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| Established Name | Fibrin Sealant (Human) |
| (Proposed) Trade Name | |
| Pharmacologic Class | |
| Formulation(s), including Adjuvants, etc | |
| Dosage Form(s) and Route(s) of Administration | Frozen solutions for topical use |
| Dosing Regimen | N/A |
| Indication(s) and Intended Population(s) | An adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques is ineffective or impractical. |

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GLOSSARY

| | |
|----------------------|-------------------------------------------------------------------------------------------------------|
| ADR | Adverse drug reaction |
| AE | Adverse event |
| BLA | Biologics license application |
| CI | Confidence Interval |
| CSR | Clinical study report |
| FS | Fibrin sealant |
| ICF | Informed consent form |
| ITT | Intent-to-treat |
| MC | Manual compression |
| PP | Per protocol |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| T ₂ | Hemostatic assessment at 2 minutes following T _{Start} |
| T ₃ | Hemostatic assessment at 3 minutes following T _{Start} |
| T ₄ | Hemostatic assessment at 4 minutes following T _{Start} |
| T ₅ | Hemostatic assessment at 5 minutes following T _{Start} |
| T ₇ | Hemostatic assessment at 7 minutes following T _{Start} |
| T ₁₀ | Hemostatic assessment at 10 minutes following T _{Start} |
| T _{Closure} | Time of completion of the surgical closure by layers of the exposed surgical field containing the TBS |
| T _{Start} | Time of start of initial study treatment |
| TBS | Target bleeding site |
| TEAE | Treatment-emergent adverse event |
| TTH | Time to hemostasis |

1. EXECUTIVE SUMMARY

This is an original Biologics License Application (BLA) for Fibrin Sealant Grifols (FS Grifols) as an adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery when control of bleeding by standard surgical techniques is ineffective or impractical. FS Grifols is a 2-component frozen sterile fibrin sealant (FS) solution, which is composed of frozen solutions of human fibrinogen and human thrombin with calcium chloride.

The applicant submitted three Phase III clinical studies in support of this application. The three pivotal studies were designed to evaluate the efficacy and safety of FS Grifols in three different surgery types: vascular surgery (Study IG1101), parenchymous surgery (Study IG1102), and soft tissue surgery (Study IG1103). All three studies were conducted under IND protocols and completed during 2015. Each of the three studies was a multicenter, patient-blind clinical trial consisting of two parts: a Preliminary Part (I) and a Primary Part (II). The efficacy evaluations were based on results from the Primary Part (II). Study IG1101 was a superiority study comparing FS Grifols to manual compression, conducted under IND 14988. Study IG1102 and Study IG1103 were non-inferiority studies comparing FS Grifols to a licensed adjunct to hemostasis (Surgicel), conducted under IND 14987 and IND 14986, respectively. For each of the studies, the primary efficacy endpoint was the proportion of subjects achieving hemostasis at the target bleeding site (TBS) at 4 minutes following initial treatment application (T₄).

In Study IG1101, the intent-to-treat (ITT) analysis for the primary efficacy endpoint revealed a significantly higher rate of hemostasis by T₄ in the FS Grifols group (83/109 subjects, 76.1%) compared to the manual compression (MC) group (13/57 subjects, 22.8%) with a p-value <0.001. The ratio (95% CI) of proportions of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to MC was 3.34 (2.01, 5.45), indicating that FS Grifols is superior to MC as an adjunct to hemostasis in peripheral vascular surgery.

Both Study IG1102 and Study IG1103 achieved their primary objective of demonstrating non-inferiority of FS Grifols against Surgicel. In Study IG1102, the ITT analysis showed a higher rate of hemostasis by T₄ in the FS Grifols group of 92.8% (103/111 subjects) compared to 80.5% (91/113 subjects) in the Surgicel group. The estimated ratio (95% CI) of proportions achieving the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.15 (1.04, 1.28), which showed FS Grifols is non-inferior to Surgicel (i.e. the lower limit of the 95% CI for the ratio ≥ 0.8 , the pre-specified non-inferiority margin). As the lower limit of the 95% CI is above 1, the result also provided evidence that FS Grifols is superior to Surgicel (p-value = 0.010) as an adjunct to hemostasis in parenchymous tissue open surgery. In Study IG1103, the ITT analysis showed the rate of hemostasis by T₄ was 82.8% (96/116 subjects) in the FS Grifols group and 77.8% (84/108 subjects) in the Surgicel group. The estimated ratio (95% CI) of proportions achieving hemostasis by T₄ in subjects receiving FS Grifols relative to Surgicel was 1.06 (0.93, 1.21). As the lower limit of the 95% CI for the ratio is greater than pre-specified margin of 0.8, the results demonstrated that FS Grifols is non-inferior

to Surgicel as an adjunct to hemostasis in soft tissue open surgery. However, FS Grifols was not statistically superior to Surgicel in terms of the primary efficacy endpoint.

There were no apparent safety concerns related to FS Grifols in any of the three pivotal studies. Further analysis of safety data is deferred to the clinical review team.

There were no statistical issues in this submission. The positive efficacy results from the three Phase III confirmatory studies provided statistical evidence supporting the hemostatic effect of FS Grifols, support the approval of the application of FS Grifols as an adjunct to hemostasis in surgery.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Control of bleeding in surgeries by standard techniques (such as suture, ligature, and cautery) may be ineffective or impractical.

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

Many products have been developed as adjuncts to hemostasis in mild to moderate bleeding. These products include topical absorbable hemostats (TAH) such as oxidized regenerated cellulose, gelatin in various forms with or without a topical thrombin solution, and collagen powder, as well as biologically active topical hemostatic products (topical thrombin solutions, fibrin sealants, etc.) and a variety of synthetic topical sealants. More recently, fibrin sealant (FS) products were licensed for use in the US as an adjunct to hemostasis in surgery, such as EVICEL™ Fibrin Sealant. The intended benefits of FS application are to support local hemostasis and sutures, “glue” surfaces of injured tissues in order to obtain adaptation or sealing of surfaces, or improve repair or healing. FS products may be used in a variety of clinical situations and surgical fields.

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

The clinical development of Fibrin Sealant Grifols (FS Grifols) for this BLA was conducted under IND protocols for different surgery settings: vascular surgery, parenchymous surgery and soft tissue surgery. All three studies were completed during year 2015.

On November 4, 2016, the applicant submitted this original BLA to seek licensure of FS Grifols for the therapeutic indication as an adjunct to hemostasis in surgery. No pre-BLA meeting was held for this submission.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

All data sources are included in the applicant's eCTD submission located in the FDA/CBER Electronic Document Room (EDR).

5.1 Review Strategy

The applicant submitted three Phase III clinical studies in support of this application (Table 1). The three pivotal studies were designed to evaluate the efficacy and safety of FS Grifols in three different surgery types: vascular surgery (Study IG1101, under IND 14988), parenchymous surgery (Study IG1102, under IND 14987), and soft tissue surgery (Study IG1103, under IND 14986). This review memo focuses on the primary efficacy analysis of each of three pivotal studies.

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

The documents reviewed in the original submission STN 125640/0 include:

- Draft Labeling (module 1.14.1.3)
- Clinical Overview (module 2.5)
- Summary of Clinical Efficacy (module 2.7.3)
- Summary of Clinical Safety (module 2.7.4)
- Clinical Study Reports and tabulations for Study IG1101, IG1102 and IG1103 (module 5.3.5.1)
- Integrated Summary of Efficacy (module 5.3.5.3)

Analyses performed within this review are based on following analysis-ready datasets provided by the applicant.

- adsl.xpt, adae.xpt and adeff.xpt from Study IG1101 (module 5.3.5.1.ig1101)
- adsl.xpt, adae.xpt and adeff.xpt from Study IG1102 (module 5.3.5.1.ig1102)
- adsl.xpt, adae.xpt and adeff.xpt from Study IG1103 (module 5.3.5.1.ig1103)

I verified all efficacy results against the data provided by the sponsor using version 9.3 of SAS.

5.3 Table of Studies/Clinical Trials

Three pivotal studies (IG1101, IG1102 and IG1103) in this original BLA submission are summarized in Table 1.

Table 1. Description of Clinical Studies for Fibrin Sealant Grifols

| Study Number | Study Phase and Period | Surgery Type | Study and Control Treatments, Dose | Number of Subjects (ITT Population) | Hypothesis testing | Primary Endpoint* |
|--------------|---------------------------------------------------------------|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|-----------------------------------------------------------------------------|
| IG1101 | Phase 3 Start: 02 Aug 2012 Completed: 26 Dec 2015 | Vascular | FS Grifols (≤ 6 mL), Single intra-operative administration MC, Single intra-operative administration | Total: 225 FS Grifols: 168 (59 in Preliminary Part (I), 109 in Primary Part (II)) MC: 57 in the Primary Part (II). | Superiority | Proportion of subjects achieving hemostasis at the TBS by T4 |
| IG1102 | Phase 3 Start: 22 Mar 2013 Completed: 28 Dec 2015 | Parenchymous (hepatic) | FS Grifols (≤ 12 mL), Single intra-operative administration Surgicel® (≤ 4 sheets), Single intra-operative administration | Total: 325 FS Grifols: 163 (52 in Preliminary Part (I), 111 in Primary Part (II)) Surgicel : 162 (49 in Preliminary Part (I), 113 in Primary Part (II)). | Non-inferiority | Proportion of subjects achieving hemostasis at the TBS by T4 |
| IG1103 | Phase 3 Start: 19 Nov 2012 Completed: 04 Jun 2015 | Soft tissue | FS Grifols (≤ 12 mL), Single intra-operative administration Surgicel® (≤ 4 sheets), Single intra-operative administration | Total: 327 FS Grifols: 167 (51 in Preliminary Part (I), 116 in Primary Part (II)) Surgicel : 160 (52 in Preliminary Part (I), 108 in Primary Part (II)). | Non-inferiority | Proportion of subjects achieving hemostasis at the TBS by T4 |

*T₄ = hemostatic assessment at 4 minutes following the start of treatment

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study IG1101

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective was to evaluate the hemostatic efficacy of FS Grifols in peripheral vascular surgery and as suture support.

