Evaluation of the safety and efficacy of a new hemostatic powder using a quantitative surface bleeding severity scale

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Abstract

Aims of the study: The safety and efficacy of a hemostatic powder (HP) versus a control agent, absorbable gelatin sponge and thrombin (G + T), were assessed, using a validated, quantitative bleeding severity scale.

Methods: Subjects were randomized to receive HP (256 subjects) or G + T (132 subjects) for treatment of minimal, mild, or moderate bleeding at 20 investigational sites. The primary efficacy endpoint was non-inferiority of HP relative to G + T for success at achieving hemostasis within 6 minutes. Secondary endpoints in rank order included: superiority of HP relative to G + T in mean preparation time; non-inferiority of HP relative to G + T for achieving hemostasis within 3 min; superiority of HP relative to

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INTRODUCTION

Level I evidence of the benefit of local hemostats in surgical operations is limited, yet research in this area is continuing to grow. Although the ideal surgical hemostat—one combining safety, efficacy, usability, cost, and approvability—has yet to be created, continued development work is resulting in new agents.

The objective of this clinical trial was to evaluate the safety and efficacy of a novel hemostatic powder (HP) containing collagen, chondroitin sulfate, and thrombin compared to an established efficacy of a novel hemostatic powder (HP) containing collagen, hemostat, hemostatic agent, hemostatic powder, thrombin.

MATERIALS AND METHODS

Study design and eligibility

This trial was a prospective, randomized, controlled, multicenter clinical investigation with subjects enrolled across 20 investigational sites in the United States. Investigational sites were composed of academic centers, hospitals, private practices, and clinical research centers. The study was conducted under a Food and Drug Administration (FDA) Investigational Device Exemption (IDE) and each site obtained Institutional Review Board (IRB) approval. This study was conducted in accordance with FDA regulations and adhered to Good Clinical Practices (GCP). An Independent Data Monitoring Committee (IDMC) and Clinical Events Committee (CEC) were established to review the data as well as to oversee the safety and welfare of subjects.

Subjects 21 years and older undergoing non-emergent cardiothoracic, abdominal, and lower extremity orthopedic operations were evaluated after providing written informed consent. Subjects were excluded if they met the following criteria: undergoing laparoscopic, thoracoscopic, robotic, neurologic, spinal, or emergency surgery; pregnant, planning on becoming pregnant during the follow-up period, or actively breast-feeding; platelet count <100,000 μL or International Normalized Ratio >1.5 within 4 weeks of surgery; receiving intravenous heparin 12 hr prior to surgery or oral warfarin 2 days prior to surgery; receiving antithrombotic medications within 5 days of surgery or aspirin within 7 days of surgery (exception: cardiothoracic subjects could receive aspirin at any time before surgery); active or suspected infection at the surgical site; planned to receive organ transplantation; known sensitivity or allergy to bovine and/or porcine substance(s) or any other component(s) of the hemostat; American Society of Anesthesiologists classification of 5; life expectancy <3 months; known psychiatric disorder, which would preclude the subject from completing the clinical study; severe congenital or acquired immunodeficiency; religious or other objections to porcine, bovine, or human components; hemostatic device would be used at the site of a heart valve replacement or repair or synthetic graft or patch implant; participated in another clinical trial within the past 30 days and received an investigational drug, device, or biologic agent; or not appropriate for inclusion per medical opinion of the Principal Investigator.

Eligibility was also assessed intraoperatively using the SBSS to confirm identification of a target bleeding site (TBS) with minimal, mild, or moderate bleeding for which conventional means of hemostasis were ineffective or impractical. Subjects were evaluated preoperatively, intraoperatively, postoperatively, and at 6 ± 2 weeks (Figure 1).

Study groups

The investigational device (HEMOBLAST Bellows, Biom'up, Lyon, France) was supplied in a bellows applicator preloaded with 1.65 g of absorbable gelatin sponge and thrombin hemostatic agent. This chondroitin sulfate, and thrombin compared to an established efficacy of a novel hemostatic powder (HP) containing collagen, thrombin.

