Summary Basis for Regulatory Action

Date:	December 19, 2024
From:	Jin Sung Hong, PhD Review Committee Chair Office of Cell Therapy and Human Tissues (OCTHT) Office of Therapeutic Products (OTP)
BLA STN:	BLA 125812/0
Applicant:	Humacyte Global, Inc.
Submission Receipt Date:	December 11, 2023
PDUFA* **Action Due Date:**	*August 10, 2024 Action Date: December 19, 2024
Proper Name:	acellular tissue engineered vessel-tyod
Proprietary Name:	SYMVESS
Indication:	SYMVESS is an acellular tissue engineered vessel indicated for use in adults as a vascular conduit for extremity arterial injury when urgent revascularization is needed to avoid imminent limb loss, and autologous vein graft is not feasible.

***** PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

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Director, Product Office

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Jin Sung Hong, PhD, OTP/OCTHT Wen (Aaron) Seeto, PhD, OTP/OCTHT Pratima Labroo, PhD, OTP/OCTHT Zainab Mansaray Storms, PhD, OCBQ/DMPQ Hyesuk Kong, OCBQ/DBSQC James Kenney, OCBQ/DBSQC Wei Tu, OCBQ/DBSQC/LBVI Salil Ghosh, MS, PhD, OCBQ/DBSQC Kenneth Phillips, OCBQ/DBSQC Marie Anderson, MS, PhD, OCBQ/DBSQC Iryna Zubkova, PhD, CBER/OCBQ/DMPQ
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Prateek Shukla, MD, OTP/OCE Bethany Baer, MD, OBPV/DPV Triet Tran, PharmD, BCSCP, OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Thomas Zhou, PhD, OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	David Cantu, PhD, OTP/OPT
Labeling • Promotional (OCBQ/APLB) • USPI Review	Michael Brony, PharmD, OCBQ/DCM/APLB Afsah Amin, MD, MPH, OTP/OCE
Other Review(s) not captured above categories, for example: Consults: • OBPV Clinical Analyst • CRDH • OPPT/Hemostasis Branch • DHT • ORMRR Regulatory Project Manager	Elin Cho, MS, OBPV/ Robert Lee, MD, CDRH/OPEQ/OHTII/DHTIIB Andrey Sarafanov, PhD CBER/OTP/OPPT/DH/HB2 Hanh Khuu, MD, CBER/OTP/OCTHT Helen Sansone, CBER/OTP/ORMRR
Advisory Committee Summary	N/A

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1. Introduction

Humacyte Global, Inc. submitted a Biologics License Application (BLA), STN 125812, for licensure of acellular tissue engineered vessel-tyod, with the proprietary name of SYMVESS. SYMVESS is an acellular tissue engineered vessel that is 42 cm in length and 6 mm in diameter. It is composed of extracellular matrix (ECM) proteins, mostly consisting of (b) (4) that are generated from (b) (4) from the final product. SYMVESS is manufactured at the Humacyte facility located at 2525 E Highway 54 Durham, NC 27713, USA. SYMVESS is supplied on a (b) (4) immersed in (b) (4) Phosphate Buffered Saline (b) (4) in a sealed and labeled container. At the surgical site, the length of SYMVESS is customized by the surgeon based on the need and is sutured to treat arterial repair.

The safety and effectiveness of SYMVESS was evaluated in patients enrolled in Study V005 (CLN-PRO-V005; NCT03005418), a prospective, open-label, single-arm, multicenter Phase 2/3 study evaluating SYMVESS for vascular replacement or reconstruction in patients with life- or limb-threatening vascular trauma. Seventy-one (71)

patients received SYMVESS in this study as a conduit, and efficacy was evaluated in a subset of 54 patients who received SYMVESS for replacement of an extremity artery. The primary efficacy outcome measure was the rate of primary vascular graft patency at Day 30 in patients with extremity arterial injury as assessed by functional graft patency without intervention, using Duplex ultrasound or equivalent (i.e., CTA, MRI). Among the 54 patients included in the primary efficacy analysis, 36 patients (66.7%) had primary patency and 39 (72.2%) patients had secondary patency at Day 30. Five (9%) patients underwent amputation of the treated limb by Day 30.

Safety was evaluated for all 71 patients receiving SYMVESS as a conduit in Study V005 for either an extremity or torso/iatrogenic indication. However, the primary efficacy analysis population consists of the 54 patients who received SYMVESS for vascular replacement or reconstruction in an extremity following life- or limb-threatening vascular trauma. The most common adverse reactions were vascular graft thrombosis, pyrexia, pain, anastomotic stenosis, vascular graft rupture or anastomotic failure and vascular graft infection. Seven patients had vascular graft rupture or anastomotic failure from SYMVESS during the study period which resulted in serious bleeding: three from mid-graft rupture and four from anastomotic failure. Six patients developed SYMVESS infection during the study. There was one death following bleeding from the proximal anastomoses of SYMVESS and the common iliac artery in a patient who had SYMVESS implanted in the torso. Following this death, SYMVESS (b) (4) to use in the extremities.