6.1.2 Design Overview

This multicenter, single-blind Phase III study consisted of two parts: a Preliminary Part (I) and a Primary Part (II). All subjects enrolled in Preliminary Part (I) were treated with FS Grifols. The main purpose of this part was to ensure that local study teams familiarized with the technique for FS Grifols application and with intra-operative procedures required by the protocol of this study. For each study participating center, the first two subjects were enrolled in Preliminary Part (I), and then the center could enroll

subjects in Primary Part (II). Subjects in Primary Part (II) were randomized in a 2:1 ratio into FS Grifols or MC treatment groups following identification of a target bleeding site (see below). Randomization was stratified by 1) study center and 2) type of intervention (peripheral arterial bypass vs. upper extremity vascular access for hemodialysis). This part had two main purposes: 1) to assess the safety of FS Grifols and 2) to assess the efficacy of FS Grifols.

In both parts of this study, a specific bleeding area/site was defined as the TBS when it was determined by the investigator that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) was ineffective or impractical and required an adjunct treatment to achieve hemostasis. When the TBS was identified, the investigator rated the intensity of the bleeding at the TBS according to a 3-point scale (mild, moderate, severe). For both parts of the study, only subjects with a TBS with bleeding of moderate intensity could be enrolled.

6.1.3 Population

Subjects were eligible for entry into the study once they met all of the following criteria:

1. Sign the written Informed Consent Form (ICF).
2. Are male or female.
3. Must be at least 18 year old with no upper age limit.
4. Must have hemoglobin (Hgb) ≥ 8.0 g/dL at Baseline (within 24 hours prior to surgical procedure).
5. Require an elective (non-emergency), primary, open (non-laparoscopic; non-endovascular) peripheral vascular surgical procedure.
6. Require one of peripheral vascular procedures listed below involving a proximal end-to-side arterial anastomosis utilizing coated or uncoated PTFE grafts:
 - a. Femoral-femoral bypass grafting.
 - b. Femoral-popliteal bypass grafting.
 - c. Femoral-distal bypass grafting.
 - d. Ilio-iliac bypass grafting.
 - e. Ilio-femoral bypass grafting.
 - f. Ilio-popliteal bypass grafting.
 - g. Aorto-iliac bypass grafting.
 - h. Aorto-femoral bypass grafting.
 - i. Axillo-femoral bypass grafting.
 - j. Upper extremity vascular access for hemodialysis (arteriovenous graft formation).
7. Intra-operative inclusion criterion:
 - a. A TBS can be identified according to the investigator's judgment, and
 - b. The TBS has a moderate arterial bleeding according to the Investigator's judgment.

Subjects were ineligible for entry into the study if they met ANY of the following criteria:

1. Are undergoing a re-operative procedure: It is defined as a second, or successive, surgical procedure on the same anatomic location.

2. Are undergoing other vascular procedures during the same surgical session (stenting and/or endarterectomy of the same artery are allowed).
3. Have an infection in the anatomic surgical area.
4. Have a history of severe (e.g. anaphylactic) reactions to blood or to any blood-derived (human or animal) product.
5. Have previous known sensitivity to any FS Grifols, heparin or protamine component.
6. Are unlikely to adhere to the protocol requirements, or to be cooperative during the study conduct.
7. Are females who are pregnant or nursing a child at Baseline (within 24 hours prior to surgical procedure).
8. Are currently participating, or have participated, in another clinical study in the context of which have received investigational drug or device within 3 months to the screening visit, or are scheduled to participate during the course of this study.
9. Have undergone a therapeutic surgical procedure within 30 days from the screening visit.
10. Were previously enrolled in clinical trials with FS Grifols.
11. Intra-operative exclusion criteria:
 - a. A TBS cannot be identified according to the investigator's judgment, or
 - b. The TBS has a mild or severe arterial bleeding according to the investigator's judgment.
 - c. Occurrence of major intraoperative complications that require resuscitation or deviation from the planned surgical procedure.
 - d. Intraoperative change in planned surgical procedure, which results in subject no longer meeting preoperative inclusion and/or exclusion criteria.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Upon identification of the TBS, subjects were treated intra-operatively with FS Grifols or MC application.

For subjects randomized to the FS Grifols group, FS Grifols was dripped onto the TBS up to 6 mL. No additional amounts of FS Grifols could be applied beyond hemostatic assessment time at 4 minutes following application (T₄).

For subjects randomized to the MC treatment group, direct MC with dry gauze/laparotomy pads was applied to the TBS completely covering the study suture line. There was no limitation to the number of gauzes/laparotomy pads applied to the TBS for achieving hemostasis. Manual compression could be applied as necessary during the 10-minute observational period, even beyond hemostatic assessment time at 4 minutes post-application.

6.1.6 Sites and Centers

This study was conducted in 35 study centers in Hungary (3 centers), Russia (5), Serbia (2) and the US (25).

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

The primary efficacy variable was the proportion of subjects in Primary Part (II) achieving hemostasis (Yes/No) at the TBS by T₄ without occurrence of re-bleeding and reapplication of study treatment after T₄ and until time of completion of the surgical closure by layers of the exposed surgical field containing the TBS (T_{Closure}), and without brisk bleeding and use of alternative hemostatic treatment after time of start of initial study treatment (T_{Start}) and until T_{Closure}.

Secondary Efficacy Endpoints

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

Safety Endpoints

- Adverse events (AEs), adverse drug reactions (ADRs), and Serious AEs (SAEs).
- Vital signs.
- Physical assessments.
- Laboratory tests.
- Viral markers.
- Antibodies.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

The sample size was calculated for Primary Part (II) as Preliminary Part (I) was not included for any statistical considerations. With a 2:1 ratio, a total of 156 subjects (104 in FS Grifols arm and 52 in MC arm) would provide 80% power to demonstrate superiority of FS Grifols to MC on the proportion of hemostasis success by T₄ (assuming 60% in the FS Grifols group vs. 35% in the MC group) with a 2-sided significance level of 5% based on a 2-group Fisher Exact test. To allow for a 5% drop-out rate after randomization, a total of 165 subjects (110 in FS Grifols arm and 55 in MC arm) would need to be randomized in Primary Part (II).

Analysis Populations

- Intent-to-treat (ITT) population:
For the Preliminary Part (I) of the study, the ITT population included all subjects who met the intra-operative inclusion criterion and whom the investigator therefore intended to treat with FS Grifols.
For the Primary Part (II) of the study, the ITT population included all subjects randomized to FS Grifols or MC.
- Per-protocol (PP) population:

The PP population included all subjects in the ITT population excluding any subject for whom there was at least one major protocol deviation that might have an impact on the primary efficacy assessment.

- **Safety population:**

The safety population consisted of all subjects who received any amount of FS Grifols (in Preliminary Part (I) or Primary Part (II)) or MC.

All efficacy analyses were performed using the ITT population and PP population in Primary Part (II). Safety analyses were based on the safety population.

Analysis for Primary Efficacy Endpoint

The primary efficacy endpoint was analyzed using a 2×2 Fisher Exact test for the treatment difference. The ratio of the proportion of hemostasis by T₄ in the two treatment groups (FS Grifols relative to MC) and its 2-sided asymptotic 95% confidence interval (CI) of the ratio was also provided. The CI was calculated using a normal approximation as:

$$\text{Exp}(\log(\text{RR}) \pm Z(\alpha/2) * \sqrt{((1-p_1)/(n_1*p_1) + (1-p_2)/(n_2*p_2)))})$$

where p₁ was the success proportion in the FS Grifols group and p₂ was the success proportion in the MC group, risk ratio (RR)=p₁/p₂. n₁ and n₂ were the number of subjects in FS Grifols group and MC group, respectively.

Analysis for Secondary Efficacy Endpoint

- Time to hemostasis was tested using Log Rank test.
- Cumulative proportion of subjects achieving hemostasis at the TBS by T₅, T₇, and T₁₀ were analyzed using a 2×2 Fisher Exact test.

The null hypotheses for the secondary endpoints were only tested if the null hypothesis for the primary efficacy endpoint was rejected. A fixed-sequence testing method was employed to address the multiplicity issue for multiple secondary efficacy endpoints. The order in which the null hypotheses were tested was predetermined as below for all secondary efficacy endpoints:

1. Time to hemostasis.
2. Cumulative proportion of subjects having achieved hemostasis at the TBS by T₅.
3. Cumulative proportion of subjects having achieved hemostasis at the TBS by T₇.
4. Cumulative proportion of subjects having achieved hemostasis at the TBS by T₁₀.

Each subsequent hypothesis was tested only if all previously tested null hypotheses were rejected at a 2-sided significance level of 5%.

Missing Data Handling

If any missing hemostatic assessment at TBS at T₄ for a randomized subject occurred, it was treated as non-hemostasis at TBS at T₄ for the subject in the primary efficacy

analysis. A sensitivity analysis with non-missing observational hemostatic assessment at TBS at T₄ was performed.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Ninety (90) subjects were screened and 31 subjects failed screening during the Preliminary Part (I). During the Primary Part (II), 193 subjects were screened, and 27 subjects failed screening. A total of 166 subjects were randomized and 162 randomized subjects completed the study (Table 2). The ITT and PP populations for efficacy are comprised of 166 and 149 subjects, respectively; the safety population is comprised of 225 subjects.