Results: A total of 388 subjects were included in the primary efficacy analysis. At 6 min, hemostasis was achieved in 93.0% (238/256) of the HP group compared to 77.3% (102/132) of the G + T group (non-inferiority \( P < 0.0001 \), superiority \( P < 0.0001 \)). All secondary endpoints were met. Complications were comparable between treatment groups.

Conclusions: HP had superior rates of hemostasis, shorter preparation time, and a similar safety profile compared to G + T in this prospective, randomized trial using quantitative bleeding severity criteria.

KEYWORDS

bleeding scale, collagen, hemostat, hemostatic agent, hemostatic powder, thrombin
hemostatic powder HP consisting of porcine collagen, bovine chondroitin sulfate, and human-derived thrombin (1500 IU) (Figure 2). HP is indicated in surgical procedures as an adjunct to hemostasis when control of minimal, mild, and moderate bleeding by conventional procedures is ineffective or impractical, except in neurosurgical, ophthalmic, and urological procedures.43

HP was compared with absorbable gelatin sponge, USP with recombinant thrombin (G + T), specifically Surgifoam 1974 (8 × 12.5 × 1 cm³) (Ethicon, Somerville, NJ) and Recothrom 5 mL kit (1000 IU/mL) (Mallinckrodt Pharmaceuticals, St. Louis, MO).47,48 These control hemostats are frequently used as comparators in clinical trials of effectiveness.4,5,15,26,34

Subjects in the trial were randomized to receive HP or G + T in a 2:1 ratio. A 2:1 ratio was chosen to collect additional safety information on HP. Randomization was stratified by surgery type and a randomized block design was implemented. Concealed allocation was achieved by requiring that all personnel present in the operating room were blinded to the treatment group assignment until after

**FIGURE 1** Clinical investigation flow. A, One subject with withdrawn intraoperatively; 46 subjects were withdrawn prior to surgery due to early termination of the study for efficacy at the interim analysis. B, Unreported or missing data not presented in subsequent tables. C, Gelatin sponge and thrombin
identification of the TBS and confirmation of intraoperative eligibility. Subjects were blinded to treatment assignment.

The first subject for each investigator without previous experience or hands-on training with HP was treated as a lead-in subject. All lead-in subjects received HP and were followed for safety, but not for efficacy. The full cohort study enrollment was stopped early on February 2, 2017 per IDMC recommendations based on the results of a planned interim analysis of the primary efficacy endpoint. The interim analysis was predetermined to occur at 240 treated subjects. The last full cohort subject follow-up was completed on March 27, 2017.

HP or G + T was applied to the source of minimal, mild, or moderate bleeding and maintained at the TBS until 3, 6, and 10 min after initial application (Figures 3a-3d).43,44 If hemostasis was not achieved at 3 and/or 6 min, repeat application of the original randomized hemostat was performed. If hemostasis was not achieved at 10 min, a rescue method of hemostasis treatment was used. Rescue treatment using another hemostatic agent containing thrombin was not allowed.

Bleeding severity and hemostasis were assessed using the SBSS at baseline and at each assessment time point. Hemostasis was defined as an SBSS score of 0 with bleeding scored from 1 (mild) to 5 (extreme) (Figure 4).44 Clinical investigators underwent training and testing on the SBSS prior to the enrollment of any subjects. In cases where hemostasis was initially achieved, but bleeding recurred prior to subject closure, the re-bleeding was documented as an adverse event.

Adverse events (AEs), serious adverse events (SAEs), rescue treatment, and reoperation due to bleeding were collected. Antibody testing for porcine collagen was performed preoperatively and at the 6 ± 2 weeks follow-up visit.