Supportive safety and effectiveness data was provided in Study V017 (CLN-PRO-V017; NCT05873959), a retrospective, observational study of SYMVESS used on a humanitarian basis in Ukrainian patients with life- or limb-threatening vascular trauma. In this retrospective study, 15 out of 16 (93.8%) patients had primary patency confirmed at Day 30. SYMVESS was deemed not patent in one patient following mid-graft rupture. No patients underwent limb amputation.

The clinical review team concluded that the benefits outweighed the risks of SYMVESS. Substantial evidence of effectiveness was provided, and given the indication and lack of appropriate treatment options for the indicated population in patients with extremity arterial injury when urgent revascularization is needed to avoid imminent limb loss, the review team recommends traditional approval of this BLA. We also recommend clinical Postmarketing Requirements (PMR) to (1) further characterize the risk of graft failure following SYMVESS placement and (2) assess the safety and efficacy of SYMVESS in patients 17 years of age or less who have reached Tanner Sexual Maturity Rating Stage 5, in the approved indication. Clinical Postmarketing Commitments are to complete the ongoing open-label, single-arm study conducted in patients treated with SYMVESS as a vascular replacement or reconstruction in life or limb-threatening vascular trauma (Study V005).

Chemistry, Manufacturing, and Control (CMC) Postmarketing Commitments (PMCs) are recommended for shipping validation, leachable study data, and establishment of upper limits for certain final product release testing.

2. Background

Arterial damage resulting from traumatic extremity injuries is a serious condition, with a high incidence of complication and risk of exsanguination and death. In the absence of vascular reconstruction, tourniquet application of the affected limb is the primary life-saving measure. The frequency and severity of vascular trauma also varies by population. In civilian trauma patients, vascular injuries account for 1% to 2% of all injuries, and patients with vascular injury account for greater than 20% of all trauma-related deaths. Vascular trauma is also a leading cause of morbidity and mortality in the military, where vascular injuries make up a small percentage of trauma injuries but are the leading cause of exsanguination, limb ischemia, and amputation.

Vascular trauma treatment depends on severity of the injury. The goal is to restore blood flow and prevent complications. This may sometimes be achieved by primary repair or endovascular stenting but requires a new conduit when the injury is not amenable to these techniques. Available options for new conduit include use of autologous vein for arterial reconstruction, synthetic grafts and temporary shunts. When arterial grafting is required, autologous vein grafts are preferred over synthetic grafts, such as Teflon (expanded polytetrafluoroethylene) or Dacron. Autologous graft is commonly the saphenous vein harvested from the leg. However, autologous blood vessel availability can be limited due to extensive trauma or preexisting peripheral vascular disease. Harvesting of the autologous vein also places the patient at risk of complications such as infection and neuropathy.

Due to the limited availability of healthy autologous vessels as well as the incidence of postoperative complications, synthetic grafts have been used as alternatives, especially for medium to large-diameter vessels. The mechanical properties of synthetic grafts provide some benefits over autologous veins such as durability, strength, and availability; however, their use is limited to instances when the autologous vein is not available due to increased rate of thrombosis and atherosclerosis affecting long-term durability, mechanical degradation, dilatation, localized aneurysmal formation, and graft rupture.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	May 19, 2015
2. IND submission	June 27, 2016
3. Pre-BLA meeting	October 24, 2022
4. Regenerative Medicine Advanced Therapy designation granted	May 4, 2023
5. BLA 125812/0 submission	December 11, 2023
6. BLA filed	February 8, 2024
7. Mid-Cycle communication	March 28, 2024
8. Late-Cycle meeting	May 20, 2024
9. Action Due Date	December 19, 2024

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

This BLA includes an adequate description of the manufacturing process of SYMVESS. The CMC review team concludes that the manufacturing material, process, and controls can yield SYMVESS with consistent quality attributes. Thus, the CMC review team recommends approval.

Product Description
SYMVESS is an acellular tissue engineered vessel composed of organized ECM proteins generated from allogeneic smooth muscle cells in culture. The product is approximately 6 mm in inner diameter and 42 cm in length.

