that was considered definitely related to study treatment. Thirteen subjects in the VISTASEAL group had any ADR that was considered possibly related to study treatment, and 50 subjects in the VISTASEAL group had any ADR that was considered unlikely related to study treatment. Of the 27 subjects with any ADR reported in the SURGICEL treatment group, 7 subjects had any ADR that was considered possibly related to study treatment, and 20 subjects had any ADR that was considered unlikely related to study treatment.

Table 41. ADRs That Occurred in ≥1% in the Safety Population of the VISTASEAL Treatment Group in All Three Studies[1]

MedDRA Preferred Term	Causal Relationship	n
Any ADR	Any	64
Any ADR	Unlikely	50
Any ADR	Possibly	13
Any ADR	Definitely	1
Procedural pain	Any	10
Procedural pain	Unlikely	8
Procedural pain	Possibly	1
Procedural pain	Definitely	1
Nausea	Unlikely	6

Source: Clinical reviewer table generated with data extracted from Tables 5.3/1.4 and 5.3/1.7 of ISS in Module 5.3.5.3
[1] N=500
Abbreviations: ADR, adverse drug reaction; ISS, integrated summary of safety; MedDRA, Medical Dictionary for Regulatory Activities; N, study population; n, sample size

Overall, there were no substantial differences in the ADR incidences noted among the VISTASEAL, SURGICEL, or MC groups. For ADRs that occurred in ≥1% in the safety population of the VISTASEAL treatment group, the most common ADRs were procedural pain and nausea (Table 41).

In pediatric Study IG1405, one (1.1%) subject from the VISTASEAL group reported a suspected ADR of procedural pain, which the investigator assessed as moderate in intensity. None of the subjects receiving EVICEL reported any suspected ADRs.

Reviewer comment: Pediatric Study IG1405 differs substantially in the number and nature of reported ADRs from Studies IG1101, IG1102, and IG1103 that enrolled mostly adults. This difference may be explained in part by the difference in definition of ADR among the studies, and in part by a difference in AE recording among investigators at study sites.

The definition of ADR differed among the initial three studies that supported the original BLA and the pediatric Study IG1405. Studies IG1101, IG1102, and IG1103 defined ADR as an AE assessed by the investigator as definitely related, probably related, or possibly related, or unlikely related. Pediatric Study IG1405 defined ADR as any AE that the investigator assessed as related. Across all study sites In pediatric Study IG1405 all but one AE were assessed as unrelated to IP. Although this reviewer assesses some AEs (e.g., events that may have been caused by thrombosis or adhesions such as myocardial infarction or bowel obstruction) that occurred in pediatric Study IG1405 as possibly or unlikely related, only a change in attribution to "related" would affect the number and nature of adverse reactions that occurred during pediatric Study IG1405. There were no AEs reported in pediatric Study IG1405 that this reviewer assesses as definitely related to study medication. Therefore, I do not recommend adding additional adverse reactions to the single identified adverse reaction of procedural pain identified in this study.

IG1405 study sites reported a notable difference in rates of AEs. See Section 6.1 that includes the rationale for concluding that the difference in reporting was due to different investigator understanding of whether an event that is expected due to underlying disease/surgical procedure should be recorded as a TEAE. This explanation is reasonable. This reviewer assesses the differences in AE reporting as not decreasing the ability of the study to support safety of VISTASEAL for use in children.

8.5 Additional Safety Evaluations

8.5.1 Immunogenicity

No immunogenicity occurred with the VISTASEAL treatment in Studies IG1101, IG1102, or IG1103. Pediatric Study IG1405 did not assess immunogenicity.