### 2.3 Study endpoints

The primary efficacy endpoint of this clinical investigation was non-inferiority of HP relative to G + T for success at achieving hemostasis within 6 min. The secondary efficacy endpoints were, in rank order: 1. Superiority of HP relative to G + T in mean preparation time from the opening of the package to the product being ready-to-use; 2. Non-inferiority of HP relative to G + T for success at achieving hemostasis within 3 minutes; 3. Superiority of HP relative to G + T for success at achieving hemostasis within 6 min; and 4. Superiority of HP relative to G + T for success at achieving hemostasis within 3 min.

### 2.4 Statistical methods

#### 2.4.1 Analytic methods

Efficacy analyses were conducted on the time to hemostasis (TTH) population, defined as all subjects who were randomized, received study intervention, and had a TTH assessment recorded regardless of whether the measurement was censored. Lead-in subjects were not part of the TTH population. Safety analyses were conducted on the Safety Population, defined as all subjects enrolled in the study, which included lead-in subjects.

The primary analysis compared the probability of TTH within 6 min in subjects receiving HP to those receiving G + T. The estimated difference in the probability of TTH at 6 min between treatment arms was adjusted for surgical indication by weighting the stratum-specific differences in observed proportions using Cochran-Mantel-Haenszel weights.49 Secondary endpoints were a priori specified and analyses were conducted using a rank-order test sequence to maintain the family-wise Type I error rate at 0.05.

The IDMC was provided with blinded efficacy data at the planned interim analysis. The IDMC was guided by a formal stopping rule based on the primary efficacy endpoint; the clinical trial could be stopped for reasons of futility or efficacy.

Summaries of the number and percent of subjects with at least one AE or SAE were computed for each treatment arm. AEs were further stratified by adverse event type.

#### 2.4.2 Sample size justification

The sample size for the study was calculated based on a level 0.025 (one-sided) test to exclude a probability of TTH within 6 min that was 10% less among subjects treated with HP compared to those treated with G + T. The 10% non-inferiority margin is based upon an FDA guidance for industry on non-inferiority clinical trials.50 With an
assumption of an 88% success rate in both arms for achieving hemostasis at 6 minutes, it was estimated that enrollment of a maximum of 400 subjects would provide 80.1% power to declare comparable efficacy between treatment groups while accounting for a single interim analysis. The single interim analysis was planned to be conducted upon accrual of 60% of the maximum sample size (240 subjects). Enrollment continued during the interim analysis and concluded with 388 randomized subjects when the IDMC recommended early closure of enrollment based on the pre-defined stopping rule; the primary efficacy endpoint was met with the interim analysis population.

All statistical analyses were done using SAS System software, Version 9.3 or above (SAS Institute, Cary, NC) or R, Version 3.3.2 (R Core Team).
3 | RESULTS

3.1 | Demographics

Between July 13, 2016 and February 2, 2017, a total of 412 subjects met all eligibility criteria and were enrolled; 24 were lead-in and 388 were randomized to receive HP or G + T in a 2:1 ratio (Figure 1). All randomized subjects completed the primary efficacy assessment, which was completed intraoperatively, while a total of 29 enrolled subjects did not complete the study as planned (withdrew from the study, non-compliant, subject death, or lost to follow-up). Demographic and baseline clinical characteristics were recorded for all enrolled subjects (Table 1). Age, race, and ethnicity data were similar between treatment groups and representative of the target intended use population, per FDA Guidance for Industry.51

The mean subject age was 55.7 years, with 39.8% of subjects being male. The surgical indication, TBS locations, and TBS tissue types—including soft tissue, muscle, bone, and parenchyma—were similar between groups (Table 2).

