BLA Clinical Review Memorandum

Application Type	BLA, Original Application
STN	125812/0
CBER Received Date	December 11, 2023
PDUFA Goal Date	August 9, 2024
Division / Office	DCEGM/OTP
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Prateek Shukla, MD
Review Completion Date / Stamped Date	December 18, 2024
Supervisory Concurrence	Vaishali Popat, MD, MPH Branch Chief, GMB3/OCE/OTP 'Lola Fashoyin-Aje, MD, MPH Director, OCE/OTP
Applicant	Humacyte Global, Inc.
Established Name	acellular tissue engineered vessel-tyod
(Proposed) Trade Name	SYMVESS
Pharmacologic Class	acellular tissue engineered vessel
Formulation(s), including Adjuvants, etc.	SYMVESS is an acellular tissue engineered vessel composed of organized extracellular matrix (ECM) proteins.
Dosage Form(s) and Route(s) of Administration	SYMVESS has dimensions of 6 mm in inner diameter and 42 cm in length (approximately 40 cm of usable length), which may be trimmed lengthwise to provide the length required for each vascular repair.
Dosing Regimen	Single treatment
Indication(s) and Intended Population(s)	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.
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

GLOSSARY

AAC	Applicant's adjudication committee
AE	adverse event
AESI	Adverse Events of Special Interest
AIS	abbreviated injury scale
ATEV	acellular tissue engineered vessel-tyod
AV	arteriovenous
AVF	arteriovenous fistula
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDRH	Center for Device and Radiological Health
DSUR	Development Safety Update Report
ECM	extracellular matrix
ESRD	end-stage renal disease
FDA	Food and Drug Administration
HAV	human acellular vessel
ICH	International Council for Harmonisation Technical Requirements for Pharmaceuticals for Human Use
IE	intercurrent events
IND	investigational new drug
IR	information request
ISS	injury severity score
KM	Kaplan-Meier
LAR	legally authorized representative
MESS	mangled extremity severity score
PAD	peripheral artery disease
PeRC	Pediatric Review Committee
PREA	Pediatric Research Equity Act
PT	preferred term
USPI	United States Prescribing Information

1. EXECUTIVE SUMMARY

On Dec. 11, 2023, Humacyte Global, Inc. (the Applicant) submitted an original BLA 125812 for licensure of Acellular tissue engineered vessel-tyod (ATEV) for the indication, "for urgent arterial repair following extremity vascular trauma (b) (4) indicated, and when autologous vein is not feasible." During labeling negotiations, the indication was revised to "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".

ATEV is an acellular tubular engineered vessel composed of human extracellular matrix (ECM) proteins. It has the proprietary name SYMVESS, and has previously been referred to as HAV (human acellular vessel).

For the purpose of demonstrating safety and effectiveness, the Applicant submitted data from two clinical studies of ATEV in vascular[1] trauma:

1) CLN-PRO-V005 (V005) is a prospective, open-label, single-arm, multicenter Phase 2/3 study evaluating the ATEV for vascular replacement or reconstruction in patients with life- or limb-threatening vascular trauma conducted under IND 16746. V005 provided the primary evidence of safety and effectiveness in the BLA. Out of 71 patients, 54 who had ATEV placed in the extremity are the primary analysis population. Seventeen patients had torso or iatrogenic injuries and were not included in the primary analysis as the proposed indication is limited for use in traumatic extremity injury. Patients were to be followed for 36 months. In this pivotal study, the primary efficacy outcome measure was the rate of primary vascular graft patency at Day 30 in 54 patients with extremity arterial injury as assessed by functional graft patency without intervention using Duplex ultrasound or equivalent (i.e., CTA, MRI). Key secondary outcome measures included Day 30 rate of secondary patency, conduit infection and limb salvage rate.

2) CLN-PRO-V017 (V017) was a retrospective, observational study of ATEV used on a humanitarian basis in Ukrainian patients with life- or limb-threatening vascular trauma. This retrospective study provided supportive safety and effectiveness data from 16 patients who received ATEV as a conduit in the extremities. Primary patency was evaluated at Day 30 as the primary endpoint. Key secondary endpoints included secondary patency at Day 30 and limb salvage rate at Day 30.

