Application Type	PAS Efficacy Supplement BLA
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CBER Received Date	07/04/2023
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Division / Office	CBER/OTP/OCE/DCEGM/GMB4
Committee Chair	Elizabeth Sharpe, MD
Clinical Reviewer(s)	Elizabeth Sharpe, MD
Project Manager	Julia Russell, MS
Priority Review	No
Reviewer Name(s)	Qianmiao Gao, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Zhenzhen Xu, Ph.D. Team Leader, FDA/CBER/OBPV/DB/TEB1
	Boguang Zhen, Ph.D. Branch Chief, FDA/CBER/OBPV/DB/TEB1
Applicant	Instituto Grifols, S.A.
Established Name	Fibrin Sealant (Human)
(Proposed) Trade Name	VistaSeal
Formulation(s), including Adjuvants, etc	fibrinogen (80 mg/mL) and thrombin (500 IU/mL).
Dosage Form(s) and Route(s) of Administration	Frozen, sterile, 2-component FS solution obtained from human plasma pools; Topical use.
Dosing Regimen	Up to the maximum allowed volume (b) (4) for subjects >2 years of age and (b) (4) for subjects <2 years of age.
Indication(s) and Intended Population(s)	(b) (4)

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1. Executive Summary

Fibrin Sealant (Human) (FS Grifols) is 2-component FS solution composed of purified sterile frozen solutions of human fibrinogen and human thrombin with calcium chloride. It was originally approved by the United States (US) Food and Drug Administration (FDA) on November 01, 2017, 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. This Efficacy Supplement Biologics Licensure Application (sBLA) seeks approval of the inclusion of pediatric indication for Fibrin Sealant (Human).

The primary source of evidence to support efficacy and safety evaluation is from a randomized, active-controlled, single-blind, non-inferiority study (IG1405). Efficacy was established based on the primary efficacy endpoint, the proportion of subjects achieving hemostasis at 4 minutes following start of initial study treatment application (T_4). A total of 88/91 (96.7%) subjects from the FS Grifols group, and 83/87 (95.4%) subjects from the active comparator (EVICEL) group achieved hemostasis by T_4. The ratio of proportions of subjects who achieved hemostasis by T_4 in FS Grifols versus EVICEL is 1.01 (95% CI: 0.96, 1.07). FS Grifols was shown to be non-inferior to the comparator (EVICEL) in achieving hemostasis by 4 minutes based on a p-value of <.001 with a non-inferiority margin of 0.2 in the ratio of proportions.

In the treated pediatric population, 1 (1.1%) subject in the FS Grifols group experienced an adverse reaction (possibly related procedural pain), and 0 subject in the control group experienced adverse reactions.

I have verified the primary efficacy endpoint analysis result. I recommend approval of FS Grifols in the proposed indication in this sBLA, as the statistical analysis result provides sufficient evidence to support the effectiveness.

6. Discussion of Individual Studies/Clinical Trials

6.1 Study IG1405

6.1.1 Objectives

To evaluate whether FS Grifols is non-inferior to EVICEL in terms of the proportion of subjects achieving hemostasis.

6.1.2 Design Overview

This is a randomized, active-controlled, single-blind, non-inferiority study. Treatment assignment for subjects participating in the study was blinded from the sponsor, except for personnel from IP supply groups.

6.1.3 Population

Pediatric subjects (<18 years of age) requiring an elective (non-emergent), open (nonlaparoscopic), pelvic, abdominal, or thoracic (non-cardiac) surgical procedure, wherein a target bleeding site (TBS) was identified, and a topical hemostatic agent was indicated.

6.1.4 Study Treatments or Agents Mandated by the Protocol

FS Grifols:
FS Grifols was supplied as a frozen, sterile, 2-component FS solution obtained from human plasma pools. FS Grifols consists of human fibrinogen (component 1) and human thrombin with calcium chloride (component 2) solutions filled in syringes, assembled on a syringe holder.

EVICEL:
EVICEL (Omrix Biopharmaceuticals N.V, Diegem, Belgium) is manufactured from pooled human plasma.

