14 December 2023
EMA/56893/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

VeraSeal

International non-proprietary name: Human fibrinogen / Human thrombin

Procedure No. EMEA/H/C/004446/II/0027

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Table of contents

List of abbreviations

ADR	adverse drug reaction
AE	adverse event
aPTT	activated partial thromboplastin time
B19V	parvovirus B19
CBC	complete blood count
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CSR	clinical study report
EDC	electronic data capture
FS Grifols	Fibrin Sealant Grifols
GPV	Global Pharmacovigilance
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HTC	haemostatic time category
IgG	immune globulin G class
IgM	immune globulin M class
INR	international normalised ratio
IP	investigational product
ISS	integrated summary of safety
ITT	intent-to-treat
MC	manual compression
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NA	not applicable
NHTC	non-haemostatic time category
OR	odds ratio
PP	per-protocol
PT	Preferred Term
RNA	ribonucleic acid
RR	risk ratio
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
T_4	haemostatic assessment at 4 minutes following T_{Start}
TBS	target bleeding site
$T_{closure}$	time of completion of the surgical closure by layers of the exposed surgical field containing the TBS
TEAE	treatment-emergent adverse event
T_{start}	time of start of initial study treatment (FS Grifols, Surgicel, or MC) application
TTH	time to haemostasis

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Instituto Grifols, S.A. submitted to the European Medicines Agency on 25 May 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of children for VeraSeal, based on final results from study IG1405; this is a prospective, randomized, active-controlled, single-blind, parallel group clinical trial to evaluate the safety and efficacy of VeraSeal as an adjunct to haemostasis during surgery in paediatric subjects. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 6.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0052/2021on the agreement of a paediatric investigation plan (PIP).

The PDCO issued an opinion on compliance for the PIP P/0052/2021.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Daniela Philadelphy Co-Rapporteur: Ewa Balkowiec Iskra

Timetable	Actual dates
Submission date	25 May 2023
Start of procedure:	17 June 2023
CHMP Rapporteur Assessment Report	11 August 2023
PRAC Rapporteur Assessment Report	21 August 2023
CHMP Co-Rapporteur Assessment	16 August 2023
PRAC members comments	23 August 2023
PRAC Outcome	31 August 2023
CHMP members comments	4 September 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 September 2023
Request for supplementary information (RSI)	14 September 2023
CHMP Rapporteur Assessment Report	14 November 2023
PRAC Rapporteur Assessment Report	20 November 2023
PRAC Outcome	30 November 2023
CHMP members comments	04 December 2023
Updated CHMP Rapporteur Assessment Report	07 December 2023
Opinion	14 December 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The human fibrin adhesion system constitutes the last phase of the physiological blood coagulation system leading to the formation of a semi-rigid fibrin clot. Fibrinogen, the main structural protein in the blood responsible for forming clots, is proteolytically cleaved and converted into fibrin monomers by thrombin. The fibrin monomers then polymerize to form insoluble fibrin. Thrombin also activates endogenous factor XIII that catalyses the formation of covalent bonds between molecules of fibrin to form a cross-linked clot capable of resisting dissolution. Calcium ions (Ca++) are required for most reactions that lead to the generation of active thrombin. The clot adheres to a variety of proteins, such as collagen, fibronectin, von Willebrand factor, and cell surface receptors, contributing to anchoring the fibrin clot to the injured site. As wound healing progresses, increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated.

The use of human plasma proteins as tissue sealants dates back to early last century. The concept of using plasma fibrinogen mixed with thrombin to form a biological adhesive was reported approximately 70 years ago. Commercial concentrates rich in clottable fibrinogen became available in Europe in the late 1970s, and, more recently, commercial fibrin sealant (FS) products were licensed for use in the United States of America (USA). Fibrin sealants may be used in various diseases and clinical situations, and actual products may differ in their composition, application sets, and technique of use. These products have been used in a large variety of surgical fields, including but not limited to, cardiac and vascular surgery, thoracic surgery, neurosurgery, plastic and reconstruction surgery, gastrointestinal surgery,

hepatic and splenic surgery, and dental surgery. Practical applications of FS products in orthopaedic surgery, interventional radiology, and minimally invasive endoscopy are growing.

Intended benefit of the FS application is to support local haemostasis, to "glue" surface of injured tissues in order to obtain adaptation or sealing of surfaces, to support sutures, or to improve repair or healing.

Disease or condition

Surgical approaches are receiving increasing attention as a way to solve many global public health problems. Data from the World Bank reported that in 2002, an estimated 164 million disability-adjusted life years, representing 11% of the entire disease burden, were attributable to surgically treatable conditions. In practice, fibrin sealants have been demonstrated to be efficacious in controlling slowly bleeding foci, diffuse oozing, bleeding from needle puncture sites, lymphatic leaks, serous fluid collections, and diffuse parenchymal organ haemorrhage.

State the claimed the therapeutic indication

Supportive treatment in adults and children where standard surgical techniques are insufficient:

- for improvement of haemostasis.

- as suture support: in vascular surgery.

Epidemiology

A study which obtained surgical data for 56 (29%) of 192 WHO member states estimated that 234.2 (95% CI 187.2– 281.2) million major surgical procedures are undertaken every year worldwide or approximately one operation annually for every 25 human beings alive. In view of the high death and complication rates of major surgical procedures, surgical safety should now be a substantial global public health concern. Many risk factors have been associated with surgery complications. Some are preoperative patient characteristics, others are related to the type and severity of the disease itself and a third group are related to the type and extent of the surgical procedure.

Clinical presentation, diagnosis and stage/prognosis

The fibrin adhesion system initiates the last phase of physiological blood coagulation. Conversion of fibrinogen into fibrin occurs by the splitting of fibrinogen into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is activated from factor XIII by thrombin, cross links fibrin. Calcium ions are required for both, the conversion of fibrinogen and the cross linkage of fibrin. As wound healing progresses, increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated.

Management

Conventional procedures used to control bleeding include the use of direct pressure, sutures, pledges, and/or electrocautery. Absorbable haemostatic agents such as bovine gelatine power and sponges, and haemostatics agents made from bovine collagen and oxidised cellulose are also used for stopping bleeding. Additionally, products containing thrombin and/or fibrinogen are used to assist body's natural clotting mechanism to achieved haemostasis. The versatility of FS is due to its capacity to cause blood to clot, creating a sealing barrier as well as gluing tissues together.

2.1.2. About the product

VeraSeal is a frozen, solvent/detergent treated and double-nanofiltered fibrin sealant (FS) consisting of two components: fibrinogen and thrombin; both derived from pooled human plasma. Thrombin contains human albumin as excipient. The product is presented in a two syringes, each syringe contains equal amounts of frozen fibrinogen and thrombin (total volume package sizes are 2ml, 4ml, 6ml and 10ml) which are held together by a syringe holder designed by Grifols. An applicator tip is supplied. A spray applicator (gas-assisted spray applicator) is an optional accessory and is provided separately.

VeraSeal was approved in 2017 for the use in adults after the review of three pivotal studies in parenchymous organ, soft tissue and vascular surgery.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical investigation programme has been designed with taking the Guideline on the Clinical Investigation of Plasma Derived Fibrin Sealant/Haemostatic Products (CPMP/BPWG/1089/00) into account.

The PDCO adopted on 26 April 2023 an opinion confirming the compliance of all studies in the agreed paediatric investigation plan as set out in the latest Agency's Decision (P/0052/2021) of 27 January 2021.

2.1.4. General comments on compliance with GCP

The MAH has submitted a statement that all clinical trials were carried out meeting the ethical requirements of Directive 2001/20/EC.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The active substance of VeraSeal is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, human fibrinogen / human thrombin are not expected to pose a risk to the environment in accordance with the Guideline on environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00).

2.2.2. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of human fibrinogen / human thrombin.

Considering the above data, human fibrinogen / human thrombin is not expected to pose a risk to the

environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

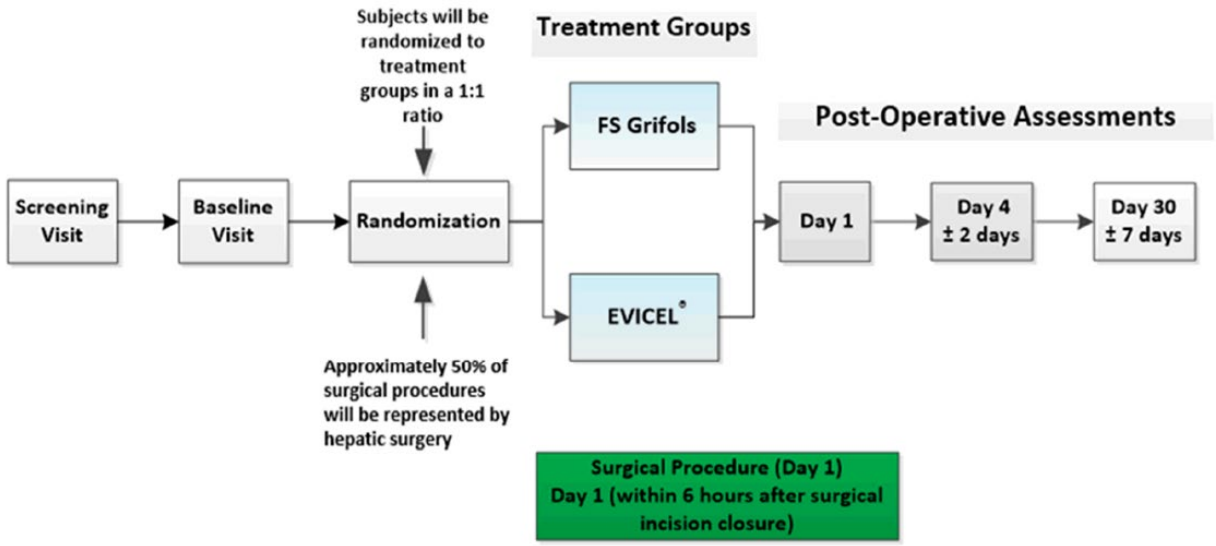
The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study no.	Phase	Surgery Type	Active Control	Hypothesis testing	Target Bleeding Site Intensity	Primary Efficacy Endpoint
IG1101	3	Vascular	Manual compression	Superiority	Moderate	Proportion of subjects achieving hemostasis (Yes/No) at the target bleeding site by T_4
IG1102	3	Parenchymous (hepatic)	Surgicel	Non-inferiority	Moderate	
IG1103	3	Soft tissue	Surgicel	Non-inferiority	Moderate	
IG1405	3b	Parenchymous (hepatic) and soft tissue	EVICEL	Non-inferiority	Mild or Moderate	

Single pivotal Phase 3b study IG1405 was submitted to support the extension of indication application of VeraSeal (Fibrin Sealant Grifols) to the paediatric population.



2.4. Clinical efficacy

2.4.1. Main study

IG1405 - A Prospective, Randomized, Active-Controlled, Single-blind, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during Surgery in Pediatric Subjects

Methods

Study participants

Inclusion Criteria

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

Pre-operative:

1. Less than 18 years of age.

2. Required an elective (non-emergent), open (non-laparoscopic), pelvic, abdominal, or thoracic (non-cardiac) 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 trial and provide written informed consent for the subject. In addition, assent was obtained from paediatric subjects who possessed the intellectual and emotional ability to comprehend the concepts involved in the clinical trial.

Intraoperative:

4. Presence of an appropriate parenchymous or soft tissue target bleeding site (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 the 5-point validated bleeding severity scale shown in Table 1.

Exclusion Criteria

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

Pre-operative:

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 (e.g., oral, injectable or implanted hormonal methods of contraception, placement of an intrauterine device or intrauterine system, condom or occlusive cap with spermicidal foam/gel/film/cream/suppository, male sterilization, or true abstinence) throughout the study.

True abstinence: When this was in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal were not acceptable methods of contraception.).

6. Subjects previously enrolled in clinical trials with VeraSeal (FS Grifols).

7. Subjects concurrently participating, or during the study had planned to participate, in any other investigational device or medicinal product study.

Intraoperative:

8. 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).

9. 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 1).

10. The TBS was in an actively infected surgical field.

11. Occurrence of major intraoperative complications that required resuscitation or deviation from the planned surgical procedure.

12. Application of any topical haemostatic agent on the resection surface of parenchyma or soft tissue prior to application of the IP.

Treatments

VeraSeal (FS Grifols)

Subjects randomized to receive VeraSeal were administered the IP intraoperatively. An initial volume of IP 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 haemostatic effect was considered incomplete, additional amounts of IP 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 IP intraoperatively. An initial volume of IP 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 haemostatic effect was considered incomplete, additional amounts of IP 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.

Objectives

The primary efficacy objective of the study was to evaluate if VeraSeal is non-inferior to EVICEL in terms of the proportion of subjects achieving haemostasis at the TBS by 4 minutes (T4) from the start of TStart with no occurrence of rebleeding until TClosure.

The secondary efficacy objectives were:

• To determine the cumulative proportion of subjects achieving haemostasis at the TBS by the defined observation time points of T7 and T10

• To determine prevalence of treatment failures

The exploratory objectives were:

• To determine the proportion of subjects achieving at least 1 point decrease in bleeding intensity according to the 5-point validated bleeding severity scale (Table 1) 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 (Table 1) at the defined observation time points of T4, T7, and T10

The safety objective was to evaluate the safety and tolerability of VeraSeal in paediatric subjects undergoing surgery.

Table 1. Validated bleeding severity scale

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[a]	>50.0

[a] Systemic resuscitation is required (e.g., volume expanders, vasopressors, blood products, etc).

Source: (Lewis 2016)

Outcomes/endpoints

Primary endpoint

The primary efficacy endpoint was defined as haemostasis at the TBS by the 4-minute observation time point T4, with no occurrence of rebleeding requiring further haemostatic intervention until the completion of the surgical closure (TClosure).

Secondary endpoints

• Haemostasis by time points T7 and T10 were defined similarly as haemostasis by T4.

• Treatment failure was to be reported if at least one of the following conditions applied:

• persistent bleeding at the TBS beyond T4,

• breakthrough bleeding of Grade 3 or 4 at the TBS jeopardizing subject's safety at any moment during the 10-minute observation period and until TClosure,

• the use of alternative topical haemostatic agents or maneuvers (other than the study treatment) at the TBS during the 10-minute observation period and until TClosure or use of study treatment at the TBS beyond the assessment of the primary efficacy endpoint at T4 and until TClosure,

• rebleeding at the TBS after T4 and until Tclosure.

Exploratory endpoints

• Achievement of at least 1 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

• 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

Sample size

The sample size of 172 subjects was calculated to provide a power of at least 80% to demonstrate non-inferiority of VeraSeal relative to EVICEL in parenchymous and soft tissue surgery. Assuming a true response rate of 80% for both the VeraSeal and the EVICEL group, a sample size of 172 subjects (86 subjects in the VeraSeal treatment group and 86 subjects in the EVICEL treatment group) was found to give a power of at least 80% to establish non-inferiority, defined as a lower bound of the 95% CI for the ratio of the proportion of subjects with haemostasis success by T4 in the 2 treatment groups (VeraSeal relative to EVICEL) above 0.80.

Randomisation

Subjects satisfying all pre-operative enrolment criteria were randomized in a 1:1 ratio into the VeraSeal or EVICEL treatment groups. Randomization was planned to be stratified by type of surgery (i.e., parenchymous versus soft tissue surgery) and age groups (i.e., 12-17 years, 2-11 years, 28 days-23 months, and 0-27 days). The investigator site pharmacy was required to use an IRT system to obtain the randomization number and the corresponding assigned treatment (VeraSeal or EVICEL).

At the beginning of the surgical procedure, before any TBS identified, all materials needed for VeraSeal or EVICEL application were required to be ready for use. If the subject met the intraoperative eligibility criteria, a randomization number would be recorded in the subject's source documents and electronic Case Report Form (eCRF). If the subject did not meet the intra-operative eligibility criteria, the study drug prepared by the pharmacist would remain unused and discarded according to the respective site standard procedures. In this case, the IRT system was set up to automatically assign the same treatment to the next subject enrolled in the same stratum.

Blinding (masking)

The study was designed to be single-blinded. Treatment assignment for subjects participating in the study were intended to be blinded from the sponsor, except for personnel from study drug supply groups. Treatment allocation was planned to only be unblinded as necessary within Grifols Global Pharmacovigilance group for subjects that experience a serious and unexpected ADR, and reported according to defined procedure.

Statistical methods

Analysis sets

Intent-to-Treat (ITT) population: all randomized subjects, regardless of meeting intra-operative enrolment criteria and regardless of administration of the IP to the subject.

Modified Intent-to-Treat (mITT) population: all subjects in the ITT population fulfilling intraoperative enrolment criteria, and thus treated with any amount of IP.

Per-Protocol (PP) population: all subjects in the mITT population who did not have any major protocol deviations (determined at a data review meeting prior to unblinding) which could impact the primary efficacy endpoint.

Safety population: subjects who receive any amount of IP.