Manufacturing Summary
SYMVESS is a tissue engineered product manufactured using a (b) (4) process. Human vascular smooth muscle cells that are derived from human aortic tissue deemed suitable for transplant are banked, expanded in (b) (4) and seeded onto a tubular (b) (4) mesh scaffold (b) (4). These cells are further cultured in a (b) (4) bioreactor system for (b) (4) to generate an intermediate tubular construct containing vascular smooth muscle cells and extracellular matrix deposited by the vascular smooth muscle cells. A final decellularization process, (b) (4) removes the human cellular and genetic material while maintaining the extracellular matrix structure, mechanical properties, and biological activity. A manufactured acellular tissue engineered vessel (SYMVESS) is submerged in (b) (4) (b) (4) within a (b) (4) which acts as a primary container. SYMVESS has an 18 month shelf-life at 2-8°C.

Manufacturing Controls
(b) (4) The final product tests and release criteria are acceptable and are sufficient to meet regulatory requirements for identity, purity, and potency. Stability studies (conventional and accelerated conditions) are appropriate and support product expiration dating. The process is well controlled and has demonstrated the ability to produce drug product of acceptable quality.

Process Validation
The Applicant validated the manufacturing process at the Humacyte commercial manufacturing site, 2525 Highway NC-54, Durham, NC 27713, using process performance qualification (PPQ) batches manufactured using the (b) (4) The process validation was supported by reliable and consistent manufacture of SYMVESS batches which met established release acceptance criteria. Stability of the final product was established using PPQ and clinical batches. Although shipper validation is performed, shipping validation is not complete and data from worst-case scenario

shipping conditions (i.e., (b) (4) conditions) are pending and will be evaluated as a PMC.

Manufacturing Risks, Potential Safety Concerns, and Management
Transmission of infectious disease is controlled by meeting donor eligibility requirements for the source material, by using adequately controlled reagents and materials for the SYMVESS manufacturing process, and by implementing an adequate manufacturing process to mitigate any potential risk.

SYMVESS is manufactured using the source material from a single donor who met the donor eligibility requirements for transmissible infectious diseases which include screening and testing of risks associated with human immunodeficiency virus 1 (HIV-1), human immunodeficiency virus 2 (HIV-2), hepatitis B virus (HBV), hepatitis C virus (HCV), and syphilis (*Treponema pallidum*). The cell banks generated from the source material are tested negative for human and animal viruses, retroviruses, bacteria, fungi, yeast, and mycoplasma. All animal-derived reagents are tested for animal viruses, bacteria, fungi, and mycoplasma before use. Fetal bovine serum is controlled to minimize the risk of transmitting a prion protein that causes bovine spongiform encephalopathy and the cause of a rare fatal condition in humans called variant Creutzfeldt-Jakob disease.

Risk mitigating measures include aseptic operations for (b) (4) under an (b) (4) biosafety cabinet with (b) (4) background and for (b) (4) under (b) (4) background. Adequate operator training and use of personal protective equipment, use of sterile single use materials, validated cleaning procedures, and environmental monitoring is being implemented.

Drug Product Stability and Shelf Life
The real-time stability studies determine the product is stable for 18 months at 2-8°C. The final container closure was evaluated for extractables and leachables and assessed to be acceptable. However, the Applicant committed to submit ≥ 18-month leachable study data to target specific compounds (i.e., (b) (4) that may need additional evaluation based on their risk assessment as a PMC.

Comparability
To support the product comparability, a comprehensive comparability study between (b) (4) system has been reviewed and found to be acceptable. In CLN-PRO-V005 and CLN-PRO-V017, SYMVESS manufactured from (b) (4) (b) (4) were used to support this BLA.

CMC PMCs
The CMC team recommends three PMCs. The rationale for the PMCs is described below, and the PMC agreements are detailed in Section 11c of this document:

1. SYMVESS is shipped using a cold shipper at a shipping temperature of 2-8°C. Humacyte provided shipping validation information for temperature control and (b) (4) testing. However, no information is available to support the shipping conditions are validated to ensure SYMVESS quality under worst-case shipping conditions in a real world situation (e.g.,

(b) (4) The Applicant agreed to perform a PMC study to evaluate product quality following worst-case shipping conditions under (b) (4) conditions.

2. The Applicant provided a full summary report of extractables and toxicology risk assessment of extractables and leachables which was assessed to be acceptable based on the available data. Additionally, toxicology safety concerns were not identified based on the available extractable and leachable toxicology risk assessment provided by the Applicant since the detected levels of leachables were below the parental permissible daily exposure (PDE) and maximum allowable concentration (MAC). The Applicant indicated that screening and toxicological assessment for the (b) (4) specific compounds (b) (4) that are missing from the current available data will be completed no later than July 5, 2024. The Applicant will also determine if additional methods validation is needed based on the results of the additional screening and toxicological assessments. Furthermore, an additional leachables study at an ≥ 18-month time point will be performed, which requires 12 weeks for completion. The Applicant committed to perform the additional screening and method validations (if needed), and provide the study report as a PMC.