6.1.8 Endpoints

Primary Endpoint:
The primary efficacy endpoint is the proportion of subjects achieving hemostasis at the target bleeding site (TBS) by 4 minutes following start of initial study treatment application (T_4), without occurrence of rebleeding or reapplication of study treatment after T_4 and until $T_{Closure}$, and without Grade 3 or 4 bleeding or use of alternative hemostatic treatment after T_{Start} and until $T_{Closure}$, where T_{Start} is defined as time of start of initial study treatment application, and $T_{Closure}$ is defined as the time of completion of the surgical closure by layers of the exposed surgical field containing the TBS. Hemostasis was defined as Grade 0 bleeding at the TBS according to the investigator's (surgeon's) judgment.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Statistical considerations proposed in the study protocol and statistical analysis plan are described in the following:

Statistical hypothesis:
Hypothesis testing of non-inferiority was to be performed with the non-inferiority margin of 0.2:

(b) (4)

where T is the response rate of hemostasis for the FS Grifols treatment group, and C is the response rate of hemostasis for the control (EVICEL) group.

The Applicant planned to claim superiority after the non-inferiority of FS Grifols to EVICEL is established, if the lower limit of 95% CI of the ratio is above 1.

Reviewer's note:
During the review of the sBLA, the FDA statistical and clinical teams considered the non-inferiority margin of 0.2 acceptable.

Multiplicity Adjustment:
The Type I error rate was controlled at one-sided 0.025 by fixed-sequence testing procedure on the non-inferiority and superiority test.

Analysis populations:
Intent-to-treat (ITT) population includes all subjects who are randomized.

Modified ITT (mITT) set includes all subjects in the ITT population who meet intra-operative enrollment criteria, and are treated. The primary efficacy analyses was to be performed in the mITT set.

Safety population includes all subjects who receive any amount of IP.

Stratification:
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, versus 0-27 days).

Statistical methods:
The primary endpoint would be analyzed using Cochran-Mantel-Haenszel (CMH) test stratified by type of surgery (i.e., parenchymous versus soft tissue surgery).

Reviewer's note:
The stratification strategy in the primary analysis method was prespecified before the study was initiated (first subject enrolled on Jan 18, 2019).

Interim Analyses:
No interim analysis for efficacy was planned or performed.

Sample size and power calculation:
Assuming that the true response rate is 80% for the FS Grifols group and 80% for the EVICEL group, the planned sample size was 172 subjects based on a Type I error rate of one-sided 0.025 and a power of 80% to establish non-inferiority of FS Grifols versus EVICEL with a non-inferiority margin of 0.2.

Missing data and Imputation:
If any missing hemostatic assessment at TBS at T4 for a randomized subject occurs, it would be treated as non-hemostasis at TBS at T4 for the subject in the primary efficacy analysis.

6.1.10 Study Population and Disposition

6.1.10.1.3 Subject Disposition

Table 1. Subjects Disposition

	FS Grifols n (%)	EVICEL n (%)
Screened		
Subjects Randomized/in the ITT Population	95	91
Subjects Dosed in the Study (mITT Population)	91 (95.8%)	87 (95.6%)
Subjects Completed the Study (After Being Dosed)	87 (91.6%)	84 (92.3%)
Subjects Discontinued Prematurely (After Being Dosed)	4 (4.2%)	3 (3.3%)
Reasons for Premature Discontinuation (After Being Dosed)		
Adverse event	0 (0.0%)	0 (0.0%)
Subject Withdrew Consent	0 (0.0%)	0 (0.0%)
Lost to follow-up	3 (3.2%)	0 (0.0%)
Death	1 (1.1%)	2 (2.2%)
Investigator's Discretion (does not include AEs)	0 (0.0%)	0 (0.0%)
Sponsor's Termination of the Trial	0 (0.0%)	0 (0.0%)
Protocol violation	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	1 (1.1%)

(Source: BLA 125640/220 Module 5.3.5)

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Among the 178 subjects in the mITT set, a total of 88/91 (96.7%) subjects from the FS Grifols group, and 83/87 (95.4%) subjects from the active comparator (EVICEL) group achieved hemostasis by T_4. The ratio of proportions of subjects who achieved hemostasis by T_4 in FS Grifols versus EVICEL is 1.01 (95% CI: 0.96, 1.07). FS Grifols was shown to be non-inferior to the comparator (EVICEL) in achieving hemostasis by 4 minutes based on a p-value of <.001 with a non-inferiority margin of 0.2 in the ratio of proportions. However, the superiority of FS Grifols vs. EVICEL was not further established since the lower limit of ratio of proportion did not exceed 1.