Primary efficacy analysis

The primary efficacy analyses were performed using the Cochran-Mantel-Haenszel (CMH) test stratified by type of surgery (i.e., parenchymous versus soft tissue surgery) on the mITT population.

The pooled ratio RR of the proportion of subjects meeting the primary efficacy endpoint in the 2 treatment groups (VeraSeal relative to EVICEL) and its 2-sided asymptotic 95% CI was provided. Non-inferiority was declared if the lower limit of the 95% CI exceeded 0.8, corresponding to the following hypotheses:

$$H_0: RR < 1 - M,$$
$$H_1: RR \geq 1 - M,$$

where $1 - M = 0.8$.

After establishing non-inferiority of VeraSeal to EVICEL, superiority could be additionally claimed if the 95% CI for the ratio was entirely above 1.
If any missing haemostatic assessment at TBS at T4 for a randomized subject occurred, it was treated as non-haemostasis in the primary efficacy analysis.

Sensitivity analyses for primary efficacy comparisons

As a sensitivity analysis the primary efficacy endpoint was planned to be analysed based on non-missing haemostatic assessments at T4.
Additionally, the primary efficacy endpoint was analyzed using the PP population and ITT population. Subjects in both treatment groups in the ITT population not meeting the intra-operative criteria and not receiving the study treatment, were deemed as not achieving haemostasis for the primary efficacy endpoint.
A sensitivity analysis for the primary efficacy endpoint using mITT was performed for the subgroups based on the use of different applicators (Fibrijet device up to 30 November 2019, VistaSeal Dual Applicator thereafter), to compare VeraSeal-treated subjects with either type of applicator device vs the Evicel treatment group. A subgroup analysis by surgery type was provided for this by applicator type analysis.
Considering that the haemostasis assessment may not be performed exactly at the scheduled time point, as supportive analyses, the haemostasis assessment data at each time point was classified into the appropriate category based on the time window in the table below, according to the elapsed time of

haemostasis assessment from the start of initial treatment application (TStart). The three resulting endpoints describing haemostasis at T4, T7 and T10, were analyzed using CMH tests.

Scheduled Event	Time Window (MM:SS)
T_4 (4 minutes from start of application)	<=4:10
T_7 (7 minutes from start of application)	>=4:11 to <=7:10
T_{10} (10 minutes from start of application)	>=7:11 to <=10:10

If multiple haemostasis assessments fell within the same time window, for purpose of the supportive analyses, the following two scenarios were considered:
(a) the first haemostasis assessment was selected;
(b) the last haemostasis assessment was selected.
If there was no haemostasis assessment within a specific time window, the last haemostasis assessment within the previous time window was carried forward. If there was no haemostasis assessment within the first time window (<=4:10), the haemostasis assessment was deemed non-haemostasis success at T4.

Secondary efficacy analysis
The cumulative proportions of subjects achieving haemostasis by T7 and by T10, were similarly analyzed as the primary efficacy endpoint using CMH tests.
The proportion of subjects with treatment failures was summarized and analyzed using CMH test.

Exploratory efficacy analysis

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 by each of the defined observation time points (i.e., T4, T7 and T10) were analyzed using CMH test stratified by type of surgery (i.e., hepatic versus soft tissue surgery).
Also, an ordered categorical analysis of the haemostatic status at each of the assessment time points (i.e., T4, T7 and T10) was presented. For this, the subjects were assigned to 1 of 4 categories on the basis of their time to haemostasis (0 to ≤4 minutes; >4 to ≤7 minutes; >7 to ≤10 minutes; >10 minutes). The comparison between treatment groups was done using an ordinal logistic model assuming proportional odds.
Change from baseline in bleeding intensity according to the 5-point validated bleeding severity scale at the defined observation time points (i.e., T4, T7 and T10) were summarized.

Subgroup analyses
For primary efficacy endpoint, subgroup analyses were provided for surgery type, age group, gender, race, baseline TBS bleeding intensity, and TBS size category.

Results

Participant flow

Table 2. Subject disposition – All screened subjects

	FS Grifols 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%)
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%)
Sponsor's Termination of the Trial	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%)

ITT=intent-to-treat; mITT=modified intent-to-treat

Percentages are based on the number of subjects randomized (ITT).

Recruitment

Study Initiated (first subject enrolled): 18 Jan 2019

Study Completed (last subject completed): 20 May 2022

Conduct of the study

Protocol Amendments

The original global protocol dated 06 Feb 2017 was amended 4 times, as shown below:

Protocol Version	Amendment Number	Date
1.0	n/a (original)	06 Feb 2017
2.0	1.0	21 May 2019
3.0	2.0	06 Nov 2019
4.0	3.0	02 Nov 2021
5.0	4.0	11 Nov 2021

Summary of main changes:

Global Protocol Amendment 2 – Version 3.0, 06 Nov 2019

- Update of the number of subjects allowed to enrol into the study.
- Updated to clarify that subjects participating or planning to participate in any other study will not be allowed to enrol in this study.
- Revision to clarify the amount of IP allowed for each age group and to correct the recommended psi for EVICEL application.

Global Protocol Amendment 3 – Version 4.0, 02 Nov 2021

- Updated to allow enrolment of preterm (up to gestational age <37 week) and term newborn infants (0 to 27 days) undergoing emergency (non-elective) surgery, per FDA advice.
- Revision to allow for flexibility in enrolment if hepatic surgeries are less than 50%.
- Update of number of subjects planned in case of under or over enrolment.

In addition, country specific protocol amendments were made.

Protocol Deviations and Contingency Measures due to COVID-19

The COVID-19 risk assessment was developed and the following risk categories were established depending on where the risk was detected: study visits, study procedures, informed consent process, data collection, protocol deviations, IP, AE reporting, study monitoring, documentation and regulatory.

The risks identified in each process were evaluated taking into account the impact on subject safety and/or data integrity in order to calculate the risk score. The risk score was then classified as low risk, medium risk, and high risk.

Five subjects reported protocol deviations due to COVID-19, all were minor: 4 subjects missed physical examination visit and visit performed by telephone call, and 1 subject's surgery was postponed until obtaining of negative COVID-19 test.

After the mitigation activities were defined, the majority of risks were decreased to low risks due to the implementation of the mitigation activities. Only 2 risks were assessed as medium risks after the mitigation activities. These medium risks were assessed as acceptable risks and no additional actions were required to reduce them to a low risk.

As for the affected subjects, 73 subjects actively participated in the study during the pandemic until 24 January 2022 and the above mitigation activities were implemented and deemed effective. Overall, no other aspects of the study were affected. In conclusion, the current standard operational procedures and the additional documents generated for this study guaranteed the correct control and mitigation of all the identified risks for this study in the context of the COVID-19 pandemic.

Serious Breaches

There were no protocol deviations that were likely to affect the safety, rights of trial participants, and/or data reliability and robustness to a significant degree in this clinical trial.

The last subject was allocated to VeraSeal (FS Grifols), since EVICEL was not available on site at the time of randomization. The randomization was forced because it was the opportunity to enrol the last subject for the study.

Baseline data

Table 3. Summary of Demographics – ITT Population

Age (years) at randomization (n)	VeraSeal (n=95)	EVICEL (n=91)	Total (n=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	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			
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Multiple			
Other			
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

BMI=body mass index; Max=maximum; Min=minimum; SD=standard deviation
n represents the number of subjects contributing to the summary.
[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.

Table 4. Summary of baseline characteristics – ITT Population

	FS Grifols (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 $\leq$10 cm^2	77 (83.7%)	78 (88.6%)	155 (86.1%)
Medium: 10 cm^2 < TBS $\leq$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%)

TBS=target bleeding site
n represents the number of subjects contributing to the summary.

Numbers analysed

Table 5. Data sets analyzed

	FS Grifols n (%)	EVICEL n (%)	Total
Screened			197
ITT Population [1]	95	91	186
mITT Population [2]	91 (95.8%)	87 (95.6%)	178 (95.7%)
SAF Population [3]	91 (95.8%)	87 (95.6%)	178 (95.7%)
PP Population [4]	88 (92.6%)	85 (93.4%)	173 (93.0%)

Percentages were based on the total number of ITT subjects in each treatment group (N).

[1] ITT population=intent-to-treat population: all subjects who were randomized.

[2] mITT population=modified ITT population: the subset of ITT subjects who were met intra-operative criteria and received any amount of IP.

[3] SAF population=safety population: subjects who received any amount of IP.

[4] PP population=per-protocol population: the subset of mITT subjects who did not present major protocol violations which could impact the primary efficacy endpoint(s).

Outcomes and estimation

Primary Efficacy Endpoint

Table 6. Summary and analysis of primary efficacy endpoint – mITT Population

Efficacy Endpoint	FS Grifols (N=91) n (%)	EVICEL (N=87) n (%)	RR (95% CI) [2][4]	*p*-value [3]
Number (%) subjects achieving hemostasis at the TBS by T_4 [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

mITT=modified intent-to-treat, TBS=target bleeding site, RR=relative risk, CI=confidence interval
[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 FS Grifols 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 non-inferiority margin 0.8, it could be claimed that FS Grifols was not inferior to EVICEL.

Table 7. Analysis of efficacy endpoints: haemostasis by each time point at TBS population: per protocol

	FS Grifols (N=88) n (%)	EVICEL (N=85) n (%)	RR (95% CI) [1][3]	P-value [2]
Primary Efficacy Endpoint				
Hemostasis by 4 Minutes	85/ 88 (96.6)	81/ 85 (95.3)	1.01 (0.95, 1.08)	<0.001
Type of Surgery				
Parenchymous	44/ 44 (100.0)	43/ 43 (100.0)	1.00 (0.92, 1.09)	<0.001
Soft Tissue	41/ 44 (93.2)	38/ 42 (90.5)	1.03 (0.91, 1.17)	<0.001

Table 8. Analysis of efficacy endpoints: haemostasis by each time point at TBS population: intent-to-treat

	FS Grifols (N=95) n (%)	EVICEL (N=91) n (%)	RR (95% CI) [1][3]	P-value [2]
Primary Efficacy Endpoint				
Hemostasis by 4 Minutes	88/ 91 (96.7)	83/ 87 (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

Secondary Efficacy Endpoints

Cumulative proportion of subjects achieving haemostasis at the TBS by the defined observation time points of T7 and T10

Table 9. Summary and analysis of subjects achieving haemostasis at TBS by T7– mITT Population

Efficacy Endpoint	FS Grifols (N=91) n (%)	EVICEL (N=87) n (%)	RR (95% CI) [2][4]	*p*-value [3]
Number (%) subjects achieving hemostasis at the TBS by T_7[1]	91 (100.0%)	87 (100.0%)	1.00 (0.96 - 1.04)	<0.001
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

mITT=modified intent-to-treat, TBS=target bleeding site, RR=relative risk, CI=confidence interval
[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 FS Grifols 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 non-inferiority margin 0.8, it could be claimed that FS Grifols was not inferior to EVICEL.

Table 10. Summary and analysis of subjects achieving haemostasis at TBS by T10– mITT Population

Efficacy Endpoint	FS Grifols (N=91) n (%)	EVICEL (N=87) n (%)	RR (95% CI) [2][4]	*p*-value [3]
Number (%) subjects achieving hemostasis at the TBS by T_{10}[1]	90* (98.9%)	87 (100.0%)	0.99 (0.97 - 1.01)	<0.001
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

mITT=modified intent-to-treat, TBS=target bleeding site, RR=relative risk, CI=confidence interval
*A missing hemostasis assessment at a time point was considered not to have achieved hemostasis at that specific time point. Patient [redacted] who achieved hemostasis at T_4 and T_7 had a missing assessment at T_{10}.
[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 FS Grifols 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 non-inferiority margin 0.8, it could be claimed that FS Grifols was not inferior to EVICEL.

Prevalence of treatment failures

There was no single occurrence of persistent bleeding, breakthrough bleeding, re-bleeding, use of additional/alternative haemostatic treatment, or re-application of IP beyond T4. All 91 (100.0%) subjects in VeraSeal group and all 87 (100.0%) subjects in EVICEL group met this secondary efficacy endpoint in

the salutary sense, with no treatment failures identified in either arm, i.e. a 0% incidence of treatment failure.

Exploratory Efficacy Endpoints

The proportion of subjects achieving at least 1 point decrease in bleeding intensity according to the 5-point validated bleeding severity scale (Table 1) by the defined observation time points of T4, T7, and T10

Table 11. Subjects achieving at least 1 point decrease in bleeding intensity by each time point at TBS– mITT Population

	FS Grifols (N=91) n (%)	EVICEL (N=87) n (%)	RR (95% CI) [1]
4 Minutes	**89/91 (97.8%)**	**87/87 (100.0%)**	**0.98 (0.95, 1.01)**
Type of Surgery			
Parenchymous	46/46 (100.0%)	43/43 (100.0%)	1.00 (0.92, 1.09)
Soft Tissue	43/45 (95.6%)	44/44 (100.0%)	0.96 (0.90, 1.02)
7 Minutes	**91/91 (100.0%)**	**87/87 (100.0%)**	**1.00 (0.96, 1.04)**
Type of Surgery			
	FS Grifols (N=91) n (%)	**EVICEL (N=87) n (%)**	**RR (95% CI) [1]**
Parenchymous	46/46 (100.0%)	43/43 (100.0%)	1.00 (0.92, 1.09)
Soft Tissue	45/45 (100.0%)	44/44 (100.0%)	1.00 (0.92, 1.09)
10 Minutes [2]	**90/90 (100.0%)**	**87/87 (100.0%)**	**1.00 (0.96, 1.04)**
Type of Surgery			
Parenchymous	45/45 (100.0%)	43/43 (100.0%)	1.00 (0.92, 1.09)
Soft Tissue	45/45 (100.0%)	44/44 (100.0%)	1.00 (0.92, 1.09)

CI=confidence interval, RR=relative risk

[1] RR is the ratio of proportions of subjects meeting the efficacy endpoint in FS Grifols versus EVICEL. For the overall category, RR is the common relative risk, stratified by type of surgery. In general, the CI is calculated by the Cochran–Mantel–Haenszel method, and it is adjusted for the type of surgery for the overall category.

When all subjects are responders in both groups, the CI is computed by the Miettinen-Nurminen score method.

[2] Bleeding intensity was not assessed at 10 minutes for subjec[redacted]and was excluded from the analysis.

The mean change from baseline in bleeding intensity according to the 5-point validated bleeding severity scale (Table 1) at the defined observation time points of T4, T7, and T10

Table 12. Summary of change from baseline in bleeding intensity– mITT Population

Timepoint	Statistics	FS Grifols (N=91)	EVICEL (N=87)
Baseline	n	91	87
	Mean (SD)	1.5 (0.50)	1.4 (0.50)
	Median	2.0	1.0
	Min, Max	1, 2	1, 2
4 Minutes	n	91	87
	Mean (SD)	0.0 (0.25)	0.0 (0.21)
	Median	0.0	0.0
	Min, Max	0, 2	0, 1
Change From Baseline	n	91	87
	Mean (SD)	-1.5 (0.54)	-1.4 (0.49)
	Median	-1.0	-1.0
	Min, Max	-2, 0	-2, -1
7 Minutes	n	91	87
	Mean (SD)	0.0 (0.00)	0.0 (0.00)
	Median	0.0	0.0
	Min, Max	0, 0	0, 0
Change From Baseline	n	91	87
	Mean (SD)	-1.5 (0.50)	-1.4 (0.50)
	Median	-2.0	-1.0
	Min, Max	-2, -1	-2, -1

Timepoint	Statistics	FS Grifols (N=91)	EVICEL (N=87)
10 Minutes	n	90	87
	Mean (SD)	0.0 (0.00)	0.0 (0.00)
	Median	0.0	0.0
	Min, Max	0, 0	0, 0
Change From Baseline	n	90	87
	Mean (SD)	-1.5 (0.50)	-1.4 (0.50)
	Median	-1.5	-1.0
	Min, Max	-2, -1	-2, -1

Note: Patient [redacted] who achieved hemostasis at T_4 and T_7, had a missing assessment at T_{10}.

Ancillary analyses

Sensitivity analysis by VeraSeal (FS Grifols) applicator device

For the primary efficacy endpoint of haemostasis by T4, the sensitivity analysis results by VeraSeal applicator device (Fibrijet device and VistaSeal Dual Applicator) were 94.5% and 100.0% in subjects applied by Fibrijet and VistaSeal, respectively compared to 95.4% in EVICEL group. The ratio and 95% CI of proportion in subjects receiving VeraSeal via Fibrijet device and VistaSeal Dual Applicator relative to EVICEL was 1.02 (0.93 – 1.11) and 1.00 (1.00 – 1.01), respectively. These results demonstrate that VeraSeal application by applicator device is non-inferior to EVICEL and supports the primary efficacy endpoint.