The primary evidence of effectiveness is based on primary patency at 30 days following use of the ATEV graft for vascular repair in extremity trauma in trial V005. 54 patients with extremity trauma in this trial demonstrated a primary patency rate at Day 30 of 66.7% (95% CI: 53.4%, 77.8%) and a secondary patency rate of 72.2% (95% CI: 59.1%, 82.4%). The limb salvage rate at Day 30 was 75.5% (95% CI: 62.4%, 85.1%). The ATEV infection rate was 1.9% in the first 30 days. Supporting data from Humanitarian use in the Ukraine provides a 30-day patency rate of 93.8%. No patients in study V017 required amputation. Day 30 outcomes in this acute trauma population is considered clinically

[1] In this review, "vascular" (e.g., vascular trauma, vascular repair, etc.) refers to arterial and not venous trauma, repair, etc.

meaningful, as this 30-day period of restoration of blood flow provides an opportunity to save a limb in clinical situations of imminent limb loss. Additionally, this period provides an opportunity for the establishment of the collateral circulation which would make later interventions possible, if needed. Based on these findings from both studies, the ATEV demonstrates a clinically meaningful benefit in restoring blood flow in the affected limb and ultimately limb salvage.

Evidence of long-term efficacy of this product is limited. Out of the 54 patients evaluated for efficacy, between Day 30 and the end of the study at Month 36, there were 10 additional patients who lost ATEV patency and 3 additional patients who underwent limb amputation. A further two patients who developed ATEV infection on days 35 and 36 following placement of ATEV in the extremity are included in the safety analysis. Long term patency and limb salvage cannot be accurately assessed as 69% of patients did not complete the study and therefore have unknown long-term outcomes.

Safety outcomes were evaluated from all 71 patients who received the ATEV for vascular repair including extremity and torso or iatrogenic indications. Despite the small number of patients in the dataset and limited long-term follow up, we identified a concerning signal for graft failure as a result of mid-graft rupture or anastomotic failure. Seven (9.9%) patients out of 71 in study V005 had graft failure which resulted in major post implantation bleeding, four from mid-graft rupture and three from anastomotic failure. Within the extremity group of 54 patients, four (7.4%) developed graft failure. One patient who received ATEV for a torso indication developed anastomotic failure and subsequently died.

When evaluating infection as a safety outcome, six (8.5%) of the 71 patients developed ATEV infection between days 7 and 40. Because there was no protocol specified evaluation of infection prior to Day 30, identified infections were limited to instances when reintervention to the graft was required due to bleeding from the ATEV.

The evidence of effectiveness provided from study V005 demonstrates a benefit in terms of 30-day patency rates and limb salvage. This product would provide an option for vascular replacement which would preserve the limb when the autologous vein is not available.

The risk mitigation includes limitation of indication to extremity trauma when urgent revascularization is needed to avoid imminent limb loss, and only when autologous vein is not feasible. In addition, a boxed warning for graft rupture and anastomotic failure is included in the United States Prescribing Information. A postmarketing requirement to further characterize the risk of graft failure and infection in patients who receive ATEV for the approved indication has been instituted along with a commitment to complete the study V005 for further characterization of risks and generate long-term follow-up data.

There is an unmet medical need for an alternative vascular graft to preserve the limb when the autologous vein is not feasible following extremity vascular injury. Use of existing synthetic graft materials is limited in the extremities due to the higher risk of complications including graft occlusion, infection, and graft failure due to repetitive motion in joint spaces.

The clinical review team concluded that substantial evidence of effectiveness was provided given the observed primary patency rate of 66.7% and limb salvage rates of

75.9% in this single arm pivotal trial. Given the identified risks and the risk mitigation strategies instituted, totality of presented data, and the unmet need, the benefits outweigh the risks for this product. This reviewer therefore recommends approval.