8.6 Safety Conclusions

Overall, VISTASEL, SURGICEL, EVICEL, and MC were well-tolerated among subjects undergoing vascular, parenchymous, and soft tissue surgeries. The following are key conclusions from the evaluation of safety in the four clinical studies:

- A total of 591 subjects were exposed to VISTASEAL, 320 subjects were treated with SURGICEL, 87 subjects received EVICEL, and 57 subject received MC treatment.
- The demographics of subjects was generally similar across all four studies. Subject demographics within each individual study did not indicate notable demographic differences among treatments with the exception of age.
- For Studies IG1101, IG1102, and IG1103, the proportions of subjects for whom TEAEs were reported were not very different among the treatment groups (VISTASEAL, 83.8%; SURGICEL, 86.9%; and MC, 77.2%). The most frequently reported TEAEs in these studies were typical of open surgeries, and the most common TEAEs in the three treatment groups were similar.
- For pediatric Study IG1405, 46 TEAEs were reported in 24 (26.4%) subjects in the VISTASEAL group, and all TEAEs except 1 occurring in one subject (1.1%) were considered unrelated to either fibrin sealant. A total of 38 TEAEs were reported in 16 (18.4%) subjects in the EVICEL group; all TEAEs were considered unrelated to treatment.
- For Studies IG1101, IG1102, and IG1103 in the VISTASEAL treatment group, 64/500 (12.8%) subjects experienced an ADR compared with 27/320 (8.4%) subjects in the SURGICEL treatment group and 3/57 (5.3%) subjects in the MC group. The majority of ADRs in each treatment group were considered unlikely related to study treatment. No substantial differences in specific ADR incidences were noted among treatment groups.
- For pediatric Study IG1405, one (1.1%) subject in the VISTASEAL treatment group reported a suspected ADR; no suspected ADRs were reported in the EVICEL treatment group.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

There were no reproduction or pregnancy studies.

9.1.2 Use During Lactation

There were no studies on the effects on lactation.

9.1.3 Pediatric Use and Pediatric Research Equity Act Considerations

This submission establishes the safety, efficacy, and dose of VISTASEAL for use in the pediatric population.

9.1.4 Immunocompromised Subjects

There were no studies in immunocompromised subjects.

9.1.5 Geriatric Use

No new information was reviewed during this submission regarding geriatric use. The clinical reviewer for the original BLA stated that overall, there was no pattern suggesting a unique safety concern for the elderly subjects. VISTASEAL was safe and well tolerated in elderly subjects.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not Applicable

10. CONCLUSIONS

VISTASEAL has been demonstrated to be effective as an adjunct to hemostasis for mild to moderate bleeding in adult and pediatric patients (0 to <18 years) undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical. There do not appear to be safety concerns in children that have not been identified in adults and included in the labeling. Expansion of the indication to include patients aged 0 to less than or equal to 18 years is recommended.

The PREA PMR was adequately addressed/satisfied completely. No postmarketing study is required.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Risk-benefit considerations are summarized in Table 42.