Subgroup analyses

Subgroup Category	VeraSeal (N=91)	EVICEL (N=87)	RR (95% CI) [1][3]	*p*-value [2]
Age				
Haemostasis by 4 Minutes	88/91 (96.7%)	83/87 (95.4%)	1.01 (0.95 - 1.07)	<0.001
<=27 days	4/4 (100.0%)	2/2 (100.0%)	Not Calculable	-
>=28 days - <=23 months	19/19 (100.0%)	18/18 (100.0%)	1.00 (0.83 - 1.22)	0.015
>=2 - <=11 years	29/32 (90. 6%)	29/31 (93.5%)	0.97 (0.84 - 1.12)	0.005
>=12 - <=17 years	36/36 (100. 0%)	34/36 (94.4%)	1.06 (0.98 - 1.15)	<0.001
Sex				
Haemostasis by 4 Minutes	88/91 (96.7%)	83/87 (95.4%)	1.02 (0.95 - 1.08)	<0.001
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				
Haemostasis by 4 Minutes	88/91 (96.7%)	83/87 (95.4%)	1.02 (0.96 - 1.08)	<0.001
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			Not Calculable	-
American Indian or Alaskan Native			Not Calculable	-
Native Hawaiian or Other Pacific Islander			Not Calculable	-
Multiple			Not Calculable	-
Other			Not Calculable	-
Bleeding Intensity at Baseline				
Haemostasis by 4 Minutes	88/91 (96.7%)	83/87 (95.4%)	1.02 (0.96 - 1.09)	<0.001
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
TBS Size at Baseline				
Haemostasis by 4 Minutes	88/91 (96.7%)	83/87 (95.4%)	1.01 (0.95 - 1.07)	<0.001
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	-

mITT=modified intent-to-treat, RR=relative risk, CI=confidence interval, TBS=target bleeding site
The CI and p-value were reported only when there were at least 5 subjects in both the treatment groups.
[1] Relative risk (RR) is the ratio of proportions of subjects meeting the efficacy endpoint in VeraSeal (FS Grifols) 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 non-inferiority margin 0.8, it could be claimed that VeraSeal (FS Grifols) was not inferior to EVICEL.

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 13. Summary of Efficacy for trial IG1405

Title: A Prospective, Randomized, Active-Controlled, Single-blind, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during Surgery in Pediatric Subjects				
Study identifier	IG1405			
Design	This was a prospective, randomized, active-controlled, single-blind, parallel group clinical trial to evaluate the efficacy and safety of FS Grifols as an adjunct to haemostasis during surgery in paediatric subjects.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Intraoperatively: 10 minutes; Post-Operative assessments were performed on Days 4 and 30 not applicable not applicable	
Hypothesis	Non-inferiority			
Treatments groups	VeraSeal		N=91	
	Evicel		N=87	
Endpoints and definitions	Primary endpoint	Haemostasis at T4	The proportion of subjects achieving haemostasis 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 (TClosure).	
	Secondary	T7 T10	Cumulative proportion of subjects achieving haemostasis at the target bleeding site by each of the following time points: T7 and T10	
	Secondary	Treatment Failure	Treatment Failures	
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Modified Intent to treat			
Descriptive statistics and estimate variability	Treatment group	VeraSeal	Evicel	
	Number of subjects	91	87	
	Haemostasis at T4	88 (96.7%)	83 (95.4%)	
	Haemostasis by T7	91 (100.0%)	87 (100.0%)	
	Haemostasis by T10	90 (98.9%)	87 (100.0%)	
	Treatment Failure	0%	0%	
Effect estimate per comparison	Primary endpoint Haemostasis at T4	VeraSeal vs. Evicel		
		RR	1.01	
		95% CI	0.96 - 1.07	
		P-value	<0.001	

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH submitted one finished phase 3 study (IG1405) in a paediatric population requiring elective, open (non-laparoscopic), pelvic, abdominal, or thoracic (non-cardiac) surgical procedures to include children into the indication. The surgeries were expected to yield target bleeding sites with Grade 1 (mild) or Grade 2 (moderate) bleeding occurring in parenchymous organs or soft tissue that were appropriate for the use of a fibrin sealant in order to achieve haemostasis. Of note, also preterm (up to gestational age <37 weeks) and term newborn infants (0 to 27 days) requiring an emergency, open (non-laparoscopic) pelvic, abdominal or thoracic (non-cardiac) surgical procedure wherein a TBS was identified, and a topical haemostatic agent was indicated, were eligible to the study.

In total 186 subjects were enrolled into the study (95 subjects in VeraSeal and 91 subjects in EVICEL arms). More male than female participants were included in the trial, and the majority of patients was White. Both groups were well-balanced in terms of baseline data. However, a slight imbalance in the number of patients with moderate bleeding was noted between both treatment groups. Moreover, a higher proportion of patients with medium TBS received VeraSeal than EVICEL. In response to the RSI, the MAH clarified that there were in total 9 VeraSeal patients and 8 Evicel patients below 2 years of age who had moderate bleeding at TBS.

The active comparator selected for the comparative evaluation of the haemostatic efficacy of VeraSeal was Evicel, which is a fibrin sealant authorised via CP in the EU since 2008 for adult patients only. Two other fibrin sealants widely available in the EU, Tisseel and Artiss, are licensed via DCP also for adult patients only. As off-label use of fibrin sealants in children can be assumed, the choice of a medicinal product that is centrally licensed as the comparator was comprehensible and acceptable. Trial IG1405 was single blind, with the patient blinded towards assigned treatment while the investigator (surgeon) was not. This was considered acceptable since VeraSeal and EVICEL have different administration patterns.

The selected primary efficacy endpoint, the proportion of subjects achieving haemostasis at 4 minutes with no occurrence of rebleeding requiring further haemostatic intervention until the completion of the surgical closure (TClosure), was considered relevant. Of note, the same primary efficacy endpoint was used in the completed adult studies. The secondary endpoints (Cumulative proportion of subjects achieving haemostasis at 7 and 10 minutes; Treatment failures) were appropriate, however, they represent mainly different aspects of the primary endpoint. There is a lack of other, clinically relevant endpoints which could have provided a more complete picture of the efficacy of VeraSeal. Transfusion requirements, postoperative rebleeding at TBS, reoperation at TBS, postoperative blood loss, length of hospital stay would have been secondary endpoints of interest. However, as VeraSeal was already investigated in three phase 3 studies in a total of 500 subjects, this deficiency does not negatively affect the efficacy evaluation.

Subgroup analyses supplement the primary analysis and substantiate the robustness of the findings in different settings, i.e., according to age group, bleeding intensity at baseline and size of the bleeding surface at the TBS. Sensitivity analyses of the primary endpoint confirm the findings of the primary analysis.

The statistical analysis was considered well preplanned and performed. Enrolled patients were randomized in a 1:1 ratio into the VeraSeal or EVICEL treatment groups. Randomization was stratified by type of surgery (i.e., parenchymous versus soft tissue surgery) and age groups (i.e., 12-17 years, 2-11 years, 28 days-23 months, and 0-27 days). In response to the RSI, the MAH clarified the method used to generate random allocation sequence was a permuted block randomisation, which is suitable to achieve

approximately balanced groups within strata. The MAH argued that randomisation was not stratified by country in order to avoid over-stratification, which can be followed. The relative and absolute frequencies describing the relationship between treatment groups and primary efficacy endpoint within centers, which were presented by the MAH in response to the RSI, do not raise any concerns.

Efficacy data and additional analyses

A total of 178 children (< 18 years of age) were randomized and treated with VeraSeal (n=91) or active control (n=87). Of the 91 subjects treated with VeraSeal, 4 were ≤ 27 days; 19 were ≥ 28 days to ≤ 23 months; 32 were ≥ 2years to ≤ 11 years; 36 were ≥ 12 years to ≤ 17 years. Forty-six children treated with VeraSeal underwent parenchyma (hepatic) surgical procedures and 45 had soft tissue surgeries. VeraSeal was shown to be non-inferior to the control group (EVICEL [sealant]) in achieving hemostasis by 4 minutes. The rate of hemostasis at the target bleeding site by 4 minutes was 96.7% (88/91 subjects) in the VeraSeal treatment group and was 95.4% (83/87) in the control group.

The provided efficacy data showed that VeraSeal is non-inferior to Evicel for the control of mild or moderate bleeding in parenchymous organ or soft tissue surgery. The noninferiority of VeraSeal has been demonstrated as the lower limit of the 95% CI at 0.96 exceeded the predefined margin of 0.8.

In the PP population, this result was mirrored with the rate of haemostasis by T4 being 96.6% (85/88) subjects in the VeraSeal treatment group and 95.3% (81/85 subjects) in the Evicel treatment group. Sensitivity and subgroup analyses supported the results of the primary efficacy evaluation.

The rate of treatment failure in the mITT population was zero in both treatment groups. All other secondary and exploratory efficacy outcomes showed comparable effects for the two fibrin sealants.

The efficacy of VeraSeal has already been demonstrated in three pivotal trials in a large number of adult patients (n= 500) covering three different surgical scenarios (peripheral vascular surgery, parenchymous and soft tissue surgery). The mechanism of action, i.e. the initiation of the last phase of blood coagulation, is identical across age groups. Satisfactory efficacy has been shown for haemostasis of parenchymous organ or soft tissue surfaces in both adult and paediatric patients. Therefore, the results of the clinical trial investigating the effect of VeraSeal as a suture support in vascular surgery (IG1101) in adult patients, could be extrapolated to the younger age cohorts without the need for a further dedicated study investigating peripheral vascular surgery. Additionally in the 3 previously described studies mainly in adult subjects that evaluated VeraSeal by specific surgery type 11 paediatric subjects aged 16 years or younger were treated with VeraSeal.

Taking into account that very few patients below the age of 27 days were included in the pivotal study and an indication without a lower age limit was envisaged at submission, the MAH was asked to provide a justification that data from older children can be extrapolated to the younger ones and that there are no excipients in the drug product not suitable for small children. Based on literature and mechanism of action, the MAH provided a thorough justification why the beneficial effects of topical fibrin sealant application can be extrapolated from adult and older paediatric age cohorts to neonates. Furthermore, all 6 patients below 27 days of age achieved haemostasis at T4, T7 and T10. The excipients used in the thrombin and the fibrinogen component do not raise any safety concerns. The granting of an indication without a lower age limit can therefore be supported.

Application of the product must be individualised by the treating physician. In the paediatric clinical trial, the individual dose ranged from 0.6 to 12 mL (see SmPC section 4.2.).

2.4.3. Conclusions on the clinical efficacy

The efficacy of VeraSeal in achieving haemostasis has been demonstrated in a phase 3 study investigating 186 paediatric subjects randomised 1:1 to VeraSeal and Evicel. The primary efficacy objective of non-inferiority was achieved. A number of subgroup analyses and sensitivity analyses substantiate the results of the primary efficacy evaluations.

2.5. Clinical safety

Introduction

Four phase 3 safety and efficacy clinical trials have been conducted using VeraSeal (FS Grifols) as an adjunct to haemostasis in surgery and as suture support in vascular surgery:

- Study IG1101: A Prospective, Single-blind, Randomised, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during Peripheral Vascular Surgery
- Study IG1102: A Prospective, Single-blind, Randomised, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis During Parenchymous Tissue Open Surgeries
- Study IG1103: A Prospective, Single-blind, Randomised, Phase III Study to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during Soft Tissue Open Surgeries
- Study IG1405: A Prospective, Randomised, Active-Controlled, Single-blind, Parallel Group Clinical Trial to Evaluate the Safety and Efficacy of Fibrin Sealant Grifols (FS Grifols) as an Adjunct to Haemostasis during Surgery in Paediatric Subjects

Data from the first three clinical trials (IG1101, IG1102, and IG1103) were included in the initial MAA. These studies were conducted using the same general trial design with each trial consisting of a Preliminary Part (I) followed by a Primary Part (II) and with the same subject monitoring and follow-up periods. The inclusion and exclusion criteria were generally the same for these clinical trials except for specifications for the types of surgeries included in each study.

With this application, the MAH provided the final results from the paediatric clinical study IG1405, which consisted of a similar trial design as the other three studies, but with fewer (3) post-operative visits. The eligibility criteria included subjects who were <18 years of age and who required an elective (non-emergent), open (non-laparoscopic), pelvic, abdominal, or thoracic (non-cardiac) surgical procedure; preterm or newborn infants could be enrolled if they required either elective or emergency open surgery. The maximum allowable volume of VeraSeal (FS Grifols) was 12 mL for subjects ≥2 years of age and 6 mL for subjects <2 years of age.

Table 14 provides an overview of the trial design and number of subjects in the safety population in each clinical trial. For studies IG1101, IG1102, and IG1103, the number of subjects listed are from Parts I and II of the study.

Table 14. List of all clinical trials

Study No.	Study Type	Subject Population	Treatment	Subjects Exposed to Study Treatment (Safety Population)	
				FS Grifols	Comparator
IG1101	Phase 3	Subjects undergoing vascular surgery	FS Grifols ≤6 mL or manual compression	168	Manual compression 57
IG1102	Phase 3	Subjects undergoing parenchymous surgery	FS Grifols ≤12 mL or Surgicel up to 4 sheets	163	Surgicel® 162
IG1103	Phase 3	Subjects undergoing soft tissue surgery	FS Grifols ≤12 mL or Surgicel up to 4 sheets	169	Surgicel 158
IG1405	Phase 3b	Paediatric subjects undergoing parenchymous or soft tissue surgery	FS Grifols ≤12 mL or EVICEL ≤12 mL	91	EVICEL® 87

Assessment of the safety and tolerability of VeraSeal was a primary objective of all 4 phase 3 trials.

In all 4 trials, subjects were identified as potential candidates for participation in the trial, and the investigator assessed if the subject's surgery qualified for inclusion in the trial. In addition, the specific TBS was identified at the time of surgery and assessed by the investigator as qualifying for inclusion in the trial. Subjects who qualified for the trial and were assigned to receive VeraSeal as an adjunct for haemostasis at the TBS were then administered the study treatment or comparator.

Safety Analysis in Study IG1405

The safety analyses were based on the Safety population (subjects who receive any amount of IP). The safety and tolerability of VeraSeal were assessed by analyzing adverse events (AEs), adverse drug reactions (ADRs), laboratory parameters, vital signs, and physical assessments. In studies IG1101, IG1102, and IG1103, virus safety and immunogenicity were also assessed.

AEs were coded and classified using MedDRA terms (SOC and PTs). When a causal relationship of an AE was classified by the investigator as definitively or possibly related, the event was defined as a suspected ADR. A suspected ADR with a causal relationship of "definitively" was defined as an AR. The sponsor considered the investigator's causality assessment and also provided its own assessment.

For summary purposes, AEs were classified as TEAEs or non-treatment-emergent AEs (non-TEAEs) depending on the comparison of AE onset date/time with the start date/time of study treatment with the IP. A TEAE was defined as an AE which occurred between the start of study treatment and the final visit of the clinical trial. A non-TEAE was defined as an AE which occurred prior to the start of study treatment. Non-TEAEs and TEAEs were summarized separately.

Patient exposure

Enumeration of Subjects

Among the 4 clinical trials, 1063 subjects were assigned or randomised to a specific study treatment. Among those, 593 subjects were assigned or randomised to receive VeraSeal (intent-to-treat [ITT] Population), 322 subjects were randomised to receive Surgicel (ITT Population), 57 subjects were randomised to receive manual compression (MC), and 91 subjects were randomised to receive EVICEL (ITT population).

In Preliminary Part (I) of Study IG1103, 2 subjects were randomised to Surgicel but actually received VeraSeal by error. In paediatric clinical study IG1405, of the 95 subjects randomised to receive VeraSeal, 91 subjects met intraoperative enrolment criteria, and therefore were treated with any amount of IP. Of the 91 subjects randomised to receive EVICEL, 87 met these enrolment criteria. Thus, the modified intent-to-treat (mITT) population included these 178 subjects who received IP.

Thus, the Safety Population for the 4 trials included 591 subjects treated with VeraSeal, 320 subjects treated with Surgicel, 57 subjects treated with MC and 87 subjects treated with EVICEL. All subjects received treatment and were included in the Safety Population based on actual treatment received.

Table 15 shows the subjects receiving VeraSeal by clinical trial.

Table 15. Subjects exposed to VeraSeal by study (all subjects assigned or randomised, all 4 studies)

Subject Disposition	IG1101 n (%)	IG1102 n (%)	IG1103 n (%)	IG1405 n (%)	Total n (%)
Subjects randomised (ITT Population)	168 (28.3)	163 (27.5)	167 (28.2)	95 (16.0)	593 (100)
Subjects valid for Safety Population (actual treatment)	168 (28.4)	163 (27.6)	169[a] (28.6)	91 (15.4)	591 (100)

Note: Percentage values are calculated using the Total column as the denominator.
[a] Two subjects were randomised to Surgicel in IG1103 but actually received FS Grifols in the Preliminary Part (I) of the trial.

Treatment Exposure

CLINICAL STUDIES IG1101, IG1102, AND IG1103

The concentration of VeraSeal administered to all subjects in clinical studies IG1101, IG1102, and IG1103 was the same; however, the volume of VeraSeal administered was up to 6 mL in the IG1101 trial (vascular surgery) and up to 12 mL in the IG1102 and IG1103 trials (parenchymous and soft tissue surgeries, respectively). The actual volume of VeraSeal applied varied for each individual subject and was based on the investigator's determination of the volume needed to achieve haemostasis at the TBS. Also, reapplications of VeraSeal to the TBS within the protocol-specified time of 4 minutes from the first application were at the discretion of the investigator. Each subject receiving VeraSeal in these trials received the application(s) at a single TBS and for a single surgery.