3. The Applicant established lower limits for acceptance criteria for testing (b) (4) performed on the final product but did not establish upper limits. The Applicant committed to establish upper limits for the acceptance criteria after accumulating data from (b) (4) additional commercial batches. The upper limits for the acceptance criteria will be provided as a PAS.

b. Testing Specifications

The analytical methods and their validations and/or qualifications reviewed for the SYMVESS drug product were found to be adequate for their intended use.

The final product commercial release specifications are shown in Table 2.

Table 2. Final Product Commercial Release Specifications

Attribute	Analytical Method	Acceptance Criteria
Mechanical Property	(b) (4)	(b) (4)
Appearance	(b) (4)	(b) (4)

		(b) (4)
Identity	(b) (4)	(b) (4)
Purity	(b) (4) (b) (4)	(b) (4) (b) (4)
	(b) (4)	(b) (4)
Potency	(b) (4)	(b) (4)
	(b) (4)	(b) (4)
Safety	(b) (4) (b) (4) (b) (4)	(b) (4) (b) (4) (b) (4)

c. CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. A lot release testing plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of the acellular tissue engineered vessel (SYMVESS) are listed in Table 3. The activities performed and inspectional histories are also noted in Table 3.

Table 3. Manufacturing Facilities Table for Acellular Tissue Engineered Vessel (SYMVESS)

Name/Address	FEI Number	DUNS number	Inspection/ Waiver	Justification /Results
Humacyte Global Inc 2525 E. NC Hwy 54 Durham, NC 27713 DP manufacturing, DP release testing	3014294024	557190449	PLI	CBER/DMPQ April 2024 VAI
(b) (4)	(b) (4)	(b) (4)	Waiver	ORA/OBPO (b) (4) VAI
(b) (4)	(b) (4)	(b) (4)	Waiver	ORA/OPQO (b) (4) NAI

DP – Drug Product; OBPO – Office of Biological Products Operations; OPQO – Office of Pharmaceutical Quality Operations; ORA – Office of Regulatory Affairs; NAI – No Action Indicated; PLI – Pre-license Inspection; VAI – Voluntary Action Indicated; WCB- Working Cell Bank

CBER/DMPQ conducted a PLI at Humacyte Global, Inc. in April 2024 and a Form FDA 483 was issued at the end of the inspection. The firm adequately responded to the observations. All inspectional issues were resolved, and the inspection was classified as VAI.

ORA/OBPO conducted a surveillance inspection at (b) (4) in (b) (4), and a Form FDA 483 was issued at the end of the inspection. The firm adequately responded to the observations. All inspectional issues were resolved, and the inspection was classified as VAI. The firm has experience in performing microbial testing on tissue samples.

ORA/OPQO conducted a surveillance inspection at (b) (4) in (b) (4) and the inspection was classified as NAI. The firm has experience in performing mycoplasma testing of unprocessed bulk harvest.

e. Container/Closure System

SYMVESS is manufactured within a custom bioreactor (b) (4) that serves as the primary container closure system. The primary packaging is composed of (b) (4)

The container closure integrity testing was performed by (b) (4) employing the (b) (4) (b) (4) test method; all acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

In vivo studies to evaluate HAV performance and safety were conducted in non-human primates (NHPs). In an initial study, an earlier HAV prototype was implanted in baboons as an upper limb arteriovenous (AV) graft. Graft patency was maintained in 5 of 8 animals at the planned 3- and 6-month timepoints. HAV suture retention strength pre-implantation and post-explant indicated that the graft retained its mechanical strength during the implantation period. Occlusions were observed in 3 baboons, with 2 HAVs partially resorbed with evidence of a severe inflammatory reaction and localized infection in 1 of the 2 baboons, possibly due to opening of the surgical incision. There were no signs of graft dilation, constriction, or aneurysm observed following angiogram assessment for the grafts that remained patent.