Table 2. Subject Populations and Disposition

| | Preliminary Part (I) N | Primary Part (II) | | | Part (I) + Part (II) N |
|-----------------------|------------------------------|-------------------|---------|--------------|------------------------------|
| | | FS Grifols N | MC N | Overall N | |
| Enrolled | 59 | 109 | 57 | 166 | 225 |
| Randomized | NA | 109 | 57 | 166 | 166 |
| ITT population | 59 | 109 | 57 | 166 | 225 |
| PP population | 43 | 97 | 52 | 149 | 192 |
| Safety population | 59 | 109 | 57 | 166 | 225 |
| Completed study | 58 | 106 | 56 | 162 | 220 |
| Discontinued study | 1 | 3 | 1 | 4 | 5 |
| Withdrawal of consent | 0 | 1 | 0 | 1 | 1 |
| Lost to follow-up | 0 | 0 | 1 | 1 | 1 |
| Death | 1 | 2 | 0 | 2 | 3 |

6.1.10.1.1 Demographics

Demographic and other baseline characteristics are summarized by treatment group using the ITT Population in Table 3. In Preliminary Part (I) and Primary Part (II), the FS Grifols group consisted of approximately 70% male subjects and 30% female subjects. The MC group had a relatively balanced ratio of male vs. female subjects (54% male vs 46% female). No pediatric subjects were enrolled in this study, and the mean age in Primary Part (II) was similar across groups (FS Grifols: 63.7 years, MC: 62.0 years). The majority of subjects were Whites/Caucasian (86.2%). There were no major differences in weight and height between the FS Grifols group and the MC group across Preliminary Part (I) and Primary Part (II).

Table 3. Demographics (ITT Population)

| Characteristics | Preliminary Part (I) | Primary Part (II) | | Part (I) + Part (II) | Total ^a (N=225) n (%) |
|-------------------------------------------|-------------------------------|--------------------------------|---------------------------------------|--------------------------------|----------------------------------------|
| | FS Grifols (N=59) n (%) | FS Grifols (N=109) n (%) | Manual Compression (N=57) n (%) | FS Grifols (N=168) n (%) | |
| Sex - n (%) | | | | | |
| Male | 41 (69.5) | 76 (69.7) | 31 (54.4) | 117 (69.6) | 148 (65.8) |
| Female | 18 (30.5) | 33 (30.3) | 26 (45.6) | 51 (30.4) | 77 (34.2) |
| Age (years) | | | | | |
| Mean (SD) | 63.53 (9.343) | 63.72 (8.908) | 62.04 (10.734) | 63.65 (9.036) | 63.24 (9.496) |
| Median | 64.0 | 64.00 | 61.00 | 64.00 | 63.00 |
| Min, Max | 41.0, 82.0 | 44.0, 84.0 | 22.0, 82.0 | 41.0, 84.0 | 22.0, 84.0 |
| Age Category (years) – n (%) | | | | | |
| ≤11 | 0 | 0 | 0 | 0 | 0 |
| 12-17 | 0 | 0 | 0 | 0 | 0 |
| 18-64 | 32 (54.2) | 58 (53.2) | 32 (56.1) | 90 (53.6) | 122 (54.2) |
| ≥65 | 27 (45.8) | 51 (46.8) | 25 (43.9) | 78 (46.4) | 103 (45.8) |
| 65-84 | 27 (45.8) | 51 (46.8) | 25 (43.9) | 78 (46.4) | 103 (45.8) |
| ≥85 | 0 | 0 | 0 | 0 | 0 |
| Race – n (%) | | | | | |
| White (Caucasian) | 44 (74.6) | 101 (92.7) | 49 (86.0) | 145 (86.3) | 194 (86.2) |
| Black or African American | 13 (22.0) | 6 (5.5) | 8 (14.0) | 19 (11.3) | 27 (12.0) |
| Asian | 0 | 2 (1.8) | 0 | 2 | 2 (0.9) |
| Native Hawaiian or Other Pacific Islander | 1 (1.7) | 0 | 0 | 1 (0.6) | 1 (0.4) |
| Multi-racial (no primary race) | 1 | 0 | 0 | 1 | 1 (0.4) |
| Height (cm) | | | | | |
| Mean (SD) | 170.7 (9.31) | 170.6 (9.50) | 167.3 (7.75) | 170.7 (9.41) | 169.8 (9.12) |
| Median | 173.0 | 170.0 | 169.0 | 171.0 | 170.0 |
| Min, Max | 150, 188 | 152, 195 | 152, 184 | 150, 195 | 150, 195 |
| Weight (kg) | | | | | |
| Mean (SD) | 79.6 (16.66) | 77.2 (17.00) | 73.6 (14.99) | 78.1 (16.87) | 76.9 (16.49) |
| Median | 79.0 | 76.0 | 74.0 | 77.0 | 77.0 |
| Min, Max | 50, 118 | 41, 130 | 46, 116 | 41, 130 | 41, 130 |

Source: Original BLA 125640/0; Module 5.3.5.1, Clinical Study Report for Study IG1101, p.73.

6.1.10.1.3 Subject Disposition

Subject disposition is summarized in Table 2.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The proportion of subjects achieving hemostasis by T₄ was 76.1% (83/109) in the FS Grifols group and was 22.8% (13/57) in the MC group. The ratio (95% CI) of proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to MC was 3.34 (2.05, 5.45). The proportion of successful hemostasis by T₄ was significantly higher in the FS Grifols group compared to the MC group (p-value <0.001), indicating that FS Grifols is superior to MC and that the primary efficacy objective was achieved in the ITT population. The supportive analysis in the PP set showed similar results. Detailed results are shown in Table 4.

Table 4. Primary Endpoint Results (ITT Population)

| Analysis Population | FS Grifols | MC | RR (95% CI) ^a | p-value ^b |
|---------------------|----------------|---------------|--------------------------|----------------------|
| ITT | 83/109 (76.1%) | 13/57 (22.8%) | 3.34 (2.05, 5.45) | <0.0001 |
| PP | 75/97 (77.3%) | 12/52 (23.1%) | 3.35 (2.02, 5.57) | <0.0001 |

^a RR was the ratio of proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part (II) (FS Grifols relative to MC).

^b P-value was calculated from Fisher Exact Test.

6.1.11.2 Analyses of Secondary Endpoints

Because effectiveness was demonstrated for the primary efficacy endpoint, the secondary endpoints were analyzed for superiority according to the sequence described in Section 6.1.9.

The median time to hemostasis (TTH) was significantly shorter (p-value <0.001) in the FS Grifols group (4.0 minutes) compared to the MC group (≥ 10.0 minutes), indicating that FS Grifols is superior to MC.

The results for cumulative proportion of subjects achieving hemostasis at the TBS by T₅, T₇, and T₁₀ show a similar pattern as the primary efficacy analysis in favor of FS Grifols (Table 5).

Table 5. Analysis of Hemostasis by T5, T7, and T10 at Target Bleeding Site (ITT Population)

| | Primary Part | | | |
|--------------------------|------------------------------|---------------------|--------------------------|----------------------|
| | FS Grifols N=109 n (%) | MC N=57 n (%) | RR (95% CI) ^a | P-value ^b |
| Hemostasis by 5 minutes | 88 (80.7) | 16 (28.1) | 2.88 (1.88, 4.40) | <0.001 |
| Hemostasis by 7 minutes | 92 (84.4) | 20 (35.1) | 2.41 (1.68, 3.46) | <0.001 |
| Hemostasis by 10 minutes | 96 (88.1) | 26 (45.6) | 1.93 (1.44, 2.59) | <0.001 |

^a RR was the ratio of proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part (II) (FS Grifols relative to MC).

^b P-value was calculated from Fisher Exact Test.

Source: Original BLA 125640/0; Module 5.3.5.1, Clinical Study Report for Study IG1101, p95.

6.1.11.3 Subpopulation Analyses

Table 6 shows the subgroup analyses by sex, race and age categories using the ITT population. The results show a similar direction as the primary efficacy analysis in favor of FS Grifols in each subgroup.

Table 6. Analysis of Hemostasis by T₄ at TBS by Treatment and Subgroups (ITT Population)

| Subgroup | FS Grifols (N=109) | MC (N=57) |
|---------------------------|-----------------------|---------------|
| Sex | | |
| Male | 59/76 (77.6%) | 4/31 (12.9%) |
| Female | 24/33 (72.7%) | 9/26 (34.6%) |
| Age | | |
| 18-64 years | 45/58 (77.6%) | 8/32 (25.0%) |
| ≥65 years | 38/51 (74.5%) | 5/25 (20.0%) |
| Race | | |
| White (Caucasian) | 77/101 (76.2%) | 11/49 (22.5%) |
| Black or African American | 4/6 (66.7%) | 2/8 (25%) |
| Asian | 2/2 (100%) | 0/0 (NA) |

6.1.11.4 Dropouts and/or Discontinuations

Since there were no missing data for the primary efficacy endpoint, no sensitivity analyses were performed.

6.1.12 Safety Analyses

6.1.12.3 Deaths

Of 168 subjects who received FS Grifols, 4 (2.4%) deaths were observed. The causes of death were myocardial infarction, gastrointestinal hemorrhage, multi-organ failure, and unknown cause. All death outcomes were considered not related to study treatment. No death occurred in the MC group.

6.1.12.4 Nonfatal Serious Adverse Events

Thirty-four out of 168 (20.2%) subjects in the FS Grifols group experienced 60 serious adverse events (SAEs), and 11 out of 57 (19.3%) subjects in the MC group experienced 14 SAEs. In the FS Grifols group, 38 of the 60 SAEs (63.3%) were reported in only single subjects. While for the MC group, 10 of the 14 SAEs (10/14; 71.4%) were reported in only single subjects.

Of the total 74 SAEs in this study, all except 5 SAEs were considered not related to study treatment: 4 SAEs in FS group and 1 SAE in the MC group. Three SAEs (2 FS Grifols subjects and 1 MC subject) were considered unlikely related to study treatment; and 2 SAEs (cellulitis and B19V test positive) from 2 subjects in the FS Grifols group were considered possibly related to study treatment.