The mean volume of VeraSeal applied among these 3 studies was 6.78 mL, with a median of 6.00 mL and a range of 0.3 to 18.0 mL.

The mean number of Surgicel treatment sheets applied was 1.59 sheets, and the median value was 1.00 sheets (IG1102 and IG1103).

PAEDIATRIC CLINICAL STUDY IG1405

The mean volume of VeraSeal used per subject in study IG1405 was 4.641 mL, with a median of 4.800 mL, and a range of 0.60 to 12.00 mL. For subjects who underwent parenchymous tissue surgery, the mean volume used per subject was 5.784 mL, with a median of 6.000 mL, and a range of 2.40 to 12.00 mL. For subjects who underwent soft tissue surgery, the mean volume used per subject was 3.473 mL, with a median of 3.000 mL, and a range of 0.60 to 10.80 mL.

The mean volume of EVICEL used per subject (for all subjects randomised to EVICEL) was 3.104 mL, with a median of 3.000 mL, and a range of 0.10 to 8.00 mL. For subjects who underwent parenchymous tissue surgery, the mean volume used per subject was 3.788 mL, with a median of 4.000 mL, and a range of 1.00 to 6.00 mL. For subjects who underwent soft tissue surgery, the mean volume used per subject was 2.436 mL, with a median of 2.400 mL, and a range of 0.10 to 8.00 mL.

Demographics and Other Characteristics of Study Population

Table 16 and 17 provide the demographic profile of subjects in the 4 clinical trials by treatment assignment (ITT Population for IG1101, IG1102, IG1103 and IG1405). Across all studies, the demographics were generally balanced across treatment groups.

Table 16. Demographics of subjects by treatment in clinical studies IG1101, IG1102, IG1103 (ITT Population)

Characteristics	FS Grifols (N=498) n (%)	Surgicel (N=322) n (%)	Manual Compression (N=57) n (%)
Sex - n (%)			
Male	255 (51.2)	131 (40.7)	31 (54.4)
Female	243 (48.8)	191 (59.3)	26 (45.6)
Age (years)			
Mean (SD)	56.86 (15.676)	51.70 (17.688)	62.04 (10.734)
Median	60.00	53.50	61.00
Min, Max	0.3, 86.0	0.6, 85.0	22.0, 82.0
Ethnicity - n (%)			
Hispanic or Latino	36 (7.2)	26 (8.1)	2 (3.5)
Not Hispanic or Latino	462 (92.8)	295 (91.6)	55 (96.5)
Not specified	[redacted]	[redacted]	[redacted]
Race – n (%)			
White (Caucasian)	434 (87.1)	272 (84.5)	49 (86.0)
Black or African American	49 (9.8)	36 (11.2)	8 (14.0)
Asian	13 (2.6)	8 (2.5)	[redacted]
American Indian or Alaskan Native	[redacted]	2 (0.6)	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]	[redacted]
Multi-racial (no primary race)	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
Not specified	[redacted]	2 (0.6)	[redacted]

Table 17. Demographics of subjects by treatment in paediatric clinical study IG1405 (ITT Population)

	FS Grifols (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	40 (42.1%)	30 (33.0%)	70 (37.6%)
If Female[a]			
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 (%)[b]	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	[redacted]	[redacted]	[redacted]
American Indian or Alaska Native			
Native Hawaiian or Other Pacific Islander			
Multiple			
Other			
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

BMI = body mass index; ITT = intent-to-treat; Max = maximum; Min = minimum; SD = standard deviation

n represents the number of subjects contributing to the summary.

[a] The percentages are based on the number of female subjects.

[b] The percentages are based on the number of female subjects with childbearing potential.

Adverse events

CLINICAL STUDIES IG1101, IG1102, AND IG1103

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0.

An overall summary of treatment-emergent AEs (TEAEs) in clinical studies IG1101, IG1102, and IG1103 is provided in Table 18 The proportions of subjects for whom TEAEs were reported were comparable among the treatment groups (VeraSeal [FS Grifols], 83.8%; Surgicel, 86.9%; MC, 77.2%).

Table 18. Summary of treatment-emergent adverse events by treatment in studies IG1101, IG1102 and IG1103 (safety Population)

	FS Grifols N=500 n (%)	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
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

ADR=adverse drug reaction; AR=adverse reaction; IP=investigational product; SAE=serious adverse event; TEAE=treatment-emergent adverse event

PAEDIATRIC CLINICAL STUDY IG1405

Adverse events were coded using MedDRA version 25.1.

A total of 46 TEAEs were reported in 24 (26.4%) subjects in the VeraSeal (FS Grifols) group, most of which were considered unrelated to treatment; only 1 (1.1%) subject reported 1 TEAE that was possibly related to treatment. A total of 38 TEAEs were reported in 16 (18.4%) subjects in the EVICEL group, all TEAEs were considered unrelated to treatment.

One (1.1%) subject in the VeraSeal treatment group reported a suspected ADR; no suspected ADRs were reported in the EVICEL treatment group. No ARs were reported in either of the treatment groups.

Eight (8.8%) subjects in the VeraSeal group reported 12 treatment-emergent SAEs and 9 (10.3%) subjects in the EVICEL group reported 11 treatment-emergent SAEs. All serious TEAEs were considered unrelated to IP.

Three subjects had TEAEs leading to death, 1 (1.1%) subject in the VeraSeal group and 2 (2.3%) subjects in the EVICEL group. All three deaths were unrelated to the study treatments.

One subject (1.1%) in the EVICEL group reported a non-fatal TEAE leading to study discontinuation.

Table 19. Summary of treatment-emergent adverse events in clinical study IG1405 (safety Population)

	FS Grifols (N=91)		EVICEL (N=87)	
	Number of Subjects[a] n (%)	Number of Events[b]	Number of Subjects[a] n (%)	Number of Events[b]
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[c]	1 (1.1%)	1	0 (0.0%)	0
Subjects with any ARs[d]	0	0	0	0
Subjects with any treatment-emergent SAE[e]	8 (8.8%)	12	9 (10.3%)	11
Subjects with any TEAEs with outcome of death	1 (1.1%)	1	2 (2.3%)	2
Subjects with any non-fatal TEAEs leading to study discontinuation	0 (0.0%)	0	1 (1.1%)	1

ADR=adverse drug reaction; AR=adverse reaction; IP=investigational product; SAE=serious adverse event; TEAE=treatment-emergent adverse event

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).

[a] 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.

[b] Number of events included all occurrences of AEs.

[c] Suspected ADRs are adverse events with a definite or possible causal relationship to study treatment.

[d] ARs are adverse events with a definite causal relationship to study treatment.

[e] Subject [redacted] 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 (EDC) database, this event was conservatively attributed as treatment emergent SAE. However, source data residing in the global pharmacovigilance (GPV) 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.

Treatment-Emergent Adverse Events

CLINICAL STUDIES IG1101, IG1102, AND IG1103

A summary of TEAEs reported for at least 5% of subjects within a treatment group is provided by preferred term for all 3 clinical trials combined in Table 20.

The most frequently reported TEAEs in these studies were typical of open surgeries. The most common TEAEs in the 3 treatment groups were similar:

- VeraSeal (FS Grifols): procedural pain (41.8%), nausea (13.4%), and pyrexia (10%)
- Surgicel: procedural pain (45.9%), nausea (17.5%), anaemia (12.5%), pyrexia (10.9%), constipation (10.6%), and procedural nausea (10.0%)
- MC: procedural pain (36.8%) and pyrexia (10.5%)

No substantial differences in TEAE incidences were noted among treatment groups.

Table 20. Treatment-emergent adverse events reported in ≥5% of subjects by preferred term within a treatment group in clinical studies IG1101, IG1102 and IG1103 (safety Population)

Preferred Term	FS Grifols N=500 n (%)	Surgicel N=320 n (%)	Manual Compression N=57 n (%)
Procedural pain	209 (41.8)	147 (45.9)	21 (36.8)
Nausea	67 (13.4)	56 (17.5)	2 (3.5)
Pyrexia	50 (10.0)	35 (10.9)	6 (10.5)
Anaemia	45 (9.0)	40 (12.5)	2 (3.5)
Constipation	46 (9.2)	34 (10.6)	4 (7.0)
Hypotension	36 (7.2)	15 (4.7)	3 (5.3)
Hypertension	35 (7.0)	24 (7.5)	1 (1.8)
Oedema peripheral	30 (6.0)	14 (4.4)	1 (1.8)
Vomiting	29 (5.8)	26 (8.1)	3 (5.3)
Incision site pain	28 (5.6)	18 (5.6)	1 (1.8)
Procedural nausea	24 (4.8)	32 (10.0)	0
Tachycardia	23 (4.6)	31 (9.7)	1 (1.8)
Pruritus	23 (4.6)	22 (6.9)	0
Body temperature increased	11 (2.2)	2 (0.6)	4 (7.0)
Hyperglycaemia	9 (1.8)	18 (5.6)	0
Hypophosphataemia	9 (1.8)	16 (5.0)	0
Vascular graft thrombosis	2 (0.4)	0	3 (5.3)

Note: For each preferred term, subjects are counted only once.

PAEDIATRIC CLINICAL STUDY IG1405

The most frequently reported TEAEs at the system organ class (SOC) level reported in ≥2 subjects were in the Gastrointestinal disorders SOC with 9/91 (9.9%) subjects in the VeraSeal (FS Grifols) treatment group and 6/87 (6.9%) subjects in the EVICEL treatment group. Also, 6/87 (6.9%) subjects in the EVICEL treatment group reported TEAEs in the General disorders and administration site conditions SOC (Table 21).

Table 21. Treatment-emergent adverse events reported in ≥2 subjects in a treatment group by system organ class and preferred term – clinical study IG1405 (safety Population)

System Organ Class Preferred Term	FS Grifols (N=91)	EVICEL (N=87)
Subjects with any TEAE	**24 (26.4%)**	**16 (18.4%)**
Blood and lymphatic system disorders	2 (2.2%)	3 (3.4%)
Anaemia	2 (2.2%)	3 (3.4%)
Gastrointestinal disorders	9 (9.9%)	6 (6.9%)
Abdominal distension	2 (2.2%)	0 (0.0%)
Nausea	1 (1.1%)	2 (2.3%)
Vomiting	6 (6.6%)	3 (3.4%)
General disorders and administration site conditions	1 (1.1%)	6 (6.9%)
Pyrexia	1 (1.1%)	5 (5.7%)
Immune system disorders	2 (2.2%)	0 (0.0%)
Anaphylactic shock*	2 (2.2%)	0 (0.0%)
Infections and infestations	5 (5.5%)	5 (5.7%)
Wound infection	2 (2.2%)	0 (0.0%)
Injury, poisoning and procedural complications	6 (6.6%)	2 (2.3%)
Wound dehiscence	2 (2.2%)	0 (0.0%)
Vascular disorders	2 (2.2%)	0 (0.0%)
Hypertension	2 (2.2%)	0 (0.0%)

IP=investigational product; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event
*Subject [redacted] experienced SAE anaphylactic shock due to *Echinococcus granulosus* cyst spillage on Day 1. Because the time of onset was not documented in the EDC database, this event was conservatively attributed as treatment emergent SAE. However, source data residing in the GPV 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).
Any subject with multiple events in one SOC was counted only once for that SOC.
Any subject with multiple events in one PT was counted only once for that PT.

Table 22. Incidence of treatment emergent adverse events population: safety

System Organ Class Preferred Term	FS Grifols Subjects (N=91) n (%)	FS Grifols Events (N=46) n (%)	EVICEL Subjects (N=87) n (%)	EVICEL Events (N=38) n (%)
Subjects with any TEAEs	24 (26.4)	46 (100.0)	16 (18.4)	38 (100.0)
Blood and lymphatic system disorders	2 (2.2)	2 (4.3)	3 (3.4)	4 (10.5)
Anaemia	2 (2.2)	2 (4.3)	3 (3.4)	3 (7.9)
Pancytopenia	0	0	1 (1.1)	1 (2.6)
Cardiac disorders	1 (1.1)	1 (2.2)	1 (1.1)	1 (2.6)
Cardiac arrest	1 (1.1)	1 (2.2)	1 (1.1)	1 (2.6)
Gastrointestinal disorders	9 (9.9)	14 (30.4)	6 (6.9)	9 (23.7)
Abdominal distension	2 (2.2)	2 (4.3)	0	0
Abdominal pain	0	0	1 (1.1)	1 (2.6)
Ascites	0	0	1 (1.1)	1 (2.6)
Constipation	0	0	1 (1.1)	1 (2.6)
Diarrhoea	1 (1.1)	1 (2.2)	0	0
Ileus	1 (1.1)	1 (2.2)	0	0
Ileus paralytic	0	0	1 (1.1)	1 (2.6)
Intra-abdominal fluid collection	1 (1.1)	1 (2.2)	0	0
Intussusception	1 (1.1)	1 (2.2)	0	0
Melaena	1 (1.1)	1 (2.2)	0	0
Nausea	1 (1.1)	1 (2.2)	2 (2.3)	2 (5.3)
Vomiting	6 (6.6)	6 (13.0)	3 (3.4)	3 (7.9)
General disorders and administration site conditions	1 (1.1)	1 (2.2)	6 (6.9)	7 (18.4)
Generalised oedema	0	0	1 (1.1)	1 (2.6)
Pyrexia	1 (1.1)	1 (2.2)	5 (5.7)	6 (15.8)
Immune system disorders	2 (2.2)	2 (4.3)	0	0
Anaphylactic shock	2 (2.2)	2 (4.3)	0	0
Infections and infestations	5 (5.5)	6 (13.0)	5 (5.7)	5 (13.2)
Bacteraemia	1 (1.1)	1 (2.2)	0	0
Pneumonia	0	0	1 (1.1)	1 (2.6)
Postoperative abscess	0	0	1 (1.1)	1 (2.6)
Postoperative wound infection	1 (1.1)	1 (2.2)	0	0
Respiratory syncytial virus infection	0	0	1 (1.1)	1 (2.6)
Respiratory tract infection	0	0	1 (1.1)	1 (2.6)
Sepsis	0	0	1 (1.1)	1 (2.6)
Staphylococcal infection	1 (1.1)	1 (2.2)	0	0
Upper respiratory tract infection	1 (1.1)	1 (2.2)	0	0
Wound infection	2 (2.2)	2 (4.3)	0	0
Injury, poisoning and procedural complications	6 (6.6)	6 (13.0)	2 (2.3)	2 (5.3)
Anaemia postoperative	1 (1.1)	1 (2.2)	0	0
Mechanical ventilation complication	0	0	1 (1.1)	1 (2.6)
Post procedural haemorrhage	0	0	1 (1.1)	1 (2.6)
Injury, poisoning and procedural complications (continued)				
Procedural pain	1 (1.1)	1 (2.2)	0	0
Procedural vomiting	1 (1.1)	1 (2.2)	0	0
Wound complication	1 (1.1)	1 (2.2)	0	0
Wound dehiscence	2 (2.2)	2 (4.3)	0	0
Investigations	4 (4.4)	5 (10.9)	1 (1.1)	1 (2.6)
Blood magnesium decreased	1 (1.1)	1 (2.2)	0	0
Haemoglobin decreased	1 (1.1)	1 (2.2)	1 (1.1)	1 (2.6)
Oxygen saturation decreased	1 (1.1)	1 (2.2)	0	0
Platelet count increased	1 (1.1)	1 (2.2)	0	0
Transaminases increased	1 (1.1)	1 (2.2)	0	0
Metabolism and nutrition disorders	1 (1.1)	1 (2.2)	3 (3.4)	3 (7.9)
Acidosis	0	0	1 (1.1)	1 (2.6)
Decreased appetite	1 (1.1)	1 (2.2)	0	0
Hypoalbuminaemia	0	0	1 (1.1)	1 (2.6)
Hypokalaemia	0	0	1 (1.1)	1 (2.6)
Reproductive system and breast disorders	0	0	1 (1.1)	1 (2.6)
Acquired hydrocele	0	0	1 (1.1)	1 (2.6)
Respiratory, thoracic and mediastinal disorders	5 (5.5)	5 (10.9)	5 (5.7)	5 (13.2)
Acute respiratory failure	0	0	1 (1.1)	1 (2.6)

Respiratory, thoracic and mediastinal disorders (continued)				
Atelectasis	1 (1.1)	1 (2.2)	0	0
Bronchospasm	1 (1.1)	1 (2.2)	1 (1.1)	1 (2.6)
Cough	0	0	1 (1.1)	1 (2.6)
Epistaxis	1 (1.1)	1 (2.2)	0	0
Pleural effusion	1 (1.1)	1 (2.2)	0	0
Pneumothorax	1 (1.1)	1 (2.2)	0	0
Pulmonary embolism	0	0	1 (1.1)	1 (2.6)
Pulmonary hypertension	0	0	1 (1.1)	1 (2.6)
Skin and subcutaneous tissue disorders	1 (1.1)	1 (2.2)	0	0
Rash	1 (1.1)	1 (2.2)	0	0
Vascular disorders	2 (2.2)	2 (4.3)	0	0
Hypertension	2 (2.2)	2 (4.3)	0	0

Adverse events are coded using MedDRA Version 25.1.
At each level of summation (System Organ Class and Preferred Term), each subject is only counted once.
Note: 'N' for events in the column headers is the total number of TEAEs and is used as the denominator for all % in that column.