In two subsequent NHP studies using an updated decellularization process, four baboons were implanted with HAV AV grafts and were followed for up to 6 months. In the second week post-implantation, 3 of the 4 grafts were occluded and required clot removal and surgical revision. After surgical revision, the grafts showed favorable blood flow and remained patent for the remainder of the study. A fourth baboon had persistent inflammation and wound infection for the first 2 weeks after HAV implantation. An aneurysm was detected following ultrasound imaging at Week 12 and was subsequently resected and the section replaced with an expanded polyfluoroethylene (ePTFE; (b) (4) (b) (4) graft. The animal was sacrificed at Week 14 due to thrombosis in the ePTFE portion of the AV graft and histological examination showed moderate to severe inflammation and graft resorption throughout the aneurysmal portion of the graft. In the HAV grafts that retained patency, minimal to mild infiltration of host cells including SMCs and endothelial cells were observed in the HAV graft wall and modest accumulation of immune cells were observed. ECM analysis showed increased collagen type I, glycosaminoglycans (GAGs), and elastin with a more circumferential alignment of collagen fibers for the 6-month explanted HAV as compared to the pre-implant HAV.

An in vivo study was also conducted to compare HAV and ePTFE grafts in a porcine hind limb ischemia model with a 0- or 6-hour ischemia time. At day 28, patency rates for grafts implanted within the 0-hour ischemia groups were 85.7% (6/7 animals) for HAV and 66.7% (6/9) for ePTFE grafts, while patency rates in the 6-hour ischemia groups were 100% (8/8) for HAV and 75% (6/8) for ePTFE grafts. In the grafts that remained patent, no aneurysms were observed and animals in the HAV group had similar mean velocity values and Tarlov gait scores as compared to the ePTFE group for the respective ischemia times (i.e., 0- or 6-hour). The clinical pathology results similarly

showed no apparent difference between animals receiving the HAV or ePTFE grafts. Histological analysis of the explants showed that both the HAV and ePTFE grafts had some native intimal hyperplasia and host reactivity. Both the HAV and ePTFE grafts showed evidence of immune cell and myofibroblast infiltration, typically from the exterior surrounding tissues, and a subset of the HAV sections showed partial luminal coverage by endothelial cells.

Additional intramuscular implantation tests were conducted in male and female adult rabbits (n = 3) for each timepoint (i.e., 1 week and 4 weeks) comparing the HAV to a (b) (4) high density polyethylene reference standard (RS) for characterization of biocompatibility in accordance with (b) (4) guidelines. The HAV test article was considered a slight irritant based on the histological observations [i.e., macrophages, eosinophils, lymphocytes, multinucleated foreign body giant cells (FBGCs), and fibrosis] as compared to the RS control article.

An additional study in a subcutaneous abscess model in (b) (4) rats (n = 21 for each bacterial species) compared the bilateral implantation of HAV to ePTFE graft inoculated with either (b) (4)
The HAV showed a lower bacterial bioburden as compared to the ePTFE graft at 2 weeks post-implantation.

No dedicated carcinogenicity or tumorigenicity studies were conducted. However, an Ames test of HAV extracts did not show evidence of bacterial mutagenicity when compared to the negative control. Additionally, an in vitro mammalian chromosome aberration test conducted using human peripheral blood lymphocytes exposed to HAV extracts showed no evidence of genotoxic activity.

No animal reproductive or developmental toxicity (DART) studies were conducted with SYMVESS. These studies are not warranted based on the product characteristics and intended use.

5. Clinical/Statistical

a. Clinical Program

Primary evidence of effectiveness for SYMVESS comes from Study V005, a prospective, open-label, single-arm, multicenter Phase 2/3 study evaluating SYMVESS for vascular replacement or reconstruction in patients with life- or limb-threatening vascular trauma, conducted under IND16746. The planned duration of follow-up for patients enrolled in the study was 36 months.

The primary efficacy outcome measure was the rate of primary vascular graft patency at Day 30 in patients with extremity arterial injury as assessed by functional graft patency without intervention using Duplex ultrasound or equivalent (i.e., CTA, MRI). Additional efficacy outcome measures included Day 30 rate of secondary patency, conduit infection, and limb salvage.

Supportive evidence of efficacy comes from Study V017, a retrospective, observational study of SYMVESS used on a humanitarian basis in Ukrainian patients with life- or limb-threatening vascular trauma. Endpoints for Study V017 were the same as for Study V005, and patients were followed for at least 6 months.

Efficacy

In Study V005, 54 patients had SYMVESS placed as a conduit for repair of an artery in the extremity and were included in the primary analysis population. The median age was 30.0 years (range: 18 to 72 years) and 74.1% were male. The demographic characteristics were as follows: 26 (48.1%) patients were Black or African American and 23 (42.6%) patients were white. The distribution of type of trauma was 31 (57.4%) penetrating trauma and 23 (42.6%) blunt trauma. Gunshot wounds represented the most frequent cause of vascular trauma followed by motor vehicle accidents. Nine (17%) patients were not evaluable at Day 30 due to death, amputation, of loss to follow-up.