6.1.12.5 Adverse Events of Special Interest (AESI)

Two subjects in the FS Grifols group (2/168; 1.2%) and three subjects in the MC group (3/57; 5.3%) each experienced a vascular graft thrombosis event. Four events (1 FS Grifols subjects and 3 MC subject) were considered not related to study treatment; and 1 thrombosis event from FS Grifols group were considered unlikely related to study treatment.

6.2 Study IG1102

6.2.1 Objectives (Primary, Secondary, etc)

The primary objective was to evaluate the hemostatic efficacy of FS Grifols in parenchymous tissue open surgeries.

6.2.2 Design Overview

This was a multicenter, single-blind Phase III clinical study consisting of two parts: a Preliminary Part (I) and a Primary Part (II). Subjects in Preliminary Part (I) were randomized in a 1:1 ratio into one of two treatment groups, FS Grifols or Surgicel, following identification of a target bleeding site (see below).. The main purpose of this part of the clinical study was to ensure that local study teams familiarized with the technique for FS Grifols application and with intra-operative procedures required by the protocol. For each study participating center, the first four subjects were to be enrolled in Preliminary Part (I). Subjects in Primary Part (II) were randomized in a 1:1 ratio into FS Grifols or Surgicel treatment groups. This part had two main purposes: (1) to assess the safety of FS Grifols and (2) to assess the efficacy of FS Grifols. For each study center, Primary Part (II) started only after enrollment of four subjects in Preliminary Part (I). Randomization was stratified by study center.

In both parts of this study, a specific bleeding area/site was defined as the TBS when it was determined by the investigator that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) was ineffective or impractical and required an adjunct treatment to achieve hemostasis. When the TBS was identified, the investigator rated the intensity of the bleeding at the TBS and the approximate size of the bleeding surface according to a 3-point scale (mild, moderate, severe for the intensity of the bleeding and small, medium, large for the bleeding surface). For both parts of the study, only subjects with a TBS with bleeding of moderate intensity could be enrolled.

6.2.3 Population

Subjects were eligible for entry into the study once they met all of the following criteria:

1. Sign the written Informed Consent Form (ICF).
2. Are male or female.
3. Must be at least 18 year old with no upper age limit.
4. Must have hemoglobin (Hgb) ≥ 8.0 g/dL at Baseline (within 24 hours prior to surgical procedure).

5. Require an elective (non-emergency), open (non-laparoscopic) hepatic resection (anatomic or non-anatomic resections of at least one anatomical hepatic segment, or equivalent tissue volume).
 - Where TBS is identified on the cut raw liver surface (resection area).
6. Intra-operative inclusion criteria: a TBS can be identified according to the investigator's judgment, and
 - The TBS has moderate bleeding according to the investigator's judgment.
 - The intensity of the bleeding at the TBS will be rated by the investigator using a pre-defined three-point scale.

Subjects were ineligible for entry into the study if they met ANY of the following criteria:

1. Require hepatic resection due to trauma.
2. Have an infection in the anatomic surgical area.
3. Have a history of severe (e.g. anaphylactic) reactions to blood or to any blood-derived (human or animal) product.
4. Have previous known sensitivity to any FS Grifols component or any Surgicel[®] component.
5. Are unlikely to adhere to the protocol requirements, or to be cooperative, during the study conduct.
6. Are females who are pregnant or nursing a child at Baseline (within 24 hours prior to surgical procedure).
7. Are receiving an organ transplant during the same surgical procedure.
8. Are undergoing another concurrent major surgical intervention beyond the liver.
9. Are currently participating or have participated in another clinical study in the context of which have received investigational drug or device within 3 months from the screening visit, or are scheduled to participate during the course of this study.
10. Have undergone a therapeutic surgical procedure within 30 days from the screening visit.
11. Were previously enrolled in clinical trials with FS Grifols.
12. Intra-operative exclusion criteria:
 - A TBS (as defined in section 7.1.3.1) cannot be identified according to the investigator's judgment.
 - The TBS has a mild or severe bleeding according to the investigator's judgment.
 - Occurrence of major intraoperative complications that require resuscitation or deviation from the planned surgical procedure.
 - Application of any topical hemostatic material on the resection surface of the liver prior to application of the study treatment.
 - Radiofrequency precoagulation of the liver resection surface, except focal use of radiofrequency as primary hemostatic treatment.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Upon identification of the TBS, subjects were treated intra-operatively with FS Grifols or Surgicel.

For subjects randomized to the FS Grifols group, FS Grifols was dripped onto the TBS up to 12 mL. No additional amounts of FS Grifols could be applied beyond T₄.

For subjects randomized to the Surgicel group, up to four 4" × 8" sheets of Surgicel were applied to the TBS. No additional Surgicel sheets could be applied at the TBS beyond T₄.

6.2.6 Sites and Centers

This study was conducted in 33 study centers in Hungary (2 centers), Russia (2), Serbia (5) and the US (24).

6.2.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

The primary efficacy variable was the proportion of subjects in Primary Part (II) of the study achieving hemostasis (Yes/No) at the TBS by T₄ without occurrence of re-bleeding and re-application of study treatment after T₄ and until T_{Closure}, and without brisk bleeding and use of alternative hemostatic treatment after T_{Start} and until T_{Closure}.

Secondary Efficacy Endpoints

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

Safety Endpoints

- AEs, ADRs and SAEs.
- Vital signs.
- Physical assessments.
- Laboratory tests.
- Viral markers.
- Antibodies.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

The sample size was calculated for Primary Part (II) as Preliminary Part (I) was not included for any statistical considerations. With a 1:1 ratio, a total of 212 subjects (106 in FS Grifols and 106 in Surgicel) would provide 80% power to show non-inferiority of FS Grifols relative to Surgicel on the proportion of hemostasis success by T₄ (assuming 65% in the FS Grifols group vs 60% in the Surgicel group). Non-inferiority was defined in terms of the lower limit of a 2-sided 95% CI for the ratio of the hemostasis success proportions in the two groups (FS Grifols relative to Surgicel). FS Grifols will be considered non-inferior to Surgicel if the lower bound of this CI is greater than 0.80. To allow for an approximate 5% drop-out rate after randomization, a total of 224 subjects (112 for each arm) would need to be randomized in Primary Part (II).

Analysis Populations

- **ITT population:** The ITT population included all subjects randomized to FS Grifols or Surgicel in either Preliminary Part (I) or Primary Part (II). **PP population:** The PP population included all subjects in the ITT population excluding any subject for whom there was at least one major protocol deviation that might have an impact on the primary efficacy assessment.
- **Safety population:** The safety population consisted of all subjects who received any amount of FS Grifols or Surgicel in either Preliminary Part (I) or Primary Part (II).

All efficacy analyses were performed using the ITT population and PP population in Primary Part (II) only. Safety analyses were based on the safety population.

Analysis for Primary Efficacy Endpoint

The primary efficacy endpoint was analyzed by providing the ratio of hemostasis success proportions by T₄ in the two treatment groups (FS Grifols relative to Surgicel) and its 2-sided asymptotic 95% CI. The CI was calculated using a normal approximation as:

$$\text{Exp}(\log(\text{RR}) \pm Z(\alpha/2) * \sqrt{((1-p_1)/(n_1*p_1) + (1-p_2)/(n_2*p_2)))}$$

where p_1 was the success proportion in the FS Grifols group and p_2 was the success proportion in the Surgicel group, risk ratio (RR)= p_1/p_2 . n_1 and n_2 were the number of subjects in FS Grifols group and Surgicel group, respectively.

FS Grifols would be considered non-inferior to Surgicel if the lower limit of the 95% CI exceeded 0.8. If non-inferiority is established, superiority may be additionally claimed if the 95% CI is entirely above 1.

Analysis for Secondary Efficacy Endpoint

- Cumulative proportion of subjects achieving hemostasis at the TBS by T₂, T₃, T₅, T₇, and T₁₀ were analyzed by providing the ratio of proportion (and its 95% CI) of subjects meeting the secondary efficacy endpoints.
- Time to hemostasis was tested using Log Rank test.

The superiority for the secondary endpoints would be tested only if non-inferiority for the primary efficacy endpoint was demonstrated. For the secondary efficacy endpoints, a fixed-sequence testing method was employed for handling the multiplicity issue to maintain the overall familywise alpha level at 0.05. Each subsequent hypothesis was tested only if superiority for the previous comparisons was shown at a 2-sided significance level of 5%. The order in which the null hypotheses were tested was predetermined as below for the secondary efficacy variables:

1. Cumulative proportion of subjects having achieved hemostasis at the TBS by T₃.
2. Time to hemostasis.
3. Proportion of subjects having achieved hemostasis at the TBS by T₂.

Missing Data Handling

If any missing hemostatic assessment at TBS at T₄ for a randomized subject occurred, it was treated as non-hemostasis at TBS at T₄. A sensitivity analysis with non-missing observational hemostatic assessment at TBS at T₄ was performed.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

One hundred and thirty-nine subjects were screened and 38 failed screening during Preliminary Part (I). During Primary Part (II), 287 subjects were screened and 63 subjects failed screening. A total of 224 subjects were randomized into either the FS Grifols treatment group or the Surgicel treatment group (Table 8), and 208 subjects in Primary Part (II) completed the study. The ITT and PP populations for efficacy are comprised of 224 and 187 subjects, respectively; the safety population is comprised of 325 subjects.