Treatment-Emergent Adverse Events by Severity

CLINICAL STUDIES IG1101, IG1102, AND IG1103

The majority of TEAEs in all treatment groups (91 to 96%) were either mild or moderate in severity. Among subjects in the VeraSeal treatment group, 60/500 (12.0%) subjects experienced a severe TEAE, 163/500 (32.6%) subjects experienced a moderate TEAE, and 196/500 (39.2%) subjects experienced a mild TEAE. Among subjects in the Surgicel treatment group, 21/320 (6.6%) subjects experienced a severe TEAE, 140/320 (43.8%) subjects experienced a moderate TEAE, and 117/320 (36.6%) subjects experienced a mild TEAE. Among subjects in the MC treatment group, 8/57 (14.0%) subjects experienced a severe TEAE, 11/57 (19.3%) subjects experienced a moderate TEAE, and 25/57 (43.9%) subjects experienced a mild TEAE.

PAEDIATRIC CLINICAL STUDY IG1405

In study IG1405, 91.3% of the TEAEs in the VeraSeal treatment group and 78.9% of the TEAEs in the EVICEL treatment group were mild-to-moderate in severity.

With respect to the proportion of subjects reporting TEAEs by severity, in the VeraSeal group, 13 (14.3%) subjects reported mild TEAEs, 8 (8.8%) subjects reported moderate TEAEs, and 3 (3.3%) subjects reported severe TEAEs. In the EVICEL group, 6 (6.9%) subjects reported mild TEAEs, 5 (5.7%) subjects reported moderate TEAEs, and 5 (5.7%) subjects reported severe TEAEs.

A total of 3 (3.3%) subjects in the VeraSeal treatment group experienced the following 4 severe TEAEs: cardiac arrest, ileus, intussusception, and anaphylactic shock. A total of 5 (5.7%) subjects in the EVICEL treatment group experienced the following 8 severe TEAEs: cardiac arrest, respiratory syncytial virus infection, post procedural haemorrhage, haemoglobin decreased, acidosis, acute respiratory failure, pulmonary embolism, and pulmonary hypertension.

Adverse Drug Reactions

CLINICAL STUDIES IG1101, IG1102, AND IG1103

When an AE was assessed for causal relationship to study treatment by the investigator as definitely related, probably related, or possibly related, or unlikely related, the event was deemed as an adverse drug reaction (ADR).

Table 23 presents a summary of all ADRs by preferred term and by treatment group in these 3 clinical studies combined.

The majority of individual ADRs (preferred terms) in the VeraSeal (FS Grifols) and Surgicel treatment groups occurred in ≤2 subjects, and all of the individual ADRs in the MC treatment group occurred in single subjects.

Of the 64 subjects with any ADR reported in the VeraSeal group, 1 subject had 1event (preferred term: procedural pain) that was considered definitely related to study treatment. Thirteen subjects in the VeraSeal group had any ADR that was considered possibly related to study treatment, and 50 subjects in the VeraSeal 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.

Of the 3 subjects with any ADRs reported in the MC treatment group, all subjects had ADRs that were considered unlikely related to study treatment.

No substantial differences in the ADR incidences were noted among treatment groups.

Table 23. Incidence of adverse drug reactions by preferred term in studies IG1101, IG1102 and IG1103 (safety Population)

Preferred Term	FS Grifols N=500 n (%)	FS Grifols Causal Relationship n		Surgicel N=320 n (%)	Surgicel Causal Relationship n		Manual Compression N=57 n (%)	Manual Compression Causal Relationship n	
Subject with any adverse drug reaction	64 (12.8)	50	Unlikely	27 (8.4)	20	Unlikely	3 (5.3)	3	Unlikely
		13	Possibly		7	Possibly		0	Possibly
		0	Probably		0	Probably		0	Probably
		1	Definitely		0	Definitely		0	Definitely
Procedural pain	10 (2.0)	8	Unlikely	6 (1.9)	4	Unlikely	1 (1.8)	Unlikely	
		1	Possibly		2	Possibly			
		1	Definitely						
Nausea	6 (1.2)	Unlikely		1 (0.3)	Unlikely		0		
Pruritus	5 (1.0)	4	Unlikely	2 (0.6)	Unlikely		0		
		1	Possibly						
Pyrexia	3 (0.6)	2	Unlikely	5 (1.6)	2	Unlikely	0		
		1	Possibly		3	Possibly			
Parvovirus B19 test positive	3 (0.6)	Possibly		0			0		
Anaemia	2 (0.4)	Unlikely		5 (1.6)	3	Unlikely	0		
					2	Possibly			
Insomnia	2 (0.4)	Unlikely		2 (0.6)	Unlikely		0		
Wheezing	2 (0.4)	Unlikely		2 (0.6)	Unlikely		0		
Hypertension	2 (0.4)	Unlikely		2 (0.6)	Unlikely		0		
Leukocytosis	2 (0.4)	Unlikely		1 (0.3)	Unlikely		0		
Ileus	2 (0.4)	Unlikely		1 (0.3)	Unlikely		0		
Prothrombin time prolonged	2 (0.4)	Possibly		1 (0.3)	Possibly		0		
Haemorrhagic anaemia	2 (0.4)	Unlikely		1 (0.3)	Unlikely		0		
Postprocedural bile leak	2 (0.4)	Unlikely		0			0		
Vascular graft complication	2 (0.4)	1	Unlikely	0			0		
		1	Possibly						
Alanine aminotransferase increased	2 (0.4)	Unlikely		0			0		
Aspartate aminotransferase increased	2 (0.4)	Unlikely		0			0		
Hypocalcaemia	2 (0.4)	Unlikely		0			0		
Hypokalaemia	2 (0.4)	Unlikely		0			0		
Hyponatraemia	2 (0.4)	Unlikely		0			0		
Headache	2 (0.4)	Unlikely		0			0		
Pulmonary embolism	2 (0.4)	Unlikely		0			0		
Erythema	2 (0.4)	Unlikely		0			0		
Deep vein thrombosis	2 (0.4)	Unlikely		0			0		
Urinary retention	2 (0.4)	Unlikely		0			0		
Constipation	1 (0.2)	Unlikely		3 (0.9)	Unlikely		0		
Anxiety	1 (0.2)	Unlikely		2 (0.6)	Unlikely		0		
Flatulence	1 (0.2)	Unlikely		1 (0.3)	Unlikely		0		

Vomiting	1 (0.2)	Unlikely	1 (0.3)	Unlikely	0	
Hyperglycaemia	1 (0.2)	Unlikely	1 (0.3)	Unlikely	0	
Ecchymosis	1 (0.2)	Unlikely	1 (0.3)	Unlikely	0	
Oedema peripheral	1 (0.2)	Unlikely	1 (0.3)	Unlikely	0	
Leukopenia	1 (0.2)	Unlikely	0		0	
Atrial fibrillation	1 (0.2)	Unlikely	0		0	
Ventricular tachycardia	1 (0.2)	Unlikely	0		0	
Conjunctival irritation	1 (0.2)	Unlikely	0		0	
Retroperitoneal haematoma	1 (0.2)	Unlikely	0		0	
Chills	1 (0.2)	Unlikely	0		0	
Hyperthermia	1 (0.2)	Possibly	0		0	
Pain	1 (0.2)	Unlikely	0		0	
Cellulitis	1 (0.2)	Possibly	0		0	
Incision site infection	1 (0.2)	Unlikely	0		0	
Liver abscess	1 (0.2)	Unlikely	0		0	
Postoperative wound infection	1 (0.2)	Unlikely	0		0	
Wound infection	1 (0.2)	Unlikely	0		0	
Contusion	1 (0.2)	Possibly	0		0	
Incision site erythema	1 (0.2)	Unlikely	0		0	
Postprocedural haemorrhage	1 (0.2)	Unlikely	0		0	
Procedural hypotension	1 (0.2)	Unlikely	0		0	
Vascular graft thrombosis	1 (0.2)	Unlikely	0		0	
Incision site pain	1 (0.2)	Unlikely	0		0	
Abdominal abscess	1 (0.2)	Unlikely	0		0	
Hyperkalaemia	1 (0.2)	Unlikely	0		0	
Hypomagnesaemia	1 (0.2)	Unlikely	0		0	
Vessel puncture site haematoma	1 (0.2)	Unlikely	0		0	
Peritonitis	1 (0.2)	Possibly	0		0	
Postprocedural infection	1 (0.2)	Unlikely	0		0	
Abdominal wound dehiscence	1 (0.2)	Possibly	0		0	
Wound secretion	1 (0.2)	Unlikely	0		0	
Activated partial thromboplastin time prolonged	1 (0.2)	Unlikely	0		0	
Blood bilirubin increased	1 (0.2)	Unlikely	0		0	
Blood glucose increased	1 (0.2)	Unlikely	0		0	
International normalised ratio increased	1 (0.2)	Unlikely	0		0	
Transaminases increased	1 (0.2)	Unlikely	0		0	
Urine output decreased	1 (0.2)	Unlikely	0		0	
Hypoglycaemia	1 (0.2)	Unlikely	0		0	
Hypoproteinaemia	1 (0.2)	Unlikely	0		0	
Back pain	1 (0.2)	Unlikely	0		0	
Pain in extremity	1 (0.2)	Unlikely	0		0	
Plasma cell myeloma	1 (0.2)	Unlikely	0		0	
Somnolence	1 (0.2)	Possibly	0		0	
Bladder spasm	1 (0.2)	Unlikely	0		0	
Dysuria	1 (0.2)	Unlikely	0		0	
Dyspnoea	1 (0.2)	Unlikely	0		0	
Hypoxia	1 (0.2)	Unlikely	0		0	

Pleural effusion	1 (0.2)	Unlikely	0		0	
Pleurisy	1 (0.2)	Unlikely	0		0	
Pulmonary oedema	1 (0.2)	Unlikely	0		0	
Rhonchi	1 (0.2)	Unlikely	0		0	
Hypotension	1 (0.2)	Unlikely	0		0	
Urinary tract infection	0		2 (0.6)	Unlikely	1 (1.8)	Unlikely
Weight decreased	0		2 (0.6)	Unlikely	0	
Asthenia	0		2 (0.6)	Unlikely	0	
Abdominal distension	0		1 (0.3)	Unlikely	0	
Cough	0		1 (0.3)	Unlikely	0	
Neutropenia	0		1 (0.3)	Unlikely	0	
Vaginal cellulitis	0		1 (0.3)	Possibly	0	
Procedural nausea	0		1 (0.3)	Unlikely	0	
Pancreatitis	0		1 (0.3)	Possibly	0	
Haematocrit decreased	0		1 (0.3)	Unlikely	0	
Haemoglobin decreased	0		1 (0.3)	Unlikely	0	
Body temperature increased	0		1 (0.3)	Unlikely	0	
White blood cell count increased	0		1 (0.3)	Possibly	0	
Joint swelling	0		1 (0.3)	Unlikely	0	
Disturbance in attention	0		1 (0.3)	Unlikely	0	
Hypoaesthesia	0		1 (0.3)	Unlikely	0	
Tachycardia	0		1 (0.3)	Unlikely	0	
Renal failure	0		1 (0.3)	Unlikely	0	
Urethral pain	0		1 (0.3)	Unlikely	0	
Urinary incontinence	0		1 (0.3)	Unlikely	0	
Laryngeal oedema	0		1 (0.3)	Unlikely	0	
Skin irritation	0		1 (0.3)	Unlikely	0	
Sepsis	0		0		1 (1.8)	Unlikely
Agitation	0		0		1 (1.8)	Unlikely
Coagulopathy	0		0		1 (1.8)	Unlikely

Note: For each preferred term, subjects are counted only once.

PAEDIATRIC CLINICAL STUDY IG1405

One (1.1%) subject from the VeraSeal group reported a suspected ADR of procedural pain, which was assessed as moderate in intensity. None of the subjects receiving EVICEL reported any suspected ADRs.

Analysis of Adverse Events by Organ System or Syndrome

CLINICAL STUDIES IG1101, IG1102, AND IG1103

Table 24 summarises TEAEs by system organ class (SOC) and treatment group occurring in ≥10% of subjects in any treatment group. No clinically meaningful differences among treatment groups were noted in the incidence of the most frequently reported system organ class of TEAEs.

The most frequently reported TEAEs by system organ class were typical of open surgeries. The most common TEAEs (≥20% of subjects by system organ class) in the 3 treatment groups were similar:

- VeraSeal (FS Grifols): Injury, poisoning and procedural complications (59.6%), gastrointestinal disorders (28.2%), general disorders and administration site conditions (21.2%)

- Surgicel: Injury, poisoning and procedural complications (58.4%), gastrointestinal disorders (36.3%), Respiratory, thoracic, and mediastinal disorders (21.3%), infections and infestations (20.6%), general disorders and administration site conditions (20.3%)
- MC: Injury, poisoning and procedural complications (49.1%), general disorders and administration site conditions (21.1%)

Table 24. Treatment-emergent adverse events by system organ class occurring in ≥10% of subjects within a treatment group in studies IG1101, IG1102 and IG1103 (safety Population)

System Organ Class	FS Grifols N = 500 n (%)	Surgicel N = 320 n (%)	Manual Compression N = 57 n (%)
Injury, poisoning and procedural complications	298 (59.6)	187 (58.4)	28 (49.1)
Gastrointestinal disorders	141 (28.2)	116 (36.3)	10 (17.5)
General disorders and administration site conditions	106 (21.2)	65 (20.3)	12 (21.1)
Vascular disorders	82 (16.4)	47 (14.7)	5 (8.8)
Respiratory, thoracic, and mediastinal disorders	80 (16.0)	68 (21.3)	1 (1.8)
Infections and infestations	76 (15.2)	66 (20.6)	8 (14.0)
Investigations	62 (12.4)	31 (9.7)	5 (8.8)
Blood and lymphatic system disorders	61 (12.2)	57 (17.8)	5 (8.8)
Metabolism and nutrition disorders	61 (12.2)	56 (17.5)	0
Cardiac disorders	54 (10.8)	44 (13.8)	3 (5.3)

PAEDIATRIC CLINICAL STUDY IG1405

The most frequently reported TEAEs at the SOC level were in the Gastrointestinal disorders SOC with 9/91 (9.9%) subjects in the VeraSeal treatment group and 6/87 (6.9%) subjects in the EVICEL treatment group. Also, 6/87 (6.9%) subjects in the EVICEL treatment group reported TEAEs in the General disorders and administration site conditions SOC (Table 21).

Serious adverse event/deaths/other significant events

All Serious Adverse Events

CLINICAL STUDIES IG1101, IG1102, AND IG1103

A summary of SAEs (including fatal SAEs) reported in ≥0.5% of subjects by preferred term in any treatment group in the integrated dataset is shown in Table 25. Eighty-one of 500 (16.2%) subjects in the VeraSeal (FS Grifols) treatment group experienced 167 SAEs, 41/320 (12.8%) subjects in the Surgicel group experienced 65 SAEs, and 11/57 (19.3%) subjects in the MC treatment group experienced 14 SAEs.

The SAEs in the VeraSeal group were considered unrelated to study treatment in all except 9 subjects. SAEs considered unlikely related to study treatment were as follows: postoperative wound infection, wound infection, abdominal abscess, deep vein thromboses (2 subjects, including 1 right femoral vein and 1 left peroneal vein in 1 subject), pulmonary embolism (2 subjects), postprocedural bile leak (2 subjects), and liver abscess. SAEs considered possibly related to study treatment were cellulitis, parvovirus B19 (B19V) test positive, abdominal wound dehiscence, and peritonitis.

All the SAEs in the Surgicel treatment group were considered unrelated to study treatment.

All the SAEs in the MC treatment group were considered unrelated to study treatment except for 1 event (sepsis, considered unlikely related).

No substantial differences in SAE incidences were noted among treatment groups.