The primary efficacy endpoint of Day 30 primary patency rate was 66.7% and the key secondary efficacy endpoint of Day 30 secondary patency rate was 72.2%. The secondary endpoint of limb salvage rate at Day 30 was 75.9%.

There were eight patients (14.8%) who had amputations in the primary analysis population, five (9.3%) who underwent amputation of the treated limb within the first 30 days and an additional three who underwent amputation of the treated limb by end of study at Month 36. FDA evaluated a limb salvage rate where patients who died, had SYMVESS explanted, or were lost to follow up were not included as amputation free. When taking into consideration these intercurrent events, the FDA calculated limb salvage rate at Day 30 to be 75.9% (95% CI: 63.1%, 85.4%) in 41 out of 54 patients.

One patient developed SYMVESS infection in the first 30 days with an additional two patients developing SYMVESS infection on days 35 and 36. This is discussed further in Section 6 - Safety and Pharmacovigilance.

Thirteen (13) of the 54 patients were not evaluable for primary patency at day 30 due to amputation (n=5), death (n=4), intraoperative thrombus (n=2), and loss to follow up (n=2). Of the 13, SYMVESS was deemed not patent in four patients. FDA had agreed to impute 30-day patency based on patency immediately before the intercurrent event in cases where the intercurrent event could be confidently adjudicated to be unrelated to SYMVESS. However, there was insufficient interim evaluation to conclude patency status at the time of intercurrent event for the remaining patients who were not evaluated at Day 30; for these patients, the patency status was considered non patent. For patency up to 36 months, a total of 37 of the 54 patients (68.5%) with SYMVESS implantation for extremity vascular trauma were non- evaluable having discontinued for reasons of due to loss to follow up (n=15), SYMVESS explant/abandonment (9), limb amputation (6), death (6) or withdrawal of consent (1).

In Study V017, which provided supportive evidence of efficacy, 15 out of 16 (93.8%) patients had primary patency confirmed at Day 30. SYMVESS was deemed not patent in one patient following mid-graft rupture. No patients underwent limb amputation.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspection assignments were issued for the sponsor and three domestic clinical study sites that participated in the conduct of Study V005. The inspections did not reveal significant issues and did not impact the data submitted in this original BLA.

c. Pediatrics

This application triggers the Pediatric Research Equity Act (PREA) for a new active ingredient and indication and was presented to the FDA Pediatric Review Committee (PeRC) on June 4, 2024.

During the IND phase, the Applicant requested informal dispute resolution regarding the requirement for pediatric studies of the HAV for the proposed trauma indication. In an informal dispute resolution from August 11, 2023, the Applicant was advised by CBER leadership in that a deferral for the pediatric studies in adolescents who have reached Tanner Maturity Rating Stage V appeared to be appropriate, as would be a partial waiver that covers the remainder of the pediatric population.

The Applicant previously requested a waiver for pediatric patients who have not completed pubertal development or have not reached Tanner Stage 5 because recruitment would be impossible or highly impracticable. Study V005 had been opened to enrollment of adolescent patients with protocol version 3.3 submitted under IND amendment 16746.64 on August 15, 2022 but the Applicant has not enrolled any adolescent patients by the time of this BLA submission. The Applicant states that it has been challenging to enroll pediatric patients due to the availability of an autologous vessel, vessel size mismatch and rarity of vascular trauma requiring repair in pediatric patients. There are also theoretical concerns that the product would be ineffective and/or unsafe in one or more of the
pediatric group(s) for which a waiver is being requested due to uncertainty regarding the ability of this product to grow with the patient.

The Applicant requested a deferral for adolescent patients between 14 and 17 years of age with sexual maturity rating of Tanner Stage 5. The Division agreed with granting the deferral of pediatric studies for adolescent patients who have reached a sexual maturity rating of Tanner Stage 5 because this product is ready for approval for use in adults and the amount of pediatric safety, efficacy and pharmacokinetic data are insufficient to ensure adequate safety/efficacy and instructions for dosing in this pediatric group. i iBased on discussion with the PeRC team, the clinical team recommend the following approach to labeling and PREA fulfillment: iiThe indication statement will include the qualifier “adults” since the product will not be approved for pediatric patients.

- Section 8.4 of the prescribing information will include the statement that “the safety and efficacy of SYMVESS in pediatric patients (0 to 17 years old) have not been established.”

- Section 8.4 of the prescribing information will not state that the product is not recommended for use in pediatric patients because there is no strong evidence to demonstrate that. The concern of potential unsafety in patients

less than Tanner Maturity Rating Stage V is valid but there is no clinical, nonclinical or product data to strongly support this safety concern.