Table 8. Subject Populations and Disposition

| | Preliminary Part (I) | | | Primary Part (II) | | | Part (I) + Part (II) N |
|-----------------------|----------------------|---------------|--------------|--------------------|---------------|--------------|------------------------------|
| | FS Grifols N | Surgicel N | Overall N | FS Grifols N | Surgicel N | Overall N | |
| Randomized | 52 | 49 | 101 | 111 | 113 | 224 | 325 |
| ITT population | 52 | 49 | 101 | 111 | 113 | 224 | 325 |
| PP population | 41 | 43 | 84 | 87 | 100 | 187 | 271 |
| Safety population | 52 | 49 | 101 | 111 | 113 | 224 | 325 |
| Completed study | 47 | 45 | 92 | 100 | 108 | 208 | 290 |
| Discontinued study | 5 | 4 | 9 | 11 | 5 | 16 | 25 |
| Withdrawal of consent | 1 | 2 | 3 | 2 | 4 | 6 | 9 |
| Lost to follow-up | 1 | 1 | 2 | 4 | 0 | 4 | 6 |
| Death | 3 | 1 | 4 | 4 | 1 | 5 | 9 |
| Other | 0 | 0 | 0 | 1 | 0 | 1 | 1 |

6.2.10.1.1 Demographics

Subject demographics by treatment and by study part are summarized in Table 9. In Part I + Part II (ITT population), the FS Grifols group consisted of 52.1% male and 47.9% female subjects. Similar results were seen in the Surgicel group (i.e. 52.5% male and 47.5% female subjects). The mean age of subjects was comparable in the FS Grifols (58.8 years) and Surgicel (57.0 years) groups. In Preliminary Part (I), two pediatric subjects (≤ 11 years) were randomized to the FS Grifols group. No pediatric subjects were enrolled in Primary Part (II). The majority of subjects in the ITT population were Whites (90.8%). There were no major differences in height and weight between the two treatment groups.

Table 9. Demographics (ITT Population)

| Characteristics | Preliminary Part (I) | | Primary Part (II) | | Part I + Part II | | Total ^a (N=325) |
|-------------------------------------|----------------------|--------------------|-----------------------|---------------------|-----------------------|---------------------|-------------------------------|
| | FS Grifols (N=52) | Surgicel (N=49) | FS Grifols (N=111) | Surgicel (N=113) | FS Grifols (N=163) | Surgicel (N=162) | |
| Sex - n (%) | | | | | | | |
| Male | 26 (50.0) | 22 (44.9) | 59 (53.2) | 63 (55.8) | 85 (52.1) | 85 (52.5) | 170 (52.3) |
| Female | 26 (50.0) | 27 (55.1) | 52 (46.8) | 50 (44.2) | 78 (47.9) | 77 (47.5) | 155 (47.7) |
| Age (years) | | | | | | | |
| Mean (SD) | 56.58 (16.464) | 55.49 (18.429) | 59.87 (12.222) | 57.71 (13.595) | 58.82 (13.753) | 57.04 (15.194) | 57.93 (14.494) |
| Median | 61.00 | 62.00 | 61.00 | 61.00 | 61.00 | 61.00 | 61.00 |
| Min, Max | 6.0, 83.0 | 1.0, 82.0 | 25.0, 82.0 | 19.0, 84.0 | 6.0, 83.0 | 1.0, 84.0 | 1.0, 84.0 |
| Age Category (years) – n (%) | | | | | | | |
| ≤11 | 2 (3.8) | 1 (2.0) | 0 | 0 | 2 (1.2) | 1 (0.6) | 3 (0.9) |
| <2 (28 days-23 months) | 0 | 1 (2.0) | 0 | 0 | 0 | 1 (0.6) | 1 (0.3) |
| 2-11 | 2 (3.8) | 0 | 0 | 0 | 2 (1.2) | 0 | 2 (0.6) |
| 12-17 | 0 | 2 (4.1) | 0 | 0 | 0 | 2 (1.2) | 2 (0.6) |
| 18-64 | 30 (57.7) | 25 (51.0) | 70 (63.1) | 76 (67.3) | 100 (61.3) | 101 (62.3) | 201 (61.8) |
| ≥65 | 20 (38.5) | 21 (42.9) | 41 (36.9) | 37 (32.7) | 61 (37.4) | 58 (35.8) | 119 (36.6) |
| 65-84 | 20 (38.5) | 21 (42.9) | 41 (36.9) | 37 (32.7) | 61 (37.4) | 58 (35.8) | 119 (36.6) |
| ≥85 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Ethnicity - n (%) | | | | | | | |
| Hispanic or Latino | 1 (1.9) | 2 (4.1) | 5 (4.5) | 7 (6.2) | 6 (3.7) | 9 (5.6) | 15 (4.6) |
| Not Hispanic or Latino | 51 (98.1) | 47 (95.9) | 106 (95.5) | 105 (92.9) | 157 (96.3) | 152 (93.8) | 309 (95.1) |
| Not specified | 0 | 0 | 0 | 1 (0.9) | 0 | 1 (0.6) | 1 (0.3) |
| Race – n (%) | | | | | | | |
| White (Caucasian) | 44 (84.6) | 42 (85.7) | 106 (95.5) | 103 (91.2) | 150 (92.0) | 145 (89.5) | 295 (90.8) |
| Black or African American | 2 (3.8) | 4 (8.2) | 1 (0.9) | 2 (1.8) | 3 (1.8) | 6 (3.7) | 9 (2.8) |
| Asian | 6 (11.5) | 1 (2.0) | 4 (3.6) | 6 (5.3) | 10 (6.1) | 7 (4.3) | 17 (5.2) |
| American Indian or Alaskan Native | 0 | 0 | 0 | 1 (0.9) | 0 | 1 (0.6) | 1 (0.3) |
| Multi-racial (no primary race) | 0 | 1 (2.0) | 0 | 0 | 0 | 1 (0.6) | 1 (0.3) |
| Other | 0 | 1 (2.0) | 0 | 0 | 0 | 1 (0.6) | 1 (0.3) |
| Not Specified | 0 | 0 | 0 | 1 (0.9) | 0 | 1 (0.6) | 1 (0.3) |
| Height (cm) | | | | | | | |
| Mean (SD) | 167.2 (12.40) | 167.4 (15.37) | 169.6 (9.17) | 170.2 (9.26) | 168.8 (10.33) | 169.4 (11.48) | 169.1 (10.90) |
| Median | 168.0 | 170.0 | 170.0 | 170.0 | 168.0 | 170.0 | 170.0 |
| Min, Max | 118, 189 | 83, 188 | 152, 190 | 147, 195 | 118, 190 | 83, 195 | 83, 195 |
| Weight (kg) | | | | | | | |
| Mean (SD) | 77.3 (21.94) | 77.9 (19.07) | 77.4 (14.80) | 78.5 (17.08) | 77.3 (17.33) | 78.3 (17.65) | 77.8 (17.47) |
| Median | 73.5 | 79.0 | 77.0 | 77.0 | 75.0 | 78.0 | 77.0 |
| Min, Max | 25, 137 | 12, 120 | 46, 113 | 51, 135 | 25, 137 | 12, 135 | 12, 137 |

Source: Original BLA 125640/0; Module 5.3.5.1, Clinical Study Report for Study IG1102, p71.

6.2.10.1.3 Subject Disposition

Subject disposition is summarized in Table 8.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The proportion of subjects with successful hemostasis by T₄ was 92.8% (103/111) in the FS Grifols treatment group and 80.5% (91/113) in the Surgicel treatment group. The ratio and 95% CI of proportions of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.15 (1.04, 1.28), indicating that FS Grifols is non-inferior to Surgicel (i.e. the lower limit of the 95% CI ≥ 0.8). Additionally, the lower limit of the 95% CI above 1 provides statistical evidence that FS Grifols is superior to Surgicel (p-value = 0.010). The supportive analysis in the PP set showed similar results. Detailed results are shown in Table 10.

Table 10. Primary Endpoint Results in Primary Part (II)

| Analysis Population | FS Grifols | Surgicel | RR (95% CI) ^a | p-value ^b |
|---------------------|------------------|----------------|--------------------------|----------------------|
| ITT | 103/111 (92.8%) | 91/113 (80.5%) | 1.15 (1.04, 1.28) | 0.01 |
| PP | 86/87 (98.9%) | 85/100 (85.0%) | 1.16 (1.07, 1.27) | <0.001 |

^a RR was the ratio of proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part (II) (FS Grifols relative to Surgicel).

^b P-value was calculated from Fisher Exact Test.

6.2.11.2 Analyses of Secondary Endpoints

Since the non-inferiority of the primary efficacy endpoint was demonstrated, the secondary endpoints were analyzed for superiority according to the sequence described in Section 6.2.9.

The proportion of hemostasis success by T₃ was 85.6% (95/111 subjects) in the FS Grifols group and 62.8% (71/113 subjects) in the Surgicel group. The ratio (95% CI) of proportion of subjects achieving hemostasis by T₃ in subjects receiving FS Grifols relative to Surgicel was 1.36 (1.16, 1.60), indicating that FS Grifols is superior to Surgicel at T₃ (p-value <0.001).

The median TTH was significantly shorter (p-value <0.001) in the FS Grifols treatment group (2.0 minutes) compared to the Surgicel treatment group (3.0 minutes), indicating that FS Grifols is superior to Surgicel.

The results for cumulative proportion of subjects achieving hemostasis at the TBS by T₂, T₅, T₇, and T₁₀ show a similar pattern as the primary efficacy analysis in favor of FS Grifols (Table 11).

Table 11. Analysis of Hemostasis by T₂, T₃, T₅, T₇, and T₁₀ at Target Bleeding Site (ITT Population)

| | Primary Part (II) | | | |
|--------------------------|------------------------------|----------------------------|--------------------------|----------------------|
| | FS Grifols N=111 n (%) | Surgicel N=113 n (%) | RR (95% CI) ^a | P-value ^b |
| Hemostasis by 2 minutes | 62 (55.9) | 47 (41.6) | 1.34 (1.02, 1.77) | 0.045 |
| Hemostasis by 3 minutes | 95 (85.6) | 71 (62.8) | 1.36 (1.16, 1.60) | <0.001 |
| Hemostasis by 5 minutes | 108 (97.3) | 96 (85.0) | 1.15 (1.05, 1.25) | 0.002 |
| Hemostasis by 7 minutes | 108 (97.3) | 99 (87.6) | 1.11 (1.03, 1.20) | 0.010 |
| Hemostasis by 10 minutes | 109 (98.2) | 104 (92.0) | 1.07 (1.01, 1.13) | 0.059 |

^a RR was the ratio of proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part II (FS Grifols relative to Surgicel)

^b P-value was calculated from Fischer Exact Test.