Table 25. Treatment-emergent serious adverse events reported in ≥0.5% of subjects in any treatment group in studies IG1101, IG1102 and IG1103 (safety Population)

Preferred Term	FS Grifols N = 500 n (%)	Surgicel N = 320 n (%)	Manual Compression N = 57 n (%)
Subjects with any treatment-emergent SAE	81 (16.2)	41 (12.8)	11 (19.3)
Total number of SAEs	167	65	14
Respiratory failure	7 (1.4)	1 (0.3)	0
Deep vein thrombosis	5 (1.0)	2 (0.6)	0
Postoperative wound infection	5 (1.0)	0	1 (1.8)
Pneumonia	5 (1.0)	0	0
Renal failure acute	5 (1.0)	0	0
Postprocedural bile leak	4 (0.8)	2 (0.6)	0
Pulmonary embolism	4 (0.8)	2 (0.6)	0
Pleural effusion	4 (0.8)	1 (0.3)	0
Wound infection	4 (0.8)	0	0
Sepsis	3 (0.6)	3 (0.9)	1 (1.8)
Pyrexia	3 (0.6)	1 (0.3)	1 (1.8)
Abdominal wound dehiscence	3 (0.6)	1 (0.3)	0
Atrial fibrillation	2 (0.4)	2 (0.6)	0
Myocardial infarction	2 (0.4)	0	1 (1.8)
Abdominal abscess	1 (0.2)	2 (0.6)	0
Gangrene	1 (0.2)	0	2 (3.5)
Vascular graft thrombosis	1 (0.2)	0	2 (3.5)
Lymphorrhoea	1 (0.2)	0	1 (1.8)
Pyelonephritis	0	3 (0.9)	0
Osteonecrosis	0	0	1 (1.8)
Noncardiac chest pain	0	0	1 (1.8)
Acute coronary syndrome	0	0	1 (1.8)
Respiratory tract infection	0	0	1 (1.8)
Carotid sinus syndrome	0	0	1 (1.8)

SAE=serious adverse event
The incidence of an SAE is presented for all treatment groups if the SAE was reported in 0.5% or more of subjects within any treatment group.

PAEDIATRIC CLINICAL STUDY IG1405

Overall, 17 subjects reported treatment-emergent SAEs, 8 (8.8%) subjects in VeraSeal (FS Grifols) group and 9 (10.3%) subjects in EVICEL group. The most frequently reported TEAEs at the SOC level were in the infections and infestations SOC with 3/91 (3.3%) subjects in the VeraSeal treatment group and 3/87 (3.4%) subjects in the EVICEL treatment group. All SAEs were considered unrelated to the study treatment (Table 26).

Table 26. List of treatment-emergent serious adverse events – clinical study IG1101, IG1102 and IG1405 (safety Population)

Treatment Group	Type of Surgery	Subject	SAE Preferred Term	Start Day of SAE[a]	Causality
FS Grifols	Parenchymous	[redacted]	Cardiac arrest	Day 10	Unrelated
			Anaphylactic shock*	Day 1	Unrelated
			Anaphylactic shock	Day 1	Unrelated
			Diarrhoea	Day 13	Unrelated
			Vomiting	Day 13	Unrelated
			Wound infection	Day 13	Unrelated
			Pyrexia	Day 3	Unrelated
			Staphylococcal infection	Day 3	Unrelated
	Soft Tissue		Ileus	Day 4	Unrelated
			Intussusception	Day 4	Unrelated
			Transaminases increased	Day 22	Unrelated
			Postoperative wound infection	Day 21	Unrelated
EVICEL	Parenchymous		Cardiac arrest	Day 2	Unrelated
			Ascites	Day 8	Unrelated
			Post procedural haemorrhage	Day 1	Unrelated
			Pancytopenia	Day 26	Unrelated
			Pulmonary embolism	Day 9	Unrelated
			Ileus paralytic	Day 4	Unrelated
			Sepsis	Day 4	Unrelated
			Respiratory tract infection	Day 26	Unrelated
	Soft Tissue		Pulmonary hypertension	Day 10	Unrelated
			Acute respiratory failure	Day 42	Unrelated
			Respiratory syncytial virus infection	Day 42	Unrelated

IP=investigational product; SAE=serious adverse event

[a] Beginning on the surgery day, day corresponds to the protocol-defined visit day.

*Subject [redacted] 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 (EDC) database, this event was conservatively attributed as a treatment-emergent SAE. However, source data residing in the Global Pharmacovigilance (GPV) 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: Treatment-emergent SAEs are SAEs that occurred on or after the date/time of IP administration.

Deaths

CLINICAL STUDIES IG1101, IG1102, AND IG1103

A list of deaths among the 3 clinical trials is shown in Table 27. Thirteen of 500 (2.6%) subjects in the VeraSeal (FS Grifols) treatment group, 4/320 (1.3%) subjects from the Surgicel treatment group, and no subjects from the MC treatment group died. All of the SAEs with a fatal outcome were considered unrelated to study treatment.

Table 27. List of deaths in clinical studies IG1101, IG1102 and IG1103 (safety Population)

Subject Number	Preferred Term	Severity	Causality
FS Grifols (frequency)	13/500 (2.6%)		
[redacted]	Myocardial infarction	Severe	Not Related
	Respiratory failure	Severe	Not Related
	Vena cava thrombosis		
	Cardiac arrest		
	Hypotension	Severe	Not Related
	Respiratory failure		
	Hepatic failure		
	Septic shock	Severe	Not Related
	Gastrointestinal haemorrhage	Severe	Not Related
	Death	Severe	Not Related
	Brain injury	Severe	Not Related
	Cardiac arrest	Severe	Not Related
	Respiratory failure	Severe	Not Related
	Multi-organ failure	Severe	Not Related
	Hepatic necrosis	Severe	Not Related
	Liver abscess		
	Abdominal wound dehiscence	Severe	Not Related
	Intestinal perforation		
	Wound evisceration		
	Sepsis syndrome		
	Deep vein thrombosis	Severe	Not Related
Surgicel (frequency)	4/320 (1.3%)		
[redacted]	Multi-organ failure	Severe	Not Related
	Haemorrhage	Severe	Not Related
	Venous injury		
	Disseminated intravascular coagulation		
	Cardiac arrest		
	Hepatic failure	Severe	Not Related
	Death (cause unknown)	Severe	Not Related

PAEDIATRIC CLINICAL STUDY IG1405

A total of 3 deaths occurred in the study, 1 in the VeraSeal (FS Grifols) group and 2 in the EVICEL group. All deaths were considered unrelated to study treatment (Table 28).

Table 28. Deaths by subject - clinical study IG1405 (safety Population)

Treatment Group	Type of Surgery	Subject	SAE Preferred Term	Start Day of SAE[a]	Causality
FS Grifols	Parenchymous	[redacted]	Cardiac arrest	Day 10	Unrelated
EVICEL	Parenchymous		Cardiac arrest	Day 2	Unrelated
	Soft Tissue		Pulmonary hypertension	Day 10	Unrelated

SAE=serious adverse event

[a] Beginning on the surgery day, day corresponds to the protocol-defined visit day.

Laboratory findings

Complete Blood Count (CBC)

CLINICAL STUDIES IG1101, IG1102, AND IG1103

Changes in CBC parameters over time were typical of open surgeries and were similar among treatment groups at all time points. Average small-to-moderate decreases were noted in haematocrit, haemoglobin, red blood cells, and lymphocytes in all treatment groups and to a similar extent beginning from the day of the surgical procedure and through postoperative Day 7 or Day 14. Eosinophils followed a similar pattern immediately after surgery except that mean values were mildly increased from baseline values in all treatment groups on postoperative Days 7 and 14. Small-to-moderate mean increases in monocytes, neutrophils, and leukocytes were noted in all treatment groups on the day of the surgical procedure through Day 14. Mean platelet counts were mildly decreased after surgery through postoperative Day 3 and were moderately increased by postoperative Day 14 in all treatment groups. By postoperative Week 6, mean CBC values were not very different from baseline values in all treatment groups. There were no notable differences between treatment groups in change from baseline values at any time point.

From a review of individual studies, no notable differences in the changes from baseline values were observed between the VeraSeal treatment group and the comparator treatment group.

From review of individual studies, no notable differences in the incidences of shifts to abnormal high or low values were observed between the VeraSeal treatment group and the comparator treatment group.

PAEDIATRIC CLINICAL STUDY IG1405

At the Post-Operative Day 4 visit, there were no clinically significant mean changes from baseline in any of the CBC parameters in either of the two treatment groups, or any clinically significant differences between the two treatment groups.

Within the normal physiological ranges, shifts were observed in nearly all CBC parameters but in fewer than 10 subjects in both treatment arms.

Clinical Chemistry

CLINICAL STUDIES IG1101, IG1102, AND IG1103

Mean changes from baseline for glucose, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, total bilirubin, blood urea nitrogen, creatinine, sodium, potassium, chloride, and calcium were small in all treatment groups at all time points.

From review of individual studies, no notable differences in the changes from baseline values were observed between the VeraSeal treatment group and the comparator treatment group.

The number of subjects with shifts from normal values at baseline to abnormal values was generally small for most clinical chemistry parameters, and for no clinical chemistry parameter was a consistent difference among treatment groups noted.

From review of individual studies, no notable differences in the incidences of shifts to abnormal high or low values were observed between the VeraSeal treatment group and the comparator treatment group.

PAEDIATRIC CLINICAL STUDY IG1405

There were small mean decreases from baseline to Post-operative Day 4 visit in alkaline phosphatase and lactate dehydrogenase in both the VeraSeal and EVICEL treatment groups. There were no notable differences in the changes from baseline values between the VeraSeal and EVICEL treatment groups. Within physiological ranges, there were shifts in clinical laboratory parameters in no more than 10 subjects in both treatment groups.

Coagulation Parameters

CLINICAL STUDIES IG1101, IG1102, AND IG1103

Mean changes from baseline for aPTT ratio and prothrombin INR were small in all treatment groups at all time points.

PAEDIATRIC CLINICAL STUDY IG1405

Mean changes from baseline to Post-operative Day 4 visit for aPTT ratio and prothrombin time were small and similar between the VeraSeal and EVICEL treatment groups.

Laboratory Values Reported as Adverse Events

CLINICAL STUDIES IG1101, IG1102, AND IG1103

A summary of TEAEs reported in at least 2 subjects within a treatment group due to individual clinically significant abnormal laboratory results by treatment group is provided in Table 29.

Most events were reported for single subjects within a treatment group. Only anaemia (VeraSeal [FS Grifols], 10/500 [2.0%] subjects; Surgicel, 9/320 ([2.8%] subjects) and coagulopathy (MC, 2/57 [3.5%] subjects) were reported by ≥2% of subjects within a treatment group.

Overall, no clinically meaningful differences were noted among treatment groups in the incidences of TEAEs due to clinically significant abnormal laboratory results.

Table 29. Treatment-emergent adverse events due to clinically significant abnormal laboratory results reported in ≥2 subjects within a treatment group in studies IG1101, IG1102 and IG1103 (safety Population)

Preferred Term	FS Grifols N=500 n (%)	Surgicel N=320 n (%)	MC N=57 n (%)
Any clinically significant abnormal laboratory result	51 (10.2)	36 (11.3)	3 (5.3)
Anaemia	10 (2.0)	9 (2.8)	0
Alanine aminotransferase increased	5 (1.0)	2 (0.6)	0
Anaemia postoperative	4 (0.8)	1 (0.3)	0
Aspartate aminotransferase increased	3 (0.6)	3 (0.9)	0
Hypocalcaemia	3 (0.6)	2 (0.6)	0
Prothrombin time prolonged	3 (0.6)	2 (0.6)	0
Hyperglycaemia	2 (0.4)	3 (0.9)	0
Hypokalaemia	2 (0.4)	2 (0.6)	0
Haemorrhagic anaemia	2 (0.4)	2 (0.6)	0
Hyponatraemia	2 (0.4)	1 (0.3)	0
Liver function test abnormal	2 (0.4)	1 (0.3)	0
Blood bilirubin increased	2 (0.4)	1 (0.3)	0
Postprocedural haemorrhage	2 (0.4)	0	0
Hepatic failure	2 (0.4)	0	0
Leukocytosis	1 (0.2)	6 (1.9)	0
Hyperkalaemia	1 (0.2)	3 (0.9)	0
Platelet count increased	1 (0.2)	2 (0.6)	0
Coagulopathy	1 (0.2)	0	2 (3.5)
Hyperbilirubinaemia	0	2 (0.6)	0

Note: For each preferred term, subjects are counted only once.

PAEDIATRIC CLINICAL STUDY IG1405

In the VeraSeal treatment group, the following TEAEs related to clinically significant laboratory values were observed: anaemia in 2 subjects (2.2%), and anaemia post-operative, haemoglobin decreased and platelet count increased in 1 subject each (1.1%). In the EVICEL treatment group, the following TEAEs related to clinically significant laboratory values were observed: anaemia in 3 subjects (3.4%), and haemoglobin decreased, hypoalbuminaemia, and hypokalaemia in 1 subject each (1.1%). All these TEAEs were considered unrelated to the study treatment.

Virus Safety Testing

CLINICAL STUDIES IG1101, IG1102, AND IG1103

At baseline, blood samples were collected from adult subjects in the VeraSeal, Surgicel, and MC treatment groups and tested for markers of acute, chronic, or previous infection with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and B19V by viral nucleic acid testing and viral serology test methods by a central laboratory. At the Day 7, Day 14, Week 6, and Month 3 visits and, when applicable, the Month 6 visit, additional blood samples were collected from adult subjects. Samples collected after baseline were analysed for a particular virus only in the event of negative results of the analysis for that particular virus performed on the samples collected at baseline.

During the studies, no samples for virus safety testing were collected for paediatric subjects in the VeraSeal or Surgicel treatment groups, and no paediatric subjects received MC treatment.

A subject was counted as a new positive if the subject had a positive postbaseline result and a negative or missing result at baseline. Each new positive was verified and thoroughly investigated as a potential treatment-emergent viral infection. Overall, there was no treatment-emergent viral infection in all 3 studies. The results are further discussed in the sections below.

Hepatitis A Virus

Fifteen subjects in the VeraSeal treatment group, 11 subjects in the Surgicel treatment group, and 1 subject in the MC treatment group were new positives for hepatitis A (immune globulin M class [IgM] + immune globulin G class [IgG]) antibody or hepatitis A IgG antibody at Week 6. For all of these subjects, the data indicated that there was exposure to HAV prior to study entry, the Week 6 result was a false positive, there was passive transmission of HAV IgG antibody with transfusion of blood products, or the baseline result was possibly a false negative.

None of these subjects exhibited any clinical signs or symptoms of an acute viral infection. Taken together, the data suggest that for each subject there was no treatment-emergent viral infection.

Hepatitis B Virus

One subject in the VeraSeal treatment group was a new positive for hepatitis B surface antigen (HBsAg) at Month 3, and 1 subject in the Surgicel treatment group and 1 subject in the MC treatment group were new positives for HBsAg at Week 6. For the VeraSeal-treated subject, the data suggested that the HBsAg result at Week 6 was due to the subject receiving a dose of hepatitis B vaccine shortly before the Week 6 visit. For the Surgicel-treated subject, the data suggested that the positive HBsAg result at Week 6 was due to a transient seroconversion as a result of hepatitis B vaccination prior to the Week 6 visit. For the MC-treated subject, the data confirmed a false positive result at Week 6.

None of these subjects exhibited any clinical signs or symptoms of an acute viral infection. Taken together, the data suggest that for each subject there was no treatment-emergent viral infection.

Hepatitis C Virus

Two subjects in the VeraSeal treatment group were new positives for HCV antibody at Month 3. For 1 subject, the data confirmed a hepatitis C infection prior to study entry. For the other subject, the data confirmed a false positive result at Month 3. Taken together, the data suggest that for each subject there was no treatment-emergent viral infection.

Human Immunodeficiency Virus

For scheduled postbaseline testing, all subjects tested in the VeraSeal, Surgicel, and MC treatment groups were negative for HIV ribonucleic acid (RNA) and HIV-1 (Group M and Group O)/HIV-2 antibody.

Parvovirus B19

One subject in the VeraSeal treatment group was positive for B19V IgG at Day 7, 18 subjects in the VeraSeal treatment group and 6 subjects in the Surgicel treatment group were new positives for B19V IgG antibody at Day 14, 2 subjects in the VeraSeal treatment group were new positives for B19V IgM antibody at Day 14, and 1 subject in the VeraSeal treatment group was a new positive for both B19V IgG antibody and B19V IgM antibody at Day 14. For each of these subjects, the data indicated that there was exposure to B19V prior to study entry, postbaseline results were false positives, the baseline results were false negatives, there was passive transmission of B19V IgG antibody with transfusion of blood products, or the baseline results were possible false negatives.

None of these subjects exhibited any clinical signs or symptoms of an acute viral infection. Taken together, the data suggest that for each subject there was no treatment-emergent viral infection.

PAEDIATRIC CLINICAL STUDY IG1405

No virus safety testing was conducted during study IG1405.

VITAL SIGNS, PHYSICAL EXAMINATION FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Vital Signs

CLINICAL STUDIES IG1101, IG1102, AND IG1103

Mean changes from baseline in systolic and diastolic blood pressure at all time points immediately before surgery, during surgery, and at the time of completion of the surgery were typical of open surgeries under general anaesthesia (median systolic changes approximately –10 to –30 mmHg, median diastolic changes approximately –10 to –20 mmHg) and were not notably different among treatment groups. At 2 hours after surgery and at all time points thereafter, no clinically meaningful mean changes from baseline were noted for systolic or diastolic blood pressure.

Mean changes from baseline in pulse rate at all time points were small in all treatment groups.