Reviewer's note:
Among the 178 subjects in the mITT set, there were 137 subjects who had hemostasis evaluation by 4 minutes following start of initial study treatment application (i.e., T_4).

For the other 41 subjects, their first hemostasis evaluation recorded in the dataset were at a range of 4 minutes 1 second to 4 minutes 37 seconds, all exceeding T_4.

According to the prespecified protocol for missing data and imputation (refer to section 6.1.9), the hemostasis evaluation for these 41 subjects at T_4 should have been considered as non-responders. However, the applicant did not follow this protocol in their primary analysis. Instead, they used the hemostasis evaluation completed at the earliest time after T_4 for these 41 subjects. As a result, 40 subjects were considered as responders and 1 subject was considered as non-responder.

In order to evaluate how this deviation from protocol impact the primary efficacy result, I performed a sensitivity analysis considering all the 41 subjects missing hemostasis evaluation by T_4 as non-responders, as prespecified in the protocol and SAP. The resultant ratio of proportion of hemostasis in the FS Grifols group versus EVICEL group is 1.06 (95% CI: 0.91, 1.24), which still establishes the non-inferiority. The deviation from protocol does not alter the conclusion of the primary analysis.

Based on assessment of the clinical team, it is reasonable to include subjects who achieved hemostasis by 4 minutes 37 seconds after application as having achieved hemostasis by T_4. The rationale includes the following:

- *Neither product application nor assessment of hemostasis are instantaneous; either may take several seconds.*
- *Achieving hemostasis by 4 min 37 seconds is clinically similar to achieving hemostasis by 4 minutes.*
- *The sensitivity analysis considering the assessment between 4:01 and 4:37 after product application non-hemostasis does not show substantial deviation from the primary analysis result.*

6.1.11.3 Subpopulation Analyses

Suparenchymous surgery

In subjects who underwent suparenchymous surgery, all 46 (100.0%) subjects in FS Grifols group and all 43 (100.0%) subjects in EVICEL group achieved hemostasis by 4 minutes. The ratio of hemostasis is 1.0.

Soft tissue surgery

In subjects who underwent soft tissue surgery, 42/45 (93.3%) subjects in FS Grifols group and 40/44 (90.9%) subjects in EVICEL group achieved hemostasis at 4 minutes. The ratio of proportions achieving hemostasis in FS Grifols versus EVICEL is 1.03 (95% CI: 0.91, 1.16).

6.1.12 Safety Analyses

In the FS Grifols group, 1 (1.1%) subject experienced an adverse reaction (possibly related procedural pain), and 0% subject in the control group experienced adverse reactions.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This sBLA seeks approval of the inclusion of pediatric indication for FS Grifols.

The primary source of evidence to support efficacy and safety evaluation is from a randomized, active-controlled, single-blind, non-inferiority study (IG1405). Efficacy was established based on the primary efficacy endpoint, the proportion of subjects achieving hemostasis at 4 minutes following start of initial study treatment application (T_4). A total of 88/91 (96.7%) subjects from the FS Grifols group, and 83/87 (95.4%) subjects from the active comparator (EVICEL) group achieved hemostasis by T_4. The ratio of proportions of subjects meeting the efficacy endpoint in FS Grifols versus EVICEL is 1.01 (95% CI: 0.96, 1.07). FS Grifols was shown to be non-inferior to the comparator (EVICEL) in achieving hemostasis by 4 minutes based on a p-value of <.001 with a non-inferiority margin of 0.2 in the ratio of proportions.

In the treated pediatric population, 1 (1.1%) subject in the FS Grifols group experienced an adverse reaction (possibly related procedural pain), and 0 subject in the control group experienced adverse reactions.

10.2 Conclusions and Recommendations

I have verified the primary efficacy endpoint analysis result. I recommend approval of FS Grifols in the proposed indication in this sBLA, as the statistical analysis results provide sufficient evidence to support the effectiveness.