Source: Original BLA 125640/0; Module 5.3.5.1, Clinical Study Report for Study IG1102, p91.

Therefore, FS Grifols is superior to Surgicel for all six secondary endpoints.

6.2.11.3 Subpopulation Analyses

Table 12 shows the subgroup analyses by sex, race and age categories using the ITT population. The results show a similar direction as the primary efficacy analysis in favor of FS Grifols in each subgroup except males who have similar treatment response proportions.

Table 12. Analysis of Hemostasis by T₄ at TBS by Treatment and Subgroups (ITT Population, Primary Part (II))

| Subgroup | FS Grifols (N=111) | Surgicel (N=113) |
|----------------------------------|-----------------------|---------------------|
| Sex | | |
| Male | 56/59 (90.9%) | 56/63 (88.9%) |
| Female | 47/52 (90.4%) | 35/50 (70%) |
| Age | | |
| 18-64 years | 64/70 (91.4%) | 59/76 (77.6%) |
| ≥65 years | 39/41 (95.1%) | 32/37 (86.5%) |
| Race | | |
| White (Caucasian) | 98/106 (92.5%) | 84/103(81.6%) |
| Black or African American | 1/1 (100%) | 0/2 (0%) |
| Asian | 4/4 (100%) | 5/6 (83.3%) |
| American Indian or Alaska Native | 0/0 (0%) | 1/1 (100%) |

6.2.11.4 Dropouts and/or Discontinuations

Since there were no missing data for the primary efficacy endpoint, no sensitivity analyses were performed.

6.2.12 Safety Analyses

6.2.12.3 Deaths

A total of 10 deaths occurred in 7(4.3%) FS Grifols subjects and 3 (1.9%) Surgicel subjects during the study. All death outcomes were considered not related to study treatment.

6.2.12.4 Nonfatal Serious Adverse Events

Thirty out of 163 (18.4%) subjects in the FS Grifols group experienced 78 SAEs, and 23 out of 162 (14.2%) subjects in the Surgicel group experienced 38 SAEs. In the FS Grifols group, 38 of the 78 SAEs (48.7%) were reported in only single subjects. While for the Surgicel group, 30 of the 38 SAEs (78.9%) were reported in only single subjects.

Of the total 78 SAEs occurring in 30 FS Grifols subjects, the SAEs were considered not related to study treatment in all except 4 subjects in which the SAEs were considered

unlikely related to study treatment. All of the 38 SAEs occurring in 23 Surgicel subjects were considered not related to study treatment.

6.2.12.5 Adverse Events of Special Interest (AESI)

Three subjects in the FS Grifols group (3/163; 1.8%) and one subject in the Surgicel group experienced a deep vein thrombosis event. Two events (1 FS Grifols subject and 1 Surgicel subject) were considered not related to study treatment; and two thrombosis events from FS Grifols group were considered unlikely related to study treatment.

6.3 Study IG1103

6.3.1 Objectives (Primary, Secondary, etc)

The efficacy objective of the study was to evaluate the hemostatic efficacy of FS Grifols in soft tissue open surgeries.

6.3.2 Design Overview

This was a multicenter, single-blind Phase III clinical study consisting of two parts: a Preliminary Part (I) and a Primary Part (II). Subjects in Preliminary Part (I) were randomized in a 1:1 ratio into one of two treatment groups, FS Grifols or Surgicel, following identification of a target bleeding site (see below). The main purpose of this part of the clinical study was to ensure that local study teams familiarized with the technique for FS Grifols application and with intra-operative procedures required by the protocol. For each study participating center, the first four subjects were to be enrolled in Preliminary Part (I). Subjects in Primary Part (II) were to be randomized in a 1:1 ratio into FS Grifols or Surgicel treatment groups. This part had two main purposes: (1) to assess the safety of FS Grifols and (2) to assess the efficacy of FS Grifols. For each study center, Primary Part (II) started only after enrollment of four subjects in Preliminary Part (I). Randomization was stratified by study center.

In both parts of this study, a specific bleeding area/site was defined as the TBS when it was determined by the investigator that control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) was ineffective or impractical and required an adjunct treatment to achieve hemostasis. When the TBS was identified, the investigator rated the intensity of the bleeding at the TBS and the approximate size of the bleeding surface according to a 3-point scale (mild, moderate, severe for the intensity of the bleeding and small, medium, large for the bleeding surface). For both parts of the study, only subjects with a TBS with bleeding of moderate intensity could be enrolled.

6.3.3 Population

Subjects were eligible once they met all of the following criteria:

1. Sign the written ICF.
2. Are male or female.
3. No lower or upper age limit.
4. Must have hemoglobin (Hgb) ≥ 8.0 g/dL at Baseline (within 24 hours prior to surgical procedure).

5. Require an elective (non-emergency), open (non-laparoscopic;) surgical procedure involving soft (non-parenchymous) tissue:
 - Where TBS is identified on soft tissue during following urologic, gynecologic or general surgery procedures:
 - i. Simple or radical nephrectomies.
 - ii. Total adrenalectomies.
 - iii. Radical prostatectomies.
 - iv. Pyeloplasties.
 - v. Radical cystectomies.
 - vi. Simple or radical hysterectomies.
 - vii. Lymphadenectomies (in the retroperitoneal or pelvic region only).
 - viii. Retroperitoneal tumor resections.
 - ix. Mastopexies.
 - x. Abdominoplasties.
6. Intra-operative inclusion criteria: a TBS can be identified according to the investigator's judgment, and
 - The TBS has a moderate bleeding according to the investigator's judgment.
 - The intensity of the bleeding at the TBS will be rated by the investigator using a pre-defined three-point scale

Subjects were ineligible if they met any of the following criteria:

1. Require thoracic, abdominal, retroperitoneal or pelvic surgery due to trauma.
2. Have an infection in the anatomic surgical area.
3. Have a history of severe (e.g. anaphylactic) reactions to blood or to any blood derived (human or animal) product.
4. Have previous known sensitivity to any FS Grifols component or any Surgicel® component.
5. Are unlikely to adhere to the protocol requirements, or to be cooperative during the study conduct.
6. Are females who are pregnant or nursing a child at Baseline (within 24 hours prior to surgical procedure).
7. Are receiving an organ transplant during the same surgical procedure.
8. Are currently participating or have participated in another clinical study in the context of which have received investigational drug or device within 3 months from the screening visit, or are scheduled to participate during the course of this study.
9. Have undergone a therapeutic surgical procedure within 30 days from the screening visit.
10. Were previously enrolled in clinical trials with FS Grifols.
11. Intra-operative exclusion criteria:
 - A TBS (as defined in section 7.1.3.1) cannot be identified according to the investigator's judgment.
 - The TBS has a mild or severe bleeding according to the investigator's judgment.

- Occurrence of major intraoperative complications that require resuscitation or deviation from the planned surgical procedure.
 - Application of any topical hemostatic material on the cut soft tissue surface identified as the TBS prior to application of the study treatment.
12. Have a known (documented) history of thrombophilia.
 13. Have a known (documented) history of IgA deficiency.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Upon identification of the TBS, subjects were treated intra-operatively with FS Grifols or Surgicel.

For subjects randomized to the FS Grifols group, FS Grifols was dripped onto the TBS up to 12 mL. No additional amounts of FS Grifols could be applied beyond T₄.

For subjects randomized to the Surgicel group, up to four 4" × 8" sheets of Surgicel were applied to the TBS. No additional Surgicel sheets could be applied at the TBS beyond T₄.

6.3.6 Sites and Centers

This study was conducted in 31 study centers in Hungary (5 centers), Serbia (7) and the US (19).

6.3.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

The primary efficacy variable was the proportion of subjects in Primary Part (II) achieving hemostasis (Yes/No) at the TBS by T₄ without occurrence of re-bleeding and re-application of study treatment after T₄ and until T_{Closure} and without brisk bleeding and use of alternative hemostatic treatment after T_{Start} and until T_{Closure}.

Secondary Efficacy Endpoints

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

Safety Endpoints

- AEs, ADRs and SAEs.
- Vital signs.
- Physical assessments.
- Laboratory tests.
- Viral markers.
- Antibodies.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Sample Size

The sample size was calculated for Primary Part (II) as Preliminary Part (I) was not included for any statistical considerations. With a 1:1 ratio, a total of 212 subjects (106 in FS Grifols and 106 in Surgicel) would provide 80% power to show non-inferiority of FS Grifols relative to Surgicel on the proportion of subjects achieving hemostasis by T₄ (assuming 65% in the FS Grifols group vs. 60% in the Surgicel group). Non-inferiority was defined in terms of the lower limit of a 2-sided 95% CI for the ratio of the hemostasis success proportions in the two groups (FS Grifols relative to Surgicel). FS Grifols will be considered non-inferior to Surgicel if the lower bound of this CI is greater than 0.80. To allow for an approximate 5% drop-out rate after randomization, a total of 224 subjects (112 for each arm) would need to be randomized in Primary Part (II).

Analysis Populations

- **ITT population:** The ITT population included all subjects randomized to FS Grifols or Surgicel in either Preliminary Part (I) or Primary Part (II).
- **PP population:** The PP population included all subjects in the ITT population excluding any subject for whom there was at least one major protocol deviation that might have an impact on the primary efficacy assessment.
- **Safety population:** The safety population consisted of all subjects who received any amount of FS Grifols or Surgicel in either Preliminary Part (I) or Primary Part (II).

All efficacy analyses were performed using the ITT population and PP population in Primary Part (II) only. Safety analyses were based on the safety population.