Mean changes from baseline in respiration rate at all time points were small in all treatment groups.

Mean changes from baseline in body temperature immediately before surgery, during surgery, and at the time of completion of the surgery were typical of open surgeries under general anaesthesia approximately –0.5°C) and were not different among treatment groups. At 2 hours after surgery and at all time points thereafter, no clinically meaningful mean changes from baseline were noted.

PAEDIATRIC CLINICAL STUDY IG1405

Similar decreases in mean systolic and diastolic blood pressure from baseline were observed in both treatment groups at all time points immediately before surgery, during surgery, and at the time of completion of the surgery (median systolic changes were approximately –2 to –12.5 mmHg, median diastolic changes were approximately –3 to –13 mmHg). At the Post-Operative Day 4 visit, there were no meaningful changes in blood pressure from baseline in either of the 2 treatment groups. Three subjects (3.4%) in the VeraSeal group, and 2 subjects (2.3%) in the EVICEL treatment group had abnormal blood pressure findings at the Post-Operative Day 4 visit.

Small variations in pulse rate occurred at all time points and both treatment groups throughout the study. At the Post-Operative Day 4 visit, the mean (±SD) pulse rates were 93.2 (±23.61) and 94.9 (±23.80) for the VeraSeal and EVICEL treatment groups, respectively. Two subjects (2.3%) in the VeraSeal group and 1 subject (1.2%) in the EVICEL treatment group had abnormal pulse rate findings at the Post-Operative Day 4 visit.

Mean changes from baseline in respiration rate at all time points were small in both treatment groups (mean changes from baseline ranged from –1 to –4 breaths per minute). At the Post-Operative Day 4 visit, the mean (±SD) respiration rates were 21.2 (±5.86) and 20.9 (±5.41) breaths per minute for the VeraSeal and EVICEL treatment groups, respectively. One subject (1.1%) in the VeraSeal group and 1 subject (1.2%) in the EVICEL treatment group had abnormal respiration rate findings at the Post-Operative Day 4 visit. Four subjects (4.5%) in the VeraSeal treatment group and 3 subjects (3.5%) in the EVICEL treatment group were on mechanical ventilation at the Post-Operative Day 4 visit.

Mean changes from baseline in body temperature at all time points in both treatment groups were typical of open surgeries under anaesthesia (mean changes from baseline in body temperature ranged from –0.3 to +0.2°C). At the Post-Operative Day 4 visit, the mean (±SD) body temperatures were 36.64 (±0.340)°C, and 36.77 (±0.362)°C for the VeraSeal and EVICEL treatment groups, respectively. One subject (1.1%) in the VeraSeal group and 0 subjects in the EVICEL treatment group had abnormal body temperature findings at the Post-Operative Day 4 visit.

Clinically Significant Abnormal Vital Signs

CLINICAL STUDIES IG1101, IG1102, AND IG1103

No clinically meaningful differences were noted among treatment groups in the incidences of TEAEs due to clinically significant abnormal vital signs results (Table 30).

Table 30. Treatment-emergent adverse events due to clinically significant abnormal vital signs in reported in studies IG1101, IG1102 and IG1103 (safety Population)

Preferred Term	FS Grifols N=500 n (%)	Surgicel N=320 n (%)	MC N=57 n (%)
Any clinically significant abnormal vital sign result	30 (6.0)	18 (5.6)	4 (7.0)
Hypertension	8 (1.6)	0	0
Hypotension	6 (1.2)	2 (0.6)	1 (1.8)
Pyrexia	4 (0.8)	3 (0.9)	3 (5.3)
Sinus tachycardia	4 (0.8)	3 (0.9)	0
Tachycardia	2 (0.4)	6 (1.9)	0
Body temperature increased	2 (0.4)	1 (0.3)	0
Hypertensive crisis	2 (0.4)	1 (0.3)	0
Procedural hypotension	2 (0.4)	0	0
Tachypnoea	2 (0.4)	0	0
Hypothermia	1 (0.2)	0	1 (1.8)
Anaemia	1 (0.2)	0	0
Supraventricular tachycardia	1 (0.2)	0	0
Portal vein thrombosis	1 (0.2)	0	0
Incision site erythema	1 (0.2)	0	0
Postoperative fever	1 (0.2)	0	0
Dyspnoea exertional	1 (0.2)	0	0
Fatigue	0	1 (0.3)	0
Arrhythmia	0	1 (0.3)	0
Procedural pain	0	1 (0.3)	0
Blood pressure diastolic decreased	0	1 (0.3)	0
Dyspnoea	0	1 (0.3)	0

MC = manual compression
Note: For each preferred term, subjects are counted only once.

PAEDIATRIC CLINICAL STUDY IG1405

In the VeraSeal treatment group, 2 TEAEs related to vital signs were observed in 2 subjects (2.2%). Both events were hypertension and considered unrelated to the study treatment. No TEAEs related to vital signs were reported in EVICEL group.

Physical Examination Findings

CLINICAL STUDIES IG1101, IG1102, AND IG1103

Physical assessment results by time point were summarised by treatment and included a summary of changes from baseline considered by the principal investigator to be clinically relevant. No clinically meaningful differences were noted among treatment groups in the number of clinically relevant abnormal physical assessments.

PAEDIATRIC CLINICAL STUDY IG1405

At the Post-operative Day 4 Visit, 86 subjects in the VeraSeal treatment group, and 85 subjects in the EVICEL group had a physical assessment performed. One subject in the VeraSeal treatment group and 2 subjects in the EVICEL treatment group had clinically relevant changes worsened from baseline. At the Post-operative Day 30 Visit, 86 subjects in the VeraSeal treatment group and 80 subjects in the EVICEL group had a physical assessment performed. Two (2) subjects in the VeraSeal treatment group showed

clinically relevant changes worsened from baseline, while none of 80 subjects in the EVICEL treatment group showed such clinically relevant changes.

Immunogenicity

CLINICAL STUDIES IG1101, IG1102, AND IG1103

According to the 3 trial protocols, subjects were tested for immunogenicity if 1 or more of their postexposure samples had inexplicable prolonged coagulation times (INR ≥2.0 or aPTT ratio ≥1.5). A total of 29 subjects from the VeraSeal (n=22), Surgicel (n=4), and MC (n=3) treatment groups were tested with the immunogenicity methods for antibodies against human coagulation factor V, human thrombin, and human fibrinogen. Testing was performed on specimens collected at baseline, postoperative Day 14 (± 2 days), and postoperative Week 6 (± 4 days) visits. Immunogenicity testing used a tiered approach which included screening and confirmatory enzyme-linked immunosorbent assay methods with statistically derived cut points.

Two specimens were found to be positive for antibodies to human thrombin: baseline and Day 14 specimens from 1 subject in the VeraSeal treatment group, with antibody titers of 9363 and 11739, respectively. Although this subject was found to have antibodies to human thrombin, the antibodies were present at both baseline and Day 14, and their titers were at similar levels, indicating no immune response was generated as a result of the treatment with VeraSeal. Therefore, no immunogenicity response was observed in subjects treated with VeraSeal or Surgicel or MC in the clinical trials, demonstrating comparable safety profiles with respect to immunogenicity.

PAEDIATRIC CLINICAL STUDY IG1405

Immunogenicity testing was not conducted in study IG1405.

Safety in special populations

Paediatric Subjects

CLINICAL STUDIES IG1101, IG1102, AND IG1103

These studies allowed the enrolment of both adult and paediatric subjects, but only 23 paediatric subjects were included and evaluated. Table 31 summarises TEAEs reported in ≥5% of subjects within a treatment group by preferred term in the paediatric and adult subgroups. None of the paediatric subjects were in the MC treatment group.

Overall, no clinically meaningful differences were noted in the incidences of TEAEs in paediatric subjects treated with VeraSeal (FS Grifols) compared with paediatric subjects treated with Surgicel.

Table 31. Treatment-emergent adverse events reported in ≥5% of subjects within a treatment group in adult (≥18 years) versus paediatric (<18 years) subjects in studies IG1101, IG1102 and IG1103 (safety Population)

	FS Grifols		Surgicel	
Preferred Term	Adult N=489 n (%)	Paediatric N=11 n (%)	Adult N=308 n (%)	Paediatric N=12 n (%)
Procedural pain	206 (42.1)	3 (27.3)	144 (46.8)	3 (25.0)
Nausea	67 (13.7)	0	55 (17.9)	1 (8.3)
Pyrexia	48 (9.8)	2 (18.2)	33 (10.7)	2 (16.7)
Constipation	46 (9.4)	0	34 (11.0)	0
Anaemia	44 (9.0)	1 (9.1)	39 (12.7)	1 (8.3)
Hypotension	36 (7.4)	0	15 (4.9)	0
Hypertension	33 (6.7)	2 (18.2)	22 (7.1)	2 (16.7)
Oedema peripheral	29 (5.9)	1 (9.1)	14 (4.5)	0
Vomiting	28 (5.7)	1 (9.1)	24 (7.8)	2 (16.7)
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)
Diarrhoea	15 (3.1)	1 (9.1)	12 (3.9)	0
Procedural haemorrhage	12 (2.5)	1 (9.1)	6 (1.9)	0
Body temperature increased	11 (2.2)	0	1 (0.3)	1 (8.3)
Hyperglycaemia	9 (1.8)	0	18 (5.8)	0

Hypophosphataemia	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)
Hypoalbuminaemia	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
Activated partial thromboplastin time prolonged	0	1 (9.1)	1 (0.3)	0
Productive cough	1 (0.2)	0	0	1 (8.3)
Procedural vomiting	0	1 (9.1)	2 (0.6)	0
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)
Influenza	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)

Note: For each preferred term, subjects are counted only once.

Two of 11 (18.2%) paediatric subjects in the VeraSeal treatment group experienced 3 SAEs, and 3/12 (25%) paediatric subjects in the Surgicel treatment group experienced 5 SAEs. All the SAEs started several days or weeks after the surgery except for 1 subject in the VeraSeal treatment group (laryngospasm) which started on Day 1 and resolved the same day. All SAEs in paediatric subjects were considered unrelated to study treatment.

The small number of paediatric subjects and the large imbalance in the numbers of adult versus paediatric subjects makes interpretation of the TEAE incidence rates in these subgroups difficult. The majority of the most frequently reported TEAEs in adults were either not reported in paediatric subjects or were reported in only a single paediatric subject within a treatment group. The TEAEs reported in paediatric subjects but not in adult subjects were reported by only single paediatric subjects treated with VeraSeal or single paediatric subjects treated with Surgicel. The exclusively paediatric study IG1405 was then performed. Although paediatric subjects were enrolled in the Preliminary Part I of studies IG1102 and IG1103, safety data for study IG1405 have not been integrated with IG1102 and IG1103 data, as IG1405 study consisted of exclusively paediatric subjects, and the comparator was different (EVICEL instead of Surgicel).

Discontinuation due to adverse events

CLINICAL STUDIES IG1101, IG1102, AND IG1103

No subject in any treatment group of any of the 3 clinical studies was withdrawn from the trial due to an AE.

PAEDIATRIC CLINICAL STUDY IG1405

No subjects were discontinued from the study due to non-fatal TEAEs in the VeraSeal group; one subject under palliative care died (cardiac arrest). One subject (1.1%) from EVICEL group experienced a non-fatal 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.

2.5.1. Discussion on clinical safety

The MAH provided data from the paediatric study IG1405 to obtain an extension of indication for the treatment of children. The submission not only includes the CSR of the paediatric study, but also a summary of the data of the previous three phase 3 trials IG1101, IG1102, and IG1103, which mainly recruited adult patients. The data from these earlier trials were presented and discussed in more detail during the initial MA procedure (also see EMA EPAR for VeraSeal, EMA/734511/2017).

Study IG1405 was a prospective, randomized, active-controlled (EVICEL), single-blind, parallel group clinical trial to evaluate the safety and efficacy of VeraSeal as an adjunct to haemostasis during surgery in paediatric subjects. The study recruited subjects <18 years of age who required an elective (non-emergent), open (non-laparoscopic), pelvic, abdominal, or thoracic (non-cardiac) surgical procedure. Preterm or newborn infants could be enrolled if they required either elective or emergency open surgery.

In the paediatric study IG1405, 91 participants were treated with VeraSeal, and 87 participants were treated with EVICEL (safety population, includes subjects who received any amount of treatment). Including the previous phase 3 trials, a total of 591 subjects of all age groups received treatment with VeraSeal (IG1101: N=168, IG1102: N=163, IG1103: N=169, IG1104: N=91). Among the participants of the first three phase 3 trials (IG1101, IG1102, IG1103), 11 were below 18 years of age. For both the IP (VeraSeal) and the comparator (EVICEL), the maximum allowable volume was 12 mL for subjects ≥2 years of age and 6 mL for subjects <2 years of age. The applied estimated mean volume per subject was higher for VeraSeal with a mean of 4.641 mL (median: 4.800 mL, range of 0.60 to 12.00 mL; mean volume for parenchymous tissue surgery: 5.784 mL; mean volume for soft tissue surgery: 3.473 mL), compared to EVICEL with a mean of 3.104 mL (median: 3.000 mL, range of 0.10 to 8.00 mL; mean volume for parenchymous tissue surgery: 3.788 mL; mean volume for soft tissue surgery: 2.436 mL). No participant received more than the prespecified maximum volumes. During the earlier phase 3 trials (IG1101, IG1102, IG1103), more volume of VeraSeal was applied, with a mean of 6.78 mL (median: of 6.00 mL; range of 0.3 to 18.0 mL).

The mean age of participants of study IG1405 was 8.63 years (ITT population, both treatment arms). Six (3.2%) participants were ≤27 days of age, 37 (19.9%) participants were between ≥28 days to ≤23 months of age, 67 (36%) were between ≥2 years - ≤11 years of age, and 76 (40.9%) participants were between 12 and ≤17 years. A higher proportion of male patients were recruited (male: 62.4%, female: 37.6%), which is not optimal but considered acceptable.

The overall size of the paediatric safety database was considered limited. Furthermore, it was noted that in total 6 subjects below 27 days of age were included in the study. In the response to the RSI, the MAH clarified that all 6 subjects below 27 days of age underwent elective procedures. Taking into account that very few patients below the age of 27 days were included in the pivotal study and an indication without a lower age limit is envisaged, the MAH was asked to provide a justification that data from older children can be extrapolated to the younger ones and that there are no excipients in the drug product not suitable

for small children. The MAH provided a thorough justification why the beneficial effects of topical fibrin sealant application can be extrapolated from adult and older paediatric age cohorts to neonates. The excipients used in the thrombin and the fibrinogen component do not raise any safety concerns. The granting of an indication without a lower age limit can therefore be supported.

The types of surgeries were balanced with 51.1% parenchymous and 48.9% soft tissue surgeries. The baseline intensity of bleeding at the target bleeding site was either mild (53.3%) or moderate (46.7%) for all participants. The size of the bleeding surface was determined as small (TBS ≤10 cm2) for most (86.1%) of the target bleeding sites, and some were considered as medium sized (between 10 cm2 and ≤ 100 cm2).

Among participants of Study IG1405 who received VeraSeal, 24 (26.4%) experienced 46 Treatment Emergent Adverse Events (TEAEs), compared to 16 participants (18.4%) with 38 TEAEs in the EVICEL group. Most of these events were mild or moderate in severity (91.3% in the VeraSeal group, 78.9% in the EVICEL group). Severe TEAEs were reported by 3 (3.3%) participants in the VeraSeal group (4 events: cardiac arrest, ileus, intussusception, and anaphylactic shock) and 5 (5.7%) participants in the EVICEL group (8 events: cardiac arrest, respiratory syncytial virus infection, post procedural haemorrhage, haemoglobin decreased, acidosis, acute respiratory failure, pulmonary embolism, and pulmonary hypertension).

In the VeraSeal group, the SOCs with the highest subject incidences of TEAEs (above 5%) were Gastrointestinal disorders (9 [9.9%] subjects with 14 TEAEs), Injury, poisoning and procedural complications (6 [6.6%] subjects with 6 TEAEs) and Infections and infestations (5 [5.5%] subjects with 6 TEAEs). In the EVICEL group, the SOCs with the highest subject incidences were General disorders and administration site conditions (6 [6.9%] subjects with 7 TEAEs), Gastrointestinal disorders (6 [6.9%] subjects with 9 TEAEs) and Infections and infestations (5 [5.7%] subjects with 5 TEAEs). The most commonly reported TEAEs by Preferred Term (PT) reported for at least 2 participants per group were vomiting (6 participants [6.6%]), anaemia, abdominal distension, anaphylactic shock, wound infection, wound dehiscence, and hypertension (each for 2 participants [2.2%]) in the VeraSeal group, compared to pyrexia (5 participants [5.7%]), vomiting, anaemia (each for 3 participants [3.4%]), and nausea (2 participants [2.3%]) in the EVICEL group.