1.1 Demographic Information: Subgroup Demographics

Demographic information for the 88 patients who received the ATEV as a conduit in studies V005 and V017 are shown in Table 1. One patient received the ATEV as a patch in V005 and one in V017. Both patients who received the ATEV as a patch were excluded from analysis.

Table 1. Key Demographic Characteristics, Study V005 and Study V017

Characteristic	Study V005 Extremity Group n=54	Study V005 Torso/Iatrogenic Group n=17	Study V017 n=17
Sex, n (%)			
Male	40 (74.1%)	11 (64.7%)	17 (100%)
Female	14 (25.9%)	6 (35.3%)	0 (0)
Age, years			
Mean (SD)	33.4 (13.6%)	48.1 (20.7%)	34.2 (9.0%)
Median (min, max)	30.0 (18,72)	54.0 (18,81)	30.5 (22,54)
Race, n (%)			
Black or African American	26 (48.2%)	8 (47.1%)	0 (0)
Native Hawaiian or other Pacific Islander	0 (0)	1 (5.9%)	0 (0)
White	23 (42.6%)	8 (47.1%)	17 (100%)
Other	5 (9.3%)	0 (0)	0 (0)
Ethnicity, n (%)			
Hispanic or Latino	12 (22.2%)	2 (11.8%)	0 (0)
Not Hispanic or Latino	42 (77.8%)	15 (88.2%)	17 (100%)
Country of participation, n (%)			
United States	50 (92.6%)	17 (100%)	0 (0)
Israel	4 (7.4%)	0 (0)	0 (0)
Ukraine	0 (0)	0 (0)	17 (100%)

Source: Applicant dataset and 120-day safety update
Data Cut-off: January 15, 2024
[1]Race, Other: Bedoiun, Mexican, Mixed, Unknown
Abbreviations: max = maximum, min = minimum, n = sample size, SD = standard deviation

Reviewer comment:
Demographic characteristics of the extremity group (the primary analysis group for efficacy analyses) were comparable to those of the entire study population. Examination of the demographic characteristics of the screen failure patients indicated no selection bias in demographic characteristics for patients screened and enrolled versus those who failed screening. The mean and median ages were similar for patients receiving the ATEV for an extremity indication in studies V005 and V017.

1.2 Patient Experience Data

Please see Patient Experience Data reviewed in this BLA, summarized in Table 2 below:

Table 2. Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Extremity arterial trauma is a serious condition with severity based on the mechanism of injury, anatomic location, concomitant injuries, and the setting in which the trauma occurs. Mechanism can be blunt, penetrating, or both. Penetrating trauma can be from objects that are missiles (e.g., bullets, fragments from a blast, etc.) or stabs (e.g., knife, coat hangers, keys, etc.). Blunt trauma often occurs in the setting of fractures or dislocations. Extremity trauma has a high incidence of complication, including wound complications (infection, necrosis, nonunion, osteomyelitis), venous thromboembolism, rhabdomyolysis, limb loss and death. Without intervention, extremity arterial trauma will lead to exsanguination and death. In the absence of vascular reconstruction, tourniquet application of the affected limb is the primary life-saving measure.

In the civilian population, vascular injuries account for 1% to 2% of all injuries reported in trauma patients. However, patients who have vascular injury account for greater than 20% of all trauma-related deaths. The most common causes of civilian vascular injury are motor vehicle accident-associated lower extremity bone fractures, gunshot wounds, and dog bites. According to the PROspective Observational Vascular Injury Treatment (PROOVIT) database, designed to collect vascular trauma injuries from 24 Level I and Level II trauma centers in the United States, vascular injuries in the lower limb, torso, upper limb and neck have a distribution of 41%, 30%, 22%, and 6%, respectively .

Vascular trauma is also a leading cause of morbidity and mortality in the military. Military injuries are often due to penetrating or combined mechanisms. While vascular injuries make up a small percentage of trauma injuries in the military setting, they are the leading cause of exsanguination, limb ischemia, and amputation.