Analysis for Primary Efficacy Endpoint

The primary efficacy endpoint was analyzed by providing the ratio of hemostasis success proportions by T₄ in the two treatment groups (FS Grifols relative to Surgicel) and its 2-sided asymptotic 95% CI. The CI was calculated using a normal approximation as:

$$\text{Exp}(\log(RR) \pm Z(\alpha/2) * \sqrt{((1-p_1)/(n_1*p_1) + (1-p_2)/(n_2*p_2)))}$$

where p_1 was the success proportion in the FS Grifols group and p_2 was the success proportion in the Surgicel group, risk ratio $(RR)=p_1/p_2$. n_1 and n_2 were the number of subjects in FS Grifols group and Surgicel group, respectively.

FS Grifols would be considered non-inferior to Surgicel if the lower limit of the 95% CI exceeded 0.8. If non-inferiority was established, superiority may be additionally claimed if the 95% CI is entirely above 1.

Analysis for Secondary Efficacy Endpoint

- Cumulative proportion of subjects achieving hemostasis at the TBS by T₂, T₃, T₅, T₇, and T₁₀ were analyzed by providing the ratio of proportion (and 95% CI) of subjects meeting the secondary efficacy endpoints. FS Grifols would be considered non-inferior to Surgicel if the lower limit of the 95% CI exceeded 0.8.
- Time to hemostasis was tested using Log Rank test.

The superiority for the secondary endpoints would be tested only if non-inferiority for the primary efficacy endpoint was demonstrated. For the secondary efficacy endpoints, a fixed-sequence testing method was employed for handling the multiplicity issue to maintain the overall familywise alpha level at 0.05. Each subsequent hypothesis was tested only if superiority for the previous comparisons was shown at a 2-sided significance level of 5%. The order in which the null hypotheses were tested was predetermined as below for the secondary efficacy variables:

1. Cumulative proportion of subjects having achieved hemostasis at the TBS by T₃.
2. Time to hemostasis.
3. Proportion of subjects having achieved hemostasis at the TBS by T₂.

Missing Data Handling

If any missing hemostatic assessment at TBS at T₄ for a randomized subject occurred, it was treated as non-hemostasis at TBS at T₄. A sensitivity analysis with non-missing observational hemostatic assessment at TBS at T₄ was performed.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

One hundred and sixty-four subjects were screened and 61 subjects failed screening during Preliminary Part (I). During Primary Part (II), 334 subjects were screened and 110 subjects failed screening. A total of 224 subjects were randomized into either the FS Grifols treatment group or Surgicel treatment group (Table 14), and 198 subjects completed the study in Primary Part (II). The ITT and PP populations for efficacy are comprised of 224 and 206 subjects, respectively; the safety population is comprised of 327 subjects.

Table 14. Subject Populations and Disposition

| | Preliminary Part (I) | | | Primary Part (II) | | | Part (I) + Part (II) N |
|---------------------------|----------------------|---------------|--------------|--------------------|---------------|--------------|---------------------------------|
| | FS Grifols N | Surgicel N | Overall N | FS Grifols N | Surgicel N | Overall N | |
| Randomized | 51 | 52 | 103 | 116 | 108 | 224 | 327 |
| ITT population | 51 | 52 | 103 | 116 | 108 | 224 | 327 |
| PP population | 44 | 41 | 85 | 104 | 102 | 206 | 291 |
| Safety population | 53 | 50 | 103 | 116 | 108 | 224 | 327 |
| Completed study | 48 | 44 | 92 | 103 | 95 | 198 | 290 |
| Discontinued study | 3 | 8 | 11 | 13 | 13 | 26 | 37 |
| Withdrawal of consent | 2 | 2 | 4 | 5 | 4 | 9 | 13 |
| Lost to follow-up | 0 | 3 | 3 | 4 | 5 | 9 | 12 |
| Death | 0 | 0 | 0 | 2 | 1 | 3 | 3 |
| Investigator's discretion | 1 | 0 | 1 | 0 | 0 | 0 | 1 |
| Other | 0 | 3 | 3 | 2 | 3 | 5 | 8 |

6.3.10.1.1 Demographics

Subject demographics by treatment and by Preliminary Part (I) and Primary Part (II) are summarized in Table 15. In Preliminary Part (I), the ITT population consisted of 47.1% male subjects and 52.9% female subjects in the FS Grifols treatment group and similarly, 46.2% male subjects and 53.8% female subjects in the Surgicel group. In Primary Part (II), there were more female subjects than male subjects: 75.0% vs 25% in FS Grifols-treated subjects and 79.6% vs 20.4% in the Surgicel-treated subjects. The ages of subjects in both treatment groups across Preliminary Part (I) and Primary Part (II) of the study were consistent. The mean age of subjects was comparable in the FS Grifols (48.1 years) and Surgicel (46.3 years) groups. No pediatric subjects (≤ 11 years) were enrolled in Primary Part (II). The majority of subjects in the ITT population were White (81.3%). There were no major differences in height and weight between the two treatment groups.

Table 15. Demographics (ITT Population)

| Characteristics | Preliminary Part (I) | | Primary Part (II) | | Part (I) + Part (II) | | Total ^a (N=327) n (%) |
|-------------------------------------|-------------------------------|-----------------------------|--------------------------------|------------------------------|--------------------------------|------------------------------|----------------------------------------|
| | FS Grifols (N=51) n (%) | Surgicel (N=52) n (%) | FS Grifols (N=116) n (%) | Surgicel (N=108) n (%) | FS Grifols (N=167) n (%) | Surgicel (N=160) n (%) | |
| Sex - n (%) | | | | | | | |
| Male | 24 (47.1) | 24 (46.2) | 29 (25.0) | 22 (20.4) | 53 (31.7) | 46 (28.8) | 99 (30.3) |
| Female | 27 (52.9) | 28 (53.8) | 87 (75.0) | 86 (79.6) | 114 (68.3) | 114 (71.3) | 228 (69.7) |
| Age (years) | | | | | | | |
| Mean (SD) | 47.17 (25.635) | 45.39 (25.024) | 48.51 (14.369) | 46.72 (14.330) | 48.10 (18.476) | 46.29 (18.424) | 47.21 (18.444) |
| Median | 48.00 | 47.00 | 46.00 | 45.00 | 46.00 | 45.50 | 46.00 |
| Min, Max | 0.3, 86.0 | 0.6, 85.0 | 15.0, 85.0 | 21.0, 84.0 | 0.3, 86.0 | 0.6, 85.0 | 0.3, 86.0 |
| Age Category (years) – n (%) | | | | | | | |
| ≤ 11 | 8 (15.7) | 8 (15.4) | 0 | 0 | 8 (4.8) | 8 (5.0) | 16 (4.9) |
| <2 (28 days-23 months) | 5 (9.8) | 6 (11.5) | 0 | 0 | 5 (3.0) | 6 (3.8) | 11 (3.4) |
| 2-11 | 3 (5.9) | 2 (3.8) | 0 | 0 | 3 (1.8) | 2 (1.3) | 5 (1.5) |
| 12-17 | 0 | 1 (1.9) | 1 (0.9) | 0 | 1 (0.6) | 1 (0.6) | 2 (0.6) |
| 18-64 | 27 (52.9) | 28 (53.8) | 98 (84.5) | 90 (83.3) | 125 (74.9) | 118 (73.8) | 243 (74.3) |
| ≥ 65 | 16 (31.4) | 15 (28.8) | 17 (14.7) | 18 (16.7) | 33 (19.8) | 33 (20.6) | 66 (20.2) |
| 65-84 | 13 (25.5) | 14 (26.9) | 16 (13.8) | 18 (16.7) | 29 (17.4) | 32 (20.0) | 61 (18.7) |
| ≥ 85 | 3 (5.9) | 1 (1.9) | 1 (0.9) | 0 | 4 (2.4) | 1 (0.6) | 5 (1.5) |
| Ethnicity - n (%) | | | | | | | |
| Hispanic or Latino | 4 (7.8) | 5 (9.6) | 20 (17.2) | 12 (11.1) | 24 (14.4) | 17 (10.6) | 41 (12.5) |
| Not Hispanic or Latino | 47 (92.2) | 47 (90.4) | 96 (82.8) | 96 (88.9) | 143 (85.6) | 143 (89.4) | 286 (87.5) |
| Race – n (%) | | | | | | | |
| White (Caucasian) | 46 (90.2) | 46 (88.5) | 93 (80.2) | 81 (75.0) | 139 (83.2) | 127 (79.4) | 266 (81.3) |
| Black or African American | 5 (9.8) | 5 (9.6) | 22 (19.0) | 25 (23.1) | 27 (16.2) | 30 (18.8) | 57 (17.4) |
| Asian | 0 | 0 | 1 (0.9) | 1 (0.9) | 1 (0.6) | 1 (0.6) | 2 (0.6) |
| American Indian or Alaskan Native | 0 | 0 | 0 | 1 (0.9) | 0 | 1 (0.6) | 1 (0.3) |
| Not Specified | 0 | 1 (1.9) | 0 | 0 | 0 | 1 (0.6) | 1 (0.3) |
| Height (cm) | | | | | | | |
| Mean (SD) | 156.2 (31.02) | 155.8 (33.50) | 167.0 (8.92) | 167.1 (8.69) | 163.7 (19.23) | 163.4 (20.94) | 163.6 (20.06) |
| Median | 165.0 | 166.0 | 165.5 | 165.0 | 165.0 | 165.0 | 165.0 |
| Min, Max | 68, 188 | 70, 188 | 146, 191 | 150, 193 | 68, 191 | 70, 193 | 68, 193 |
| Weight (kg) | | | | | | | |
| Mean (SD) | 70.0 (28.90) | 69.0 (28.41) | 75.6 (16.26) | 78.4 (17.76) | 73.9 (21.01) | 75.4 (22.15) | 74.6 (21.56) |
| Median | 75.0 | 75.0 | 71.0 | 74.5 | 73.0 | 75.0 | 74.0 |
| Min, Max | 6, 118 | 8, 111 | 48, 135 | 48, 156 | 6, 135 | 8, 156 | 6, 156 |

Source: Original BLA 125640/0; Module 5.3.5.1, Clinical Study Report for Study IG1103, p71.