Upon request, the MAH provided tables indicating TEAEs by gender. Although some imbalances regarding subject incidences of TEAES are noted in participants who received VeraSeal (e.g., more females reported TEAEs in the SOCs of Investigations and Infections and infestations), these numbers need to be interpreted with caution due to the few participants. Overall, the incidences of subjects who reported any TEAEs were comparable between female (28.2%) and male (25%) participants.

As response to the RSI, the MAH provided tables comparing intraoperative (defined as TEAEs from the time of induction of anaesthesia until the completion of surgery) and surgical (defined as TEAEs starting from completion of surgery until 24 hours after the completion of surgery or the time of recovery from anaesthesia, whichever is later) TEAEs between VeraSeal and the comparator EVICEL. Among the surgical TEAEs, the event of vomiting was more frequent in the VeraSeal group (5 events) compared to the EVICEL group (1 event). Apart from that, no meaningful differences were noted between the groups. The event of vomiting is already included in section 4.8 of the SmPC.

Except for one TEAE of procedural pain ("possibly related"), all other events were considered as unrelated to treatment by the Investigator. This event was the only suspected ADR (adverse drug reaction). Suspected ADRs were defined as adverse events with a definite or possible causal relationship to study treatment. Of note, this definition deviates from the previous trials, where also "unlikely" related events were a possible category and deemed as an ADR. The ADR of procedural pain is already included in section 4.8 of the SmPC.

The TEAEs of wound infection (2 subjects), wound dehiscence (2 subjects), wound complication (1 subject) and procedure pain (1 subject) are reported in the VeraSeal group, as compared to zero of these TEAEs in Evicel group. All TEAE except for one TEAE of procedural pain were considered unrelated to VeraSeal by the Investigator. The MAH was asked to justify in detail the causality assessment of these TEAE and discuss the higher rate of wound / procedure TEAE in VeraSeal group versus comparator group. The MAH stated that the causality assessment was to be performed by the investigator in accordance with the study protocol. The MAH further argued that the investigator as treating physician/surgeon had the most complete medical understanding of the patient's clinical condition thereby best suited to determine association/causality determinations. In principle, this can be agreed. However, imbalances for certain TEAEs of interest such as the mentioned events still require special scrutiny, even if they were not considered related. Overall, the additional information provided for the described events (see the response to the RSI) do not give reason to assume that they could have been caused by the investigational product. Wound infection is already included in section 4.8 of the SmPC. When comparing the safety data of the previous trials with the paediatric trial, striking differences in incidences of AEs for patients who received VeraSeal are noted, e.g., for subjects with any TEAE (phase 3 trials in adults: 83.8% vs. paediatric trial: 26.4%), or subjects with any ADRs (phase 3 trials in adults: 16.2% vs. paediatric trial: 1.1%). These differences may to a large extent be explainable by aspects such as the longer observation period in the previous trials (3 months ± 7 Days vs. 30 days ±7 Days), the age difference (mean 56.86 years of age vs. mean 8.43 years of age; both numbers representing the age in the VeraSeal groups), and different eligibility criteria. For example, patients with mild and severe bleedings at the target bleeding site were excluded in the previous trials in adults, while cases with mild bleedings were still eligible for the paediatric trial. However, the fact that the event of procedural pain was reported by 41.8% of adults recruited for the earlier trials compared to only one participant (1.1%) in the paediatric trial might suggest differences in reporting between the trials and that the comparability of the results may be limited.

Treatment-emergent serious adverse events were reported by 8 (8.8%) subjects in VeraSeal group and 9 (10.3%) subjects in EVICEL group and all were considered unrelated by the Investigator. The provided background information does not give any reason to doubt this assessment. Two events of anaphylactic shock were reported and both events were linked to spillage of hydatide cysts (Echinococcus granulosus), which is a known cause for such events. One anaphylactic shock occurred prior to administration of study drug and the second event occurred 45 minutes after closure of the abdominal site. Given the time point of the second event, a potential relationship to administration of study medication cannot be completely excluded, however, spillage of hydatide cyst fluid appears as a reasonable cause. The risk for hypersensitivity reactions (including anaphylaxis) is already reflected as a class effect in the SmPC section 4.8.

Three children died during the trial: two participants in the EVICEL group (cardiac arrest and pulmonary hypertension) and one participant in the VeraSeal group (cardiac arrest). The MAH provided detailed narratives for these cases. The children suffered from severe conditions caused by hepatic tumours or pulmonary hypertension. According to the Investigator, none of these events were considered related to treatment, which can be agreed.

One participant in the EVICEL group experienced a non-fatal TEAE (acute respiratory failure secondary to RSV infection) leading to discontinuation from the trial, while no such event was reported for participants who received VeraSeal.

No unexpected findings or clinically meaningful differences between the treatment groups were detected regarding clinical laboratory, vital signs, and physical assessments.

Immunogenicity was not investigated during the paediatric. However, no subject developed antibodies to coagulation factor V, human thrombin or human fibrinogen during the previous phase 3 trials. In addition

to the uncertainty regarding immunogenicity, as with all plasma derived products, transmission of infectious entities cannot be completely excluded. For VeraSeal, the implementation of double nanofiltration lessens this concern and leads to a final product with a high safety standard.

Summarizing, while a slightly higher rate of TEAEs was noted in the VeraSeal groups, the overall safety profile was comparable between the treatment groups. Only one TEAE of procedural pain was considered related to treatment by the Investigator, which is already reflected in section 4.8 of the SmPC.

2.5.2. Conclusions on clinical safety

The paediatric trial did not reveal new safety concerns and the safety profile of VeraSeal was considered acceptable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version 6.0 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 7.0 is acceptable.

The main changes in this RMP version encompass: Inclusion of paediatric indication; updated data lock point to include post marketing information; and inclusion of information from finalized paediatric study IG1405.

The CHMP endorsed the Risk Management Plan version 7.0 with the following content:

Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None identified
Important potential risks	• None identified
Missing information	• None identified

Pharmacovigilance plan

Not applicable, as there are no specific ongoing or planned additional pharmacovigilance activities in the Pharmacovigilance Plan. Routine pharmacovigilance activities are considered sufficient for post-authorisation safety monitoring.

Risk minimisation measures

There are no additional risk minimization measures for VeraSeal.

Routine risk minimisation activities are sufficient to manage the safety concerns of VeraSeal.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

A user Testing for Readability was conducted on the package leaflet of VeraSeal submitted to the Agency as part of the procedure EMEA/H/C/004446/R/0018. The results of the study indicated that the package leaflet was legible, clean and easy to use and that potential users would be able to locate, understand and appropriately act upon the information contained in it.

Although the tested package leaflet did not incorporate the changes related to the inclusion of the paediatric indication, the MAH considers that the proposed changes do not affect the readability of the package leaflet and the conclusions of the user testing are fully relevant.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

When surgical haemostasis using sutures, ligature or cautery is inadequate or impractical, topical haemostatic agents are routinely employed to achieve haemostasis during surgical procedures. Two different approaches are implemented, i.e. physical agents, which promote haemostasis using a passive substrate and which are licensed as devices, and biologically active agents, which enhance coagulation at the bleeding site and are licensed as medicinal products.

The objective of the use of such topical agents is to stop surgical wound bleeding, therefore time to haemostasis, proportion of subjects achieving haemostasis at a certain time point and treatment failure are commonly used efficacy endpoints.

The MAH has applied for the following paediatric indication:

"Supportive treatment in adults and children where standard surgical techniques are insufficient:

- for improvement of haemostasis.

- as suture support: in vascular surgery."

3.1.2. Available therapies and unmet medical need

A number of devices are in widespread clinical use, e.g., collagen patches, gelatine sponges or powder, regenerated oxidised cellulose. At the same time, several fibrin sealants are licensed in the EU either nationally, like Tisseel, or via the centralised procedure, like EVICEL.

3.1.3. Main clinical studies

The MAH submitted one finished phase 3 study (IG1405) in a paediatric population requiring elective (non-emergent), open (non-laparoscopic), pelvic, abdominal, or thoracic (non-cardiac) surgical procedures in order to include children into the indication. Preterm or newborn infants could be enrolled if they required either elective or emergency open surgery. The surgeries were expected to yield target bleeding sites occurring in parenchymous organs or soft tissue that were appropriate for the use of a fibrin sealant in order to achieve haemostasis.

186 paediatric subjects were randomised to treatment with VeraSeal (95) or Evicel (91). The age range of the recruited subjects reached from newborns to babies and toddlers up to adolescents. More male than female participants were included in the trial, and the majority of patients was White.

The active comparator selected for the comparative evaluation of the haemostatic efficacy of VeraSeal was Evicel, which is a fibrin sealant that is authorised via the CP in the EU since 2008 for adult patients only. Two other fibrin sealants widely available in the EU, Tisseel and Artiss, are licensed via DCP also for adult patients only. As off-label use of fibrin sealants in children can be assumed, the choice of a medicinal product that is centrally licensed as the comparator is comprehensible and acceptable. Trial IG1405 was single blind with the patient blinded towards assigned treatment and not the investigator (surgeon).

The selected primary efficacy endpoint, the proportion of subjects achieving haemostasis at 4 minutes, is considered relevant. The secondary endpoints (Cumulative proportion of subjects achieving haemostasis at 7 and 10 minutes; Treatment failures) are considered appropriate.

Subgroup analyses and sensitivity analyses supplement the primary analysis and substantiate the robustness of the findings.

3.2. Favourable effects

The provided efficacy data show that VeraSeal is non-inferior to Evicel for the control of mild or moderate bleeding in parenchymous organ or soft tissue surgery. The rate of haemostasis by T4 in the mITT population in trial IG1405 was 88/91 (96.7%) subjects in the VeraSeal treatment group and 83/87 (95.4%) subjects in the Evicel treatment group. The noninferiority of VeraSeal has been demonstrated as the lower limit of the 95% CI at 0.96 exceeded the predefined margin of 0.8.

In the PP population, this result is mirrored with the rate of haemostasis by T4 being 96.6% (85/88) subjects in the VeraSeal treatment group and 95.3% (81/85 subjects) in the Evicel treatment group. Sensitivity and subgroup analyses support the results of the primary efficacy evaluation.

The rate of treatment failure in the mITT population was zero in both treatment groups. All other secondary and exploratory efficacy outcomes showed comparable effects for the two fibrin sealants.

3.3. Uncertainties and limitations about favourable effects

The secondary endpoints (Cumulative proportion of subjects achieving haemostasis at 7 and 10 minutes; Treatment failures) were considered appropriate, however, representing mainly different aspects of the primary endpoint. There is a lack of other, clinically relevant endpoints which could have provided a more complete picture of the efficacy of VeraSeal. Transfusion requirements, postoperative rebleeding at TBS, reoperation at TBS, postoperative blood loss, length of hospital stay would have been secondary endpoints of interest. However, as VeraSeal was already investigated in three phase 3 studies in a total of 500 subjects, this deficiency does not negatively affect the efficacy evaluation.

Taking into account that very few patients below the age of 27 days were included in the pivotal study and an indication without a lower age limit was envisaged, the MAH was asked to provide a justification that data from older children could be extrapolated to the younger ones and that there are no excipients in the drug product not suitable for small children. In total data from 6 patients <27 days of age are available. All 6 patients achieved haemostasis at T4, T7 and T10. The MAH justifies extrapolation of efficacy from older children to younger ones based on the mechanism of action and topical administration. Additional justification for extrapolation comes from a published study considering oesophageal anastomosis. From the quality perspective, no excipients that would not be adequate for young children are included in the product. In consequence, an indication without a lower age limit can be supported.

3.4. Unfavourable effects

In the submitted paediatric Study IG1405, 91 participants were treated with VeraSeal, and 87 participants were treated with EVICEL. Including the previous phase 3 trials, a total of 591 subjects of all age groups received treatment with VeraSeal (IG1101: N=168, IG1102: N=163, IG1103: N=169, IG1104: N=91). Of the participants of the first three phase 3 trials (IG1101, IG1102, IG1103), 11 were below 18 years of age.

Among subjects of Study IG1405 who received VeraSeal, 24 (26.4%) experienced 46 Treatment Emergent Adverse Events (TEAEs), compared to 16 participants (18.4%) with 38 TEAEs in the EVICEL group. Most of these events were mild or moderate in severity (91.3% in the VeraSeal group, 78.9% in the EVICEL group).

In the VeraSeal group, the SOCs with the highest subject incidences of TEAEs (above 5%) were Gastrointestinal disorders (9.9%), Injury, poisoning and procedural complications (6.6%) and Infections and infestations (5.5%). These are reflected in section 4.8 of the SmPC.

Treatment-emergent SAEs were reported by 8 (8.8%) subjects in VeraSeal group and 9 (10.3%) subjects in EVICEL group and all were considered unrelated by the Investigator. Three children died during the trial: two participants in the EVICEL group (cardiac arrest and pulmonary hypertension) and one participant in the VeraSeal group (cardiac arrest). The MAH provided detailed narratives for these cases. The children suffered from severe conditions caused by hepatic tumours or pulmonary hypertension.

Two events of anaphylaxis were reported for children who underwent hydatic cyst surgery. One anaphylactic shock actually occurred prior to administration of study drug and the event in the second subject occurred 45 minutes after closure of the abdominal site. Both events were linked to spillage of hydatide cysts (Echinococcus granulosus), which is a known cause for anaphylactic reactions. The risk for hypersensitivity reactions (including anaphylaxis) is already reflected as a class effect in the SmPC section 4.8.

Only one TEAE of procedural pain was considered related to treatment by the Investigator, which is already included as adverse drug reaction in section 4.8 of the SmPC.

No new safety concern emerged from the paediatric trial.

3.5. Uncertainties and limitations about unfavourable effects

Immunogenicity and viral safety were not investigated in the paediatric trial. However, it is acknowledged that no concerning signals on immunogenicity nor treatment-emergent viral infections were detected in the previous three phase 3 trials submitted for the initial MAA.

With the available safety database, especially for the paediatric population, potential rare adverse events cannot be detected. Safety will continue to be monitored post-authorisation via routine pharmacovigilance activities.

3.6. Effects Table

Table 32. Effects Table for VeraSeal (FS Grifols) for supportive treatment where standard surgical techniques are insufficient.

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
			VeraSeal	Evicel	Surgeon unblinded	CSR IG 1405
T4	Haemostasis at 4 minutes	%	96.7% (88/91)	95.4% (83/87)		
Treatment failures	Persistent, break- through or re-bleeding, use of additional/alternative haemostatic treatment, or re-application of IP beyond T4	%	0	0		
Unfavourable Effects						
			VeraSeal (N=91)	EVICEL (N=87)		
TEAEs	Incidence of treatment-emergent AEs	n	24 subjects (26.4%) with 46 AEs	16 subjects (18.4%) with 38 AEs		CSR IG1405
Related AEs	AE considered related by the Investigator	n	1 (Procedural pain)	0	"Possibly related" event, already reflected in SmPC	CSR IG1405
SAEs	Serious adverse events	n	8 subjects (8.8%) with 12 SAEs	9 subjects (10.3%) with 11 SAEs	All SAEs considered unrelated by Investigator	CSR IG1405

Abbreviations: TEAEs = treatment-emergent adverse events, AEs = adverse events, SAEs = serious adverse events FS Grifols = fibrin sealant Grifols, CSR = Clinical study report

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary endpoint of the paediatric study (IG1405) was met. The noninferiority has been demonstrated as the lower limit of the 95% CI exceeded 0.8. The findings of the primary analysis were confirmed by the sensitivity analyses and supported by the secondary endpoints. The observed favourable effects, i.e.

achievement of haemostasis in a timely manner, are expected to translate into further benefits for patients with regard to blood loss, time in the operating theatre and probably even length of hospital stay. As already discussed earlier, these measures would have also served as informative secondary endpoints. Unfortunately, they were not implemented and thus it can only be speculated about the effect of VeraSeal use on clinical outcomes. However, the availability of a reliable method to stop otherwise difficult to handle surgical bleedings is considered a tangible benefit on the patient level but also the hospital and public health level.

No new safety issues were identified in the submitted paediatric Study IG1405. Safety concerns may arise due to ABs against coagulation factor V, human thrombin, and human fibrinogen, which may compromise efficacy and in consequence the safety profile.

3.7.2. Balance of benefits and risks

Satisfactory local haemostatic efficacy could be shown in a paediatric population whose age ranged from newborn to adolescent. Extrapolation of efficacy to younger age cohorts was justified based on the mechanism of action and topical administration of VeraSeal and on the basis of a published study considering oesophageal anastomosis. From the quality perspective, no excipients that would not be adequate for young children are included in the product. In consequence, an indication without a lower age limit can be supported.

The observed AE profile did not give rise to concern. No unexpected safety signals other than those typical for major surgeries or the underlying medical condition (co-morbidities) could be observed.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of VeraSeal is positive for this paediatric extension of indication for supportive treatment where standard surgical techniques are insufficient for improvement of haemostasis and as suture support in vascular surgery.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of children for VeraSeal, based on final results from study IG1405; this is a prospective, randomized, active-controlled, single-blind, parallel group clinical trial to

evaluate the safety and efficacy of VeraSeal as an adjunct to haemostasis during surgery in paediatric subjects. As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7.0 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0052/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.