Table 42. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Surgery may create large areas of bleeding that must be addressed before surgical closure. Incomplete hemostasis can lead to surgical complications such as mild to life-threatening bleeding, hematomas, infection, and wound dehiscence.	VISTASEAL has demonstrated safety and efficacy for use as an adjunct to hemostasis in parenchymal (liver), soft tissue, and vascular surgery in adults, hepatic, and soft tissue surgery in children aged 0 to <18 years.
Unmet Medical Need	There are several FDA approved fibrin sealant products and devices available for use as an adjunct to hemostasis in various surgical settings.	There is no unmet medical need.
Clinical Benefit	The indication for use of VISTASEAL as an adjunct to hemostasis for mild to moderate bleeding in patients undergoing surgery when control of bleeding by standard surgical techniques (such as suture, ligature, and cautery) is ineffective or impractical is supported by the results of clinical Studies IG1405, IG1101, IG1102 and IG1103. Fibrin sealant products, when used as adjuncts to hemostasis, have not been able to demonstrate a clinical benefit based on mortality or morbidity endpoints. For this reason, CBER has accepted the surrogate endpoints of percent of subjects achieving hemostasis at a defined time point as acceptable primary endpoints for licensure.	VISTASEAL has demonstrated clinical benefit for use as an adjunct to hemostasis in adult surgery, per the primary endpoint, hemostasis at 4 minutes, without rebleeding prior to surgical closure.
Risk	Because VISTASEAL contains human thrombin and human fibrinogen, there are theoretical risks of hypercoagulability, transmitted infection from donors, and immunogenicity. None of these risks were identified as related to VISTASEAL the clinical studies conducted to support the requested indication. Inadvertent intravenous administration of VISTASEAL can lead to life-threating thromboembolism and DIC. This event has occurred with other fibrin sealant product but has not been reported with VISTASEAL. Administration of VISTASEAL using the spray device carries a potential risk of air embolism if used inappropriately. This risk has been reported for a different fibrin sealant but not with VISTASEAL.	Evidence from pivotal clinical studies and postmarketing reporting indicates that the risks associated with the use of VISTASEAL occur rarely if at all. Clinical study evidence strongly supports efficacy of VISTASEAL as an adjunct to hemostasis for mild to moderate bleeding during surgery. Therefore, the benefit of VISTASEAL outweighs the potential risk.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	Postmarketing reports include cases of postoperative adhesions that may have been due to VISTASEAL.	
Risk Management	VISTASEAL labeling adequately identifies the risks. Postmarketing reporting is available and encouraged.	Routine postmarketing monitoring could detect thromboembolic events, allergic adverse events, and adhesions. Labeling and medical provider education may prevent or detect a potential for air embolism. Only medical providers trained in proper application technique and identification of adverse reactions should apply VISTASEAL. The training is expected to be part of routine surgical training.

Source: Original table by clinical reviewer; includes content identified in prior clinical review memos of human fibrin sealant
Abbreviations: DIC, disseminated intravascular coagulation (DIC)

11.2 Risk-Benefit Summary and Assessment

Data submitted to this BLA supplement establish an acceptable benefit-risk profile for children aged 0 to <18 years.

11.3 Discussion of Regulatory Options

The Applicant submitted adequately designed and well-controlled studies with an acceptable clinically meaningful primary endpoint. These studies demonstrate the safety and efficacy of VISTASEAL for use in the pediatric population as an adjunct to hemostasis of mild to moderate bleeding in parenchymal (liver) and soft tissue (fat, connective tissue, muscle) surgery. These surgeries adequately represent the types of surgeries that are likely to be performed in children if VISTASEAL is approved for the general surgical indication in pediatrics as it is currently approved in adults. I recommend approval of expanding the indication of VISTASEAL (as an adjunct to hemostasis for mild to moderate bleeding in patients undergoing surgery when control of bleeding by standard surgical techniques [such as suture, ligature, and cautery] is ineffective or impractical) to include pediatric patients ages 0 to 18 years.

11.4 Recommendations on Regulatory Actions

I recommend that STN 125640/220 be approved.

11.5 Labeling Review and Recommendations

Changes to the label include:

- Updates to the Indications and Usage (Section 1) to expand the age to patient aged 0 to 18 years
- Updates to the Adverse Reactions (Section 6), to include
  - Data from pediatric Study IG1405 and
  - Adverse reactions reported postmarketing (adhesions)
- Updates to the Pediatric Use (Section 8.4) to state
  - The safety and effectiveness of VISTASEAL have been established in pediatric patients as an adjunct to hemostasis during surgery. The use of VISTASEAL for this indication is supported by evidence from adequate and well-controlled studies for assessment of safety and efficacy in pediatric patients in the following age groups: 4 neonates (aged ≤ 27 days), 24 infants (aged ≥ 28 days to 23 months), 39 children (aged 2 years to < 12 years) and 39 adolescents aged 12 years to < 18 years of age
- Updates to the Clinical Studies (Section 14) to include data from pediatric study IG1405
- Updates to Patient Counseling Information (Section 17) to include warnings and precaution

11.6 Recommendations on Postmarketing Actions

No postmarketing commitments or requirements are recommended.