6.3.10.1.3 Subject Disposition

Subject disposition is summarized in Table 14.

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

The proportion of subjects achieving hemostasis by T₄ was 82.8% (96/116) in the FS Grifols group and 77.8% (84/108) in the Surgicel group. The ratio (95% CI) of the

proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to Surgicel was 1.06 (0.93, 1.21), indicating that FS Grifols is non-inferior to Surgicel (i.e., the lower limit of the 95% CI ≥ 0.8) in the ITT population. However, the rate of hemostasis by T₄ was not statistically superior in the FS Grifols group compared to the Surgicel group since the lower limit of the 95% CI is not greater than 1. The supportive analysis in the PP set showed similar results. Detailed results are shown in Table 16.

Table 16. Primary Endpoint Results in Primary Part (II)

| Analysis Population | FS Grifols | Surgicel | RR (95% CI) ^a | p-value ^b |
|---------------------|----------------|----------------|--------------------------|----------------------|
| ITT | 96/116 (82.8%) | 84/108 (77.8%) | 1.06 (0.93, 1.21) | 0.401 |
| PP | 87/104 (83.7%) | 78/102 (76.5%) | 1.09 (0.95, 1.26) | 0.224 |

^a RR was the ratio of proportion of subjects meeting the efficacy endpoint in the two treatment groups in Primary Part (II) (FS Grifols relative to Surgicel).

^b P-value was calculated from Fisher Exact Test.

6.3.11.2 Analyses of Secondary Endpoints

Since superiority of the primary efficacy endpoint was not demonstrated, the analyses for secondary endpoints were not conducted with strong family-wise Type I error rate control.

The proportion of subjects achieving hemostasis at the TBS by T₃ was 75.9% (88/116) in the FS Grifols group and 60.2% (65/108) in the Surgicel group. The 95% CI of proportion of subjects achieving hemostasis at the TBS by T₃ in subjects receiving FS Grifols relative to Surgicel was 1.26 (1.05, 1.52), indicating that FS Grifols is superior to Surgicel at T₃ (p-value=0.015).

The median TTH was not significantly shorter (p-value=0.06) in the FS Grifols treatment group (2.0 minutes) compared to the Surgicel treatment group (3.0 minutes), indicating that FS Grifols is not superior to Surgicel.

The results for cumulative proportion of subjects achieving hemostasis at the TBS by T₂, T₅, T₇, and T₁₀ show a similar pattern as the primary efficacy analysis indicating that FS Grifols is non-inferior to Surgicel (Table 17).

Table 17. Analysis of Hemostasis by T₂, T₃, T₅, T₇, and T₁₀ at Target Bleeding Site (ITT Population)

| | Primary Part (II) | | | |
|--------------------------|------------------------------|----------------------------|--------------------------|----------------------|
| | FS Grifols N=116 n (%) | Surgicel N=108 n (%) | RR (95% CI) ^a | P-value ^b |
| Hemostasis by 2 minutes | 62 (53.4) | 47 (43.5) | 1.23 (0.93, 1.62) | 0.144 |
| Hemostasis by 3 minutes | 88 (75.9) | 65 (60.2) | 1.26 (1.05, 1.52) | 0.015 |
| Hemostasis by 5 minutes | 97 (83.6) | 85 (78.7) | 1.06 (0.9364, 1.21) | 0.394 |
| Hemostasis by 7 minutes | 100 (86.2) | 88 (81.5) | 1.06 (0.94, 1.19) | 0.367 |
| Hemostasis by 10 minutes | 104 (89.7) | 90 (83.3) | 1.08 (0.97, 1.19) | 0.176 |

^a RR was the ratio of proportion of subjects meeting the efficacy endpoint in the 2 treatment groups in Primary Part II (FS Grifols relative to Surgicel)

^b P-value was calculated from Fisher Exact Test.

Source: Original BLA 125640/0; Module 5.3.5.1, Clinical Study Report for Study IG1103, p92.

6.3.11.3 Subpopulation Analyses

Table 18 shows the subgroup analyses by sex, race and age categories using the ITT population. The results are similar to the primary efficacy analysis, indicating non-inferiority of FS Grifols as compared to Surgicel in each subgroup.

Table 18. Analysis of Hemostasis by T₄ at TBS by Treatment and Subgroups (ITT Population, Primary Part (II))

| Subgroup | FS Grifols (N=116) | Surgicel (N=108) |
|----------------------------------|-----------------------|---------------------|
| Sex | | |
| Male | 22/29 (75.9%) | 18/22 (81.8%) |
| Female | 74/87 (85.1%) | 66/86 (76.7%) |
| Age | | |
| 12-17 years | 1/1 (100%) | 0/0 (NA) |
| 18-64 years | 82/98 (83.7%) | 67/90 (74.4%) |
| ≥65 years | 13/17 (76.5%) | 17/18 (94.4%) |
| Race | | |
| White (Caucasian) | 77/93 (82.8%) | 68/81 (84.0%) |
| Black or African American | 18/22 (81.8%) | 14/25 (56%) |
| Asian | 1/1 (100%) | 1/1 (100%) |
| American Indian or Alaska Native | 0/0 (NA) | 1/1 (100%) |

6.3.11.4 Dropouts and/or Discontinuations

Since there were no missing data for the primary efficacy endpoint, no sensitivity analyses were performed.

6.3.12 Safety Analyses

6.3.12.3 Deaths

A total of three deaths occurred in two (1.2%) FS Grifols subjects and one (0.6%) Surgicel subject. All death outcomes were considered not related to study treatment.

6.3.12.4 Nonfatal Serious Adverse Events

Seventeen out of 169 (10.1%) subjects in the FS Grifols treatment group experienced 29 SAEs, and 18 out of 158 (11.4%) subjects in the Surgicel treatment group experienced 27 SAEs. In the FS Grifols treatment group, 19 of the 29 (65.5%) SAEs were reported in only single subjects. While for the Surgicel treatment group, 20 of the 27 (74.0%) SAEs were reported in only single subjects.

Of the total 29 SAEs occurring in 17 FS Grifols-treated subjects, all except 2 SAEs were considered not related to study treatment. The 2 SAEs (abdominal wound dehiscence and peritonitis) occurred in 1 FS Grifols-treated subject considered possibly related to study treatment were also considered attributable to application technique. Of the 27 SAEs occurring in 18 Surgicel-treated subjects, all were considered not related to study treatment.

6.3.12.5 Adverse Events of Special Interest (AESI)

One subject in the FS Grifols group (1/169; 0.6%) and one subject in the Surgicel group (1/158; 0.6%) each experienced a deep vein thrombosis event. All thrombosis events were considered not related to study treatment.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Three Phase III clinical studies were submitted to the FDA to support this original BLA for FS Grifols. All three studies included two parts: a Preliminary Part (I) and a Primary Part (II). For all three studies, the efficacy evaluations for FS Grifols were based on results from Primary Part (II), and the primary efficacy endpoint was the proportion of subjects achieving hemostasis at the TBS by T₄.

The first study, Study IG1101, was a multicenter, single-blind, superiority study conducted under IND 14988 in four countries including the US to evaluate the hemostatic efficacy of FS Grifols in peripheral vascular surgery. A total of 166 subjects were randomized to Primary Part (II). The success proportion was significantly higher in the FS Grifols group (83/109 subjects, 76.1%) compared to the MC group (13/57 subjects, 22.8%) with a p-value <0.001, indicating that FS Grifols is superior to MC for the primary efficacy endpoint in the ITT population. The ratio (95% CI) of the proportion of subjects meeting the primary efficacy endpoint in subjects receiving FS Grifols relative to MC was 3.34 (2.05, 5.45).

The second study is Study IG1102, which was a multicenter, single-blind, non-inferiority study conducted under IND 14987 in four countries including the US to evaluate the

hemostatic efficacy of FS Grifols in parenchymous tissue open surgery. A total of 224 subjects were randomized to Primary Part (II). The success proportion was 92.8% (103/111 subjects) in the FS Grifols group and 80.5% (91/113 subjects) in the Surgicel group. The estimated ratio (95% CI) of proportion achieving hemostasis by T₄ in subjects receiving FS Grifols relative to Surgicel was 1.15 (1.04, 1.28), indicating that FS Grifols is non-inferior to Surgicel (i.e., the lower limit of the 95% CI ≥ 0.8). As the lower limit of the 95% CI is above 1, it further indicated that FS Grifols is superior to Surgicel (p-value = 0.010) for the primary efficacy endpoint in the ITT population. These results were supported by the PP analysis.

The third study, Study IG1103, was a multicenter, single-blind, non-inferiority study conducted under IND 14986 in three countries including the US to evaluate the hemostatic efficacy of FS Grifols in soft tissue open surgery. A total of 224 subjects were randomized to Primary Part (II). The success proportion was 82.8% (96/116 subjects) in the FS Grifols group and 77.8% (84/108 subjects) in the Surgicel group. The estimated ratio (95% CI) of proportion achieving hemostasis by T₄ in subjects receiving FS Grifols relative to Surgicel was 1.06 (0.93, 1.21), demonstrating that FS Grifols is non-inferior to Surgicel (i.e., the lower limit of the 95% CI ≥ 0.8) for the primary efficacy endpoint in the ITT population. However, FS Grifols was not statistically superior to Surgicel in terms of the primary efficacy endpoint. These results were consistent in the PP population.

There were no safety concerns related to FS Grifols in all three trials. All death outcomes in the three studies were considered not related to study treatment. Further analysis of safety data is deferred to the clinical team.

10.2 Conclusions and Recommendations

There were no statistical issues in this submission. The positive efficacy results from the three pivotal studies IG1101, IG1102 and IG 1103 provided statistical evidence to show the hemostatic effect of FS Grifols and support the application of FS Grifols as an adjunct to hemostasis for mild to moderate bleeding in adults undergoing surgery.