- The approval will include a PREA PMR for evaluation of adolescent patients who have reached Tanner Maturity Rating Stage V.

d. Other Special Populations

None

6. Safety and Pharmacovigilance

Safety
Safety of SYMVESS was evaluated in all 71 patients who received SYMVESS as a conduit for arterial repair in the prospective Study V005. This included the 54 patients evaluated for efficacy who received SYMVESS as a conduit in an extremity and 17 patients who received SYMVESS for a torso or iatrogenic indication. The most frequently occurring adverse reactions reported following implantation of SYMVESS were graft thrombosis, fever, pain, anastomotic stenosis, SYMVESS rupture or anastomotic failure, and SYMVESS infection.

Six (8.5%) patients developed SYMVESS infection during the study. The analysis of SYMVESS infection includes patients who had graft infection confirmed during surgical reintervention with either positive graft culture, histology demonstrating bacteria in the graft or signs of graft infection noted by the surgeon.

During the study period, seven (9.9%) patients had loss of SYMVESS integrity following mid-graft rupture or anastomotic failure. Four (5.6%) patients had either proximal or distal anastomotic failure and three (4.2%) patients had mid-graft rupture of SYMVESS. Failure of the proximal anastomosis occurred in one patient who died.

Given the serious risk of arterial bleeding from mid-graft rupture or anastomotic failure (9.9%) following implantation of SYMVESS in this small cohort, the clinical team included this information as a boxed warning in SYMVESS prescribing information. Additionally, a prospective observational post-marketing study to further characterize the risk of graft failure in patients who have received SYMVESS for the approved extremity indication will be required upon approval. Institution of these mitigation measures provides an acceptable level of risk in adults as a vascular conduit for extremity arterial injury when urgent revascularization is needed to avoid imminent limb loss, and autologous vein graft is not feasible.

Pharmacovigilance Plan

The Applicant submitted a pharmacovigilance plan for SYMVESS. The important identified risks associated with SYMVESS include thrombosis/occlusion of SYMVESS during surgery, post-operative thrombosis/occlusion, SYMVESS rupture due to prolonged air exposure after implantation, anastomotic stenosis and anastomotic site bleeding. Postmarketing safety monitoring will include:

- Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80 and submission of quarterly periodic safety reports for 3 years and annual thereafter.

Data available at this time do not suggest safety signals that warrant a Risk Evaluation and Mitigation Strategy. Completion of the ongoing clinical study V005 and a safety-related postmarketing requirement study to further characterize the risk of graft failure in patients with extremity vascular injury who have received SYMVESS for the approved indication will further characterize the safety of SYMVESS in the indicated population.

7. Labeling

The proposed proprietary name, SYMVESS, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on February 27, 2024, and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on March 1, 2024.

Proposed proper name suffixes were reviewed on March 18, 2024, and May 21, 2024, and the proposed suffix *-tyod* was found conditionally acceptable.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed Prescribing Information and package and container labels on May 7, 2024.

Tissue engineered products are excluded from USAN naming schemes for cell-based products. Thus, the Agency designated a proper name “acellular tissue engineered vessel” based on the nature of the product.

The proposed prescribing information was reviewed and revised by the relevant review teams to ensure that it meets regulatory/statutory requirements, is consistent with current labeling practice, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the product, and provides clear and concise information for the healthcare providers. With the agreed revisions, the prescribing information is acceptable.

Boxed Warning, Warnings and Precautions
Risk mitigation strategies will be instituted in the United States Prescribing Information (USPI) through a Boxed Warning for graft failure and Warnings and Precautions section for graft rupture, anastomotic failure, and thrombosis as well as via the Patient Counseling Information section.

8. Advisory Committee Meeting

No advisory committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion. Three government employees external to the FDA with expertise in trauma vascular surgery were individually consulted to obtain additional input regarding specific questions that arose during the review of the file.

9. Other Relevant Regulatory Issues

This application received RMAT and Priority Review designations.

The application is designated as a Priority Product by the Department of Defense (DoD). Public Law 115-92 authorized DoD to request, and the U.S. FDA to provide, assistance to expedite development and the FDA's review of products to diagnose, treat, or prevent serious or life-threatening diseases or conditions facing American military personnel.

10. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness based on patency at Day 30 from a single open label study. The observed safety risks of graft rupture, anastomotic failure, and thrombosis can be adequately mitigated through product labeling.