Grading scales are used to classify and describe the severity of injuries and assess the threat to life and limb associated with the injury. The mangled extremity severity score (MESS) utilizes the extent of skeletal and soft tissue injury, limb ischemia, shock, and age to predict the need for amputation after extremity injury. Clinical and demographic data early in a patient's course are used to predict the likelihood of success in limb salvage efforts. MESS scores can range from 2 to 11. A score of 7 or higher considered predictive of amputation . The abbreviated injury scale (AIS) is based on the type, location and severity of a traumatic injury . The AIS scale is a measurement tool for injuries ranging from mild (AIS score =1) to fatal (AIS score =6) with a score of 5 or more making survival uncertain.

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

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 because of their durability of patency and lower risk of complications including thrombosis. The saphenous vein harvested from the leg is most commonly used as an autologous graft. However, autologous blood vessel availability can be limited due to extensive trauma or preexisting peripheral vascular disease. Harvesting of the autologous vein may also place the patient at increased 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 ranging between 6 to 8 millimeters in diameter. Synthetic grafts provide some benefits over autologous veins such as strength and availability; however, their use is limited in the extremities due to the higher risk of complications including graft occlusion, infection, and graft failure due to repetitive motion in joint spaces. There are no clinical guidelines advising when synthetic grafts should be used in the extremities, but clinical guidelines used by the military state that

prosthetic conduits may be acceptable as a last resort in extremities when the vein cannot be harvested and use in joint spaces should be avoided. (Rasmussen, 2016)

There is a paucity of data regarding long-term outcomes following arterial graft placement. Table 3 summarizes available data on the expected outcomes following arterial vascular repair in the extremities for the civilian population. There is some variability in the published outcomes of existing therapies.

Table 3. Published Outcomes of Existing Therapies for Arterial Vascular Grafts

Outcome	Autologous Vein	Synthetic Graft
Primary patency	85-92%[A,B]	82%[B]
Secondary patency	97%[A]	79%[D-J]
Conduit infection	0-2%[K,O]	3% (0-6%)[B,C,D]
Conduit/anastomotic failure	0-6%[K,N]	2%[M]
Thrombosis	9.3% (intraoperative) 15-24.3% (graft thrombosis)[A]	6% (early)[1] 17% (late)
Amputation	2.8-30%[A]	6-24.3%[D,E,G,H,L]
Death	–	3%[B,D,E]

Source: FDA literature review, [A]Forsyth 2024, [B]Stonko 2022, [C]Rudstrom 2008, [D]Rayamajhi 2019, [E]Vertrees 2009, [F]Watson 2015, [G]Shamrock 2019, [H]Lin 2022, [I]Laverty 2021, [J]Fox 2005, [K]Rehman 2020, [L]Urrechaga 2022, [M]Feliciano 1985, [N]Greer 2012, [O]Reilly 2019

[1]Early refers to thrombosis occurring within the first 30 days. Late refers to thrombosis occurring at any point after 30 days.

Reviewer comment:
Review of the literature is limited by a paucity of data for outcomes following extremity arterial repair in the civilian population.

The BLA included the Applicant's meta-analysis of published studies aiming to determine incidence of primary patency, secondary patency, amputations and conduit infections with synthetic grafts in patients undergoing extremity arterial repair. However, the meta-analysis included data from the military which were not the population evaluated in this study. We have provided a list of published outcomes in the civilian population in Table 3. Further limitations of the Applicant's meta-analysis have been outlined in the statistical review.

2.3 Safety and Efficacy of Pharmacologically Related Products

There are no pharmacologically related products currently available.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

The ATEV has not been approved in any country. Experience with the ATEV comes from clinical studies conducted in patients with end-stage renal disease (ESRD), peripheral artery disease (PAD) in addition to vascular trauma (Table 4). In addition to the 10 clinical studies, the ATEV has been implanted in 26 patients through expanded-access including 20 (77%) patients for peripheral arterial disease, five (19%) for hemodialysis access and one (4%) for traumatic injury.

The Applicant reports that