3.2 | Efficacy

HP met all pre-specified primary and secondary efficacy endpoints. HP was non-inferior to G + T in achieving hemostasis at 6 min (93.0% for HP; 77.3% for G + T; \( P < 0.0001 \) (Table 3). The preparation time for HP group was significantly shorter than for the G + T group, with a mean of 0.38 min (2 min, 23s) for the HP group and a mean of 2.28 min (2 min, 17s) for the G + T group (\( P < 0.0001 \)) (Table 4). HP also demonstrated non-inferiority and superiority at 3 min as well as superiority at 6 min compared to G + T (Table 3). For subjects with the highest degree of bleeding permitted for enrollment in the trial, a baseline SBSS of 3 (moderate bleeding), 89.6% of the HP group compared to 56.3% of the G + T group achieved hemostasis within 6 min (\( P < 0.0001 \) for non-inferiority; \( P = 0.0003 \) for superiority) (Table 5). At the 3 min time point, 74 of 256 (28.9%) patients in the HP arm required re-application compared to 63 of 132 (47.7%) patients in the G + T arm (\( P = 0.0003 \)). At the 6-min time point 15 of 256 (5.9%) patients in the HP arm required reapplication compared to 23 of 131 (17.6%) in the G + T arm (\( P = 0.0005 \)).

Estimates of the distribution of TTH over a maximum follow-up of 10 min were computed using the Kaplan-Meier method.
Kaplan-Meier estimates for the probability of achieving hemostasis at all scheduled assessment times were determined (Figure 5).

### Safety results

All 412 enrolled subjects were included in the safety analysis (280 HP, 132 G + T). Five hundred and thirty-five AEs were reported in 195 subjects (47.3%) during the conduct of the clinical investigation. There were 358 events in 129 subjects (46.1%) in the HP group and 177 events in 66 subjects (50.0%) in the G + T group (Table 6). The proportion of subjects experiencing at least one AE was comparable between treatment groups ($P = 0.4073$). The five most common AE types included pain, cardiac arrhythmias, fluid accumulation, surgical wound-related events, and anemia.

The proportion of subjects experiencing a SAE was comparable between treatment groups (11.4% for HP vs. 12.1% for G + T, $P = 0.7912$). There were five SAEs that resulted in death, all within the G + T group ($P = 0.1417$).

There was one serious adverse device effect (SADE) identified by the CEC as possibly related to HP consisting of a generalized skin reaction with hives 11 days postoperatively. The subject’s serum tested negative for porcine collagen antibodies, and the event resolved with no sequelae. No unanticipated adverse device effects (UADEs) were identified.

Significantly fewer rescue procedures were required intraoperatively to achieve hemostasis in the HP group compared to the G + T group (9 of 280 [3.2%] vs 15 of 132 [11.4%], $P = 0.0119$). There were no significant differences in intraoperative red blood cell, platelet, and fresh frozen plasma administration between the test and control groups ($P = 0.6597$, $P = 0.7784$, and $P = 0.3297$, respectively).

Serum samples were collected preoperatively and at the 6 ± 2-week follow-up visit to test for the development of antibodies to porcine collagen. In the HP group, 2.5% of subjects displayed preoperative antibodies against porcine collagen and 12.1% demonstrated anti-collagen antibodies at 6 ± 2 weeks postsurgery (Table 7). In the G + T group, 4.1% of subjects had preoperative antibodies against porcine collagen and 6.8% had positive titers postoperatively. Subjects with postoperative titers against porcine collagen showed no

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### Table 1: Demographic and baseline clinical characteristics by treatment group for the safety analysis population

| Measure                           | All          | HP           | G + T         |
|-----------------------------------|--------------|--------------|---------------|
| Age (Years)                       | 55.7 ± 15.01 | 55.5 ± 14.83 | 56.1 ± 15.43  |
| Age category (years)              |              |              |               |
| <30                               | 22/411 (5.4%)| 13/280 (4.6%)| 9/131 (6.9%)  |
| 30-39                             | 46/411 (11.2%)| 33/280 (11.8%)| 13/131 (9.9%)|
| 40-49                             | 71/411 (17.3%)| 48/280 (17.1%)| 23/131 (17.6%)|
| 50-59                             | 80/411 (19.5%)| 62/280 (22.1%)| 18/131 (13.7%)|
| 60-69                             | 120/411 (29.2%)| 76/280 (27.1%)| 44/131 (33.6%)|
| 70-79                             | 58/411 (14.1%)| 38/280 (13.6%)| 20/131 (15.3%)|
| ≥80                               | 14/411 (3.4%)| 10/280 (3.6%)| 4/131 (3.1%)  |
| Gender                            |              |              |               |
| Male                              | 164/412 (39.8%)| 107/280 (38.2%)| 57/132 (43.2%)|
| Female                            | 248/412 (60.2%)| 173/280 (61.8%)| 75/132 (56.8%)|
| Ethnicity                         |              |              |               |
| Hispanic or Latino                | 48/410 (11.7%)| 33/278 (11.9%)| 15/132 (11.4%)|
| Not Hispanic or Latino            | 362/410 (88.3%)| 245/278 (88.1%)| 117/132 (88.6%)|
| Race                              |              |              |               |
| Caucasian                         | 291/412 (70.6%)| 200/280 (71.4%)| 91/132 (68.9%)|
| African American                  | 50/412 (12.1%)| 32/280 (11.4%)| 18/132 (13.6%)|
| American Indian or Alaska Native  | 4/412 (1.0%) | 4/280 (1.4%) | 0/132 (0.0%) |
| Asian                             | 22/412 (5.3%) | 12/280 (4.3%) | 10/132 (7.6%) |
| Native Hawaiian or other Pacific Islander | 15/412 (3.6%) | 11/280 (3.9%) | 4/132 (3.0%) |
| Other                             | 30/412 (7.3%) | 21/280 (7.5%) | 9/132 (6.8%)  |

*Numbers are mean ± standard deviation, (N), median [p25, p75] for continuous measures; and n/N (percent) for categorical measures.

†HEMOBLAST Bellows.

‡Gelatin sponge and thrombin.
| Measure                              | HP | G + T | P-value |
|-------------------------------------|----|-------|---------|
| **Surgical indication**             |    |       |         |
| Cardiothoracic                      | 109/280 (38.9%) | 51/132 (38.6%) | 0.9726  |
| Abdominal                           | 88/280 (31.4%)  | 43/132 (32.6%)  |         |
| Orthopedic                          | 83/280 (29.6%)  | 38/132 (28.8%)  |         |
| **Location—tissue type**            |    |       |         |
| **Abdominal**                       |    |       |         |
| Muscle                              | 11/279 (3.9%)   | 7/132 (5.3%)    |         |
| Soft tissue                         | 77/279 (27.6%)  | 34/132 (25.8%)  |         |
| Adrenal gland—parenchyma            | 0/279 (0.0%)    | 2/132 (1.5%)    |         |
| Aorta—aortic tissue                 | 9/279 (3.2%)    | 3/132 (2.3%)    |         |
| Ascending aorta—aortic tissue       | 4/279 (1.4%)    | 2/132 (1.5%)    |         |
| Cannulation site—aortic tissue      | 2/279 (0.7%)    | 1/132 (0.8%)    |         |
| Cardiac anastomosis—adipose         | 1/279 (0.4%)    | 0/132 (0.0%)    |         |
| Cardiac anastomosis—suture line     | 3/279 (1.1%)    | 2/132 (1.5%)    |         |
| Femur—fibrous membrane              | 0/279 (0.0%)    | 1/132 (0.8%)    |         |
| Hamstring—muscle                    | 1/279 (0.4%)    | 0/132 (0.0%)    |         |
| **Hip**                             |    |       |         |
| Bone                                | 1/279 (0.4%)    | 1/132 (0.8%)    |         |
| Capsule/synovium                    | 11/279 (3.9%)   | 10/132 (7.6%)   |         |
| Fat                                 | 5/279 (1.8%)    | 1/132 (0.8%)    |         |
| Ligament                            | 1/279 (0.4%)    | 0/132 (0.0%)    |         |
| Muscle                              | 20/279 (7.2%)   | 8/132 (6.1%)    |         |
| Soft tissue                         | 0/279 (0.0%)    | 2/132 (1.5%)    |         |
| Intercostal—muscle                  | 1/279 (0.4%)    | 0/132 (0.0%)    |         |
| **Knee**                            |    |       |         |
| Capsule/synovium                    | 12/279 (4.3%)   | 6/132 (4.5%)    |         |
| Femoral condyle soft tissue         | 2/279 (0.7%)    | 0/132 (0.0%)    |         |
| Medial-patellar soft tissue         | 1/279 (0.4%)    | 0/132 (0.0%)    |         |
| Retinaculum cartilage               | 1/279 (0.4%)    | 0/132 (0.0%)    |         |
| Retinaculum soft tissue             | 8/279 (2.9%)    | 4/132 (3.0%)    |         |
| Soft tissue                         | 3/279 (1.1%)    | 1/132 (0.8%)    |         |
| Supra-patellar soft tissue          | 7/279 (2.5%)    | 3/132 (2.3%)    |         |
| Supra-patellar tendon               | 2/279 (0.7%)    | 0/132 (0.0%)    |         |
| Left atrium—suture line             | 1/279 (0.4%)    | 0/132 (0.0%)    |         |
| Liver—parenchyma                    | 18/279 (6.5%)   | 7/132 (5.3%)    |         |
| Mediastinum—soft tissue             | 2/279 (0.7%)    | 1/132 (0.8%)    |         |
| Mesentery—ileum                     | 1/279 (0.4%)    | 0/132 (0.0%)    |         |
| Pancreatic head—pancreatic tissue   | 0/279 (0.0%)    | 1/132 (0.8%)    |         |
| Pericardium                         | 2/279 (0.7%)    | 2/132 (1.5%)    |         |
| Proximal tibia—bone                 | 0/279 (0.0%)    | 1/132 (0.8%)    |         |
| Quadriceps—tendon                   | 12/279 (4.3%)   | 5/132 (3.8%)    |         |
| Retroperitoneum—soft tissue         | 2/279 (0.7%)    | 0/132 (0.0%)    |         |
| Right atrium—atrial                 | 1/279 (0.4%)    | 0/132 (0.0%)    |         |
| Right hilum bronchial artery—vessel | 1/279 (0.4%)    | 0/132 (0.0%)    |         |

(Continues)
TABLE 2  (Continued)

| Measure                        | HP   | G + T | P-value |
|-------------------------------|------|-------|---------|
| Sternum—bone                  | 52/279 (18.6%) | 25/132 (18.9%) |       |
| Subcutaneous tissue—adipose   | 1/279 (0.4%)  | 0/132 (0.0%)  |       |
| Thymus—gland                  | 1/279 (0.4%)  | 0/132 (0.0%)  |       |
| Ventricle—epicardial          | 0/279 (0.0%)  | 1/132 (0.8%)  |       |
| Ventricle—muscle              | 2/279 (0.7%)  | 1/132 (0.8%)  |       |

*Numbers are n/N (percent) for categorical measures. P-value is based on Fisher's exact test for categorical measures.

HEMOBLAST Bellows.

Gelatin sponge and thrombin.

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TABLE 3  Comparison (non-inferiority and superiority) of HP to G + T for success at achieving hemostasis within 3 and 6 min for the efficacy analysis population

| Time                        | All HP | G+T  | Difference (95%CI) | P-value |
|-----------------------------|--------|------|--------------------|---------|
| Non-inferiority of hemostasis within 3 min (Secondary Endpoint) | 250/388 (64.4%) | 182/256 (71.1%) | 68/132 (51.5%) | 20.3% (9.9%, 30.7%) | <0.0001 |
| Superiority of hemostasis within 3 min (Secondary Endpoint) | 250/388 (64.4%) | 182/256 (71.1%) | 68/132 (51.5%) | 20.3% (9.9%, 30.7%) | 0.0001 |
| Non-inferiority of hemostasis within 6 min (Primary Endpoint) | 340/388 (87.6%) | 238/256 (93.0%) | 102/132 (77.3%) | 15.6% (7.8%, 23.5%) | <0.0001 |
| Superiority of hemostasis within 6 min (Secondary Endpoint) | 340/388 (87.6%) | 238/256 (93.0%) | 102/132 (77.3%) | 15.6% (8.0%, 23.2%) | <0.0001 |

*Numbers are n/N (percent) for categorical measures. Difference calculations were stratified by surgery type.

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Gelatin sponge and thrombin.

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TABLE 4  Comparison of preparation time (minutes) by treatment group for the efficacy analysis population

| Comparison of preparation time (minutes) by treatment group for the efficacy analysis population | All | HP  | G + T | Difference (95%CI) | P-value |
|------------------------------------------------------------------------------------------------|-----|-----|-------|--------------------|---------|
| Preparation time 1.03 ± 1.016 (388) | 0.38 ± 0.188 (256) | 2.28 ± 0.768 (132) | −1.90 (−2.02, −1.77) | <0.0001 |

*Numbers are mean ± standard deviation, (N), median [p25, p75] for continuous measures. P-value and 95% confidence interval (CI) for the difference is calculated based on a linear regression model stratified by surgery type.

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Gelatin sponge and thrombin.

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TABLE 5  Comparison (non-inferiority and superiority) of hp to G + T for success at achieving hemostasis within 6 min for baseline SBSS = 3 in the efficacy analysis population

| Time                        | All HP | G + T  | Difference (95%CI) | P-value |
|-----------------------------|--------|--------|--------------------|---------|
| Non-inferiority of hemostasis within 6 min for baseline SBSS = 3 | 78/99 (78.8%) | 60/67 (89.6%) | 18/32 (56.3%) | 33.2% (15.2%, 51.2%) | <0.0001 |
| Superiority of hemostasis within 6 min for baseline SBSS = 3 | 78/99 (78.8%) | 60/67 (89.6%) | 18/32 (56.3%) | 33.2% (15.2%, 51.2%) | 0.0003 |

*Numbers are n/N (percent) for categorical measures. P-value and confidence interval (CI) for the estimated difference were calculated using the Cochran-Mantel-Haenszel estimator stratified by surgery type. SBSS = surface bleeding severity scale.

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unusual or remarkable adverse events. A single subject with a preoperative titer of 1600 was treated with HP and had no adverse events after surgery. The frequency of adverse events among subjects with positive titers against collagen was not different from those subjects not exhibiting anti-collagen antibodies.

4 | DISCUSSION

HP effectively treated quantified degrees of surgical bleeding compared to an established comparator. HP was superior to G + T in the achievement of hemostasis at both 3 and 6 min as well as in preparation time, meeting all prespecified primary and secondary efficacy endpoints. These data suggest that HP may offer blood management advantages when used during cardiothoracic, abdominal, and orthopedic procedures to control quantified levels of minimal, mild, and moderate bleeding in bony and soft tissues.43,44 Tissues specific to cardiothoracic surgery in which HP successfully achieved hemostasis include: aortic tissue and cannulation sites, cardiac anastomoses and suture lines, atrial tissue, the pericardium, sternal bone, and ventricular tissue (Table 2). The difference between groups was most pronounced at a baseline SBSS of 3, which is defined as moderate bleeding with a maximum flow rate of 117 mL/min. These findings imply that HP may be most beneficial at higher levels of bleeding within the range indicated for the product. As a ready-to-use powder, HP may offer advantages in preparation time when compared to other currently available hemostatic agents.1,40–42,52,53

The safety of HP was also demonstrated. The HP group appeared to have a trend towards lower rates of subjects experiencing AEs and SAEs compared to the control group. The findings regarding porcine collagen titer changes postoperatively for HP (9.2%) are consistent with those published in the clinical evaluation of CoStasis Surgical Hemostatic Agent, an FDA-approved hemostatic agent containing bovine collagen (7.6%).54 HP may offer advantages in achieving hemostasis with reduced complications on the sternal bone compared to bone wax. The American Association of Thoracic Surgery has a Class III recommendation against the use of bone wax as it may impair bacterial clearance and bone union, and it presents an independent risk

### TABLE 6 Overview of adverse events occurring in ≥5% of subjects in either treatment group for the safety analysis population

| Subjects with any adverse event | All subjects (N = 412) n (%) | HPa (N = 280) n (%) | G+Tb (N = 132) n (%) | P-valuec |
|---------------------------------|-----------------------------|---------------------|---------------------|----------|
| Subjects with any serious adverse event | 48 (12) | 32 (11) | 16 (12) | 0.7912 |
| Subjects with a treatment-related event | 13 (3) | 5 (2) | 8 (6) | 0.1185 |
| Subjects with common adverse events by type | | | | |
| Abnormal bloodworkd | 26 (6) | 17 (6) | 9 (7) |
| Anemia | 28 (7) | 16 (6) | 12 (9) |
| Cardiac arrhythmias | 46 (11) | 31 (11) | 15 (11) |
| Constipation/ileus | 21 (5) | 14 (5) | 7 (5) |
| Fluid accumulation/overloadd | 34 (8) | 24 (9) | 10 (8) |
| Infection (non-surgical wound related) | 26 (6) | 16 (6) | 10 (8) |
| Nausea | 24 (6) | 21 (8) | 3 (2) |
| Pain | 57 (14) | 42 (15) | 15 (11) |
| Respiratory insufficiency | 17 (4) | 11 (4) | 6 (5) |
| TBS re-bleed | 9 (2) | 1 (<1) | 8 (6) |
| Urinary retention/oliguria | 12 (3) | 6 (2) | 6 (5) |
| Surgical wound relatedd | 29 (8) | 23 (8) | 6 (5) |

aHEMOBLAST Bellows.
bGelatin sponge and thrombin.
cP-value computed using logistic regression model with stratified adjustment for surgical arm.
dAbnormal bloodwork included electrolyte imbalances (eg, hypokalemia, hypophosphatemia, etc.), elevated troponins, transaminitis, and hypo/hyperglycemia.
eFluid accumulation/overload events include edema, hypervolemia, pericardial effusion, pleural effusion, and ascites.
fSurgical wound-related events include dehiscence, hematoma, infection, non-healing, seroma, abscess, and skin necrosis.
factor for sternal dehiscence. For the HP arm of the study, there was only one AE of sternal dehiscence (1 of 83 cardiothoracic patients [1.2%]) which was not attributed to the use of HP by the investigator and the CEC. In a 10-year prospective observational study, Alhan et al found sternal dehiscence to be attributable to the use of bone wax in 2.4% of cardiac cases in which it was used. No instances of sternal non-union were reported in patients treated with HP.

This investigation utilized a quantitative and validated method for assessing bleeding severity and hemostasis. Previous investigations have used subjective methods for assessing bleeding severity and success (hemostasis); other bleeding scales developed to assess hemostat performance have not been validated in a clinical setting. This study is unique in that it is the first clinical investigation to employ a clinically validated and quantitative bleeding scale, thus providing a higher level of evidence in assessing comparative performance.

### 4.1 Limitations

Investigators were not blinded to study treatment due to the visual differences between HP and G + T. Once TBSs were identified and baseline SBSS scores assigned, subjects were then randomized and the investigator was notified of the treatment assignment. Therefore, investigators were aware which intervention the subject would undergo during assessment of bleeding severity at 3, 6, and 10 min. This lack of allocation concealment represented a possible source of bias in the study. Additionally, HP was not compared to the latest thrombin agents, sealants, or adhesives. G + T was selected as the control agent for several reasons. G + T is one of the most frequently used hemostatic agents in the United States. The components of the control article are very similar to those of the investigational device (porcine gelatin with recombinant human thrombin vs. porcine collagen with human pooled plasma thrombin, respectively). G + T is approved for use in all three surgical areas evaluated in this trial and is recognized by FDA as an appropriate control that has been used in multiple other hemostatic studies.

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