Based on the totality of presented data and in consideration of the risk mitigation measures, the benefits outweigh the risks for this product. We therefore recommend traditional approval.

b. Benefit/Risk Assessment

The benefit of SYMVESS was demonstrated in Study V005. The study demonstrated a Day 30 primary patency rate of 66.7% and a Day 30 secondary patency rate of 72.2% which is considered a clinically meaningful benefit in the indicated population. SYMVESS' effects on the key secondary endpoint of limb salvage provides supportive evidence of benefit with a rate of 75.9% at Day 30. SYMVESS is indicated for use in adults as a vascular conduit for extremity arterial injury when urgent revascularization is needed to avoid imminent limb loss, and autologous vein graft is not feasible.

Supportive evidence of benefit derives from Study V017 which showed Day 30 primary and secondary patency rates of 93.8%. All patients had limb salvaged at Day 30.

Vascular graft thrombosis, pyrexia, pain, and anastomotic stenosis were common adverse reactions identified during this study and consistent with the risks seen with existing vascular repair options. More concerning is the risk of mid-graft rupture or anastomotic failure of SYMVESS. This risk has not been adequately characterized in the studies included in this BLA submission. While the risk of mid-graft rupture or anastomotic failure is seen in other vascular grafts (i.e., autologous vein or synthetic graft), there is insufficient information in the literature to support the observed rates seen in Study V005. Therefore, risk mitigation strategies will be instituted including limiting use of this product to extremity arterial injury when urgent revascularization is needed to avoid imminent limb loss, and autologous vein graft is not feasible. Inclusions to the United States Prescribing Information (USPI) via the Boxed Warning for graft failure and Warnings and Precautions section for graft rupture or anastomotic failure will also be instituted. The Applicant has also agreed to a postmarketing requirement to further characterize the risk of graft failure in patients with extremity vascular injury who have received SYMVESS for the approved indication. SYMVESS infection was also identified

as a risk in the setting of overlying wound infection during this study. This is a known risk of existing vascular grafts. Based on the totality of presented data and the unmet need for a vascular conduit when current therapies are not available, the benefit outweighs the risks for this product.

c. Recommendation for Postmarketing Activities

The Applicant agreed to the following PMRs and PMCs:

Post Marketing Requirements (PMR)

Clinical PMR Items

PMR #1: Conduct a prospective, multi-center, open-label study, to assess the safety and efficacy of SYMVESS in patients 17 years of age or younger who have reached Tanner Sexual Maturity Rating Stage 5, in the approved indication. The study will enroll a minimum of 10 patients who will be followed for a minimum of 1 year and will evaluate primary and secondary patency rate, and characterize the incidence of graft thrombosis, rupture, anastomotic failure, infection, limb amputation, and safety and tolerability.

Final Protocol Submission Date: March 31, 2025
Study Completion Date: December 31, 2028
Final Report Submission Date: June 30, 2029

PMR #2: Conduct long-term observational study to further characterize the risk of graft failure and infection in patients with extremity vascular injury who have received SYMVESS for the approved indication. The study should evaluate a minimum of 100 patients for a minimum follow up period of 1 year and should evaluate the incidence of graft rupture, anastomotic failure, and thrombosis, and describe the incidence of limb amputation and death.

Final Protocol Submission Date: April 30, 2025

Study Completion Date: September 30, 2030

Final Report Submission Date: April 30, 2031

Post Marketing Commitments (PMC)

Clinical PMC item subject to reporting requirements under section 506B:

PMC #3: Complete and submit the study report and dataset for Study CLN-PRO-V005, an open-label, single-arm study conducted in patients

treated with SYMVESS as a vascular replacement or reconstruction in life or limb-threatening vascular trauma.

Final Protocol Submission Date: n/a
Study Completion Date: August 31, 2026
Final Report Submission Date: December 31, 2026

CMC PMC items not subject to reporting requirements under section 506B:

PMC #4: Humacyte commits to conduct a shipping validation study to evaluate relevant critical quality attributes of SYMVESS following shipment in (b) (4) shipping conditions. Humacyte will submit the final study report by February 28, 2025.

Final Report Submission: February 28, 2025

PMC #5: Humacyte commits to submit ≥18-month leachable study data targeting (b) (4) specific compounds (b) (4) (b) (4) identified in additional extractables assessment requested by FDA, and additional method validation report (if found required) by January 31, 2025.

Final Report Submission: January 31, 2025

PMC #6: Humacyte commits to establish upper limits for the (b) (4) (b) (4) acceptance criteria used for final product release testing. The upper limits will be established based on data from a total of (b) (4) SYMVESS batches. Humaycte will provide a justification for the updated acceptance release criteria based on the collected information (i.e., data from at (b) (4) SYMVESS batches) and submit a study report as a Prior Approval Supplement by September 30, 2025.

Prior Approval Supplement Submission: September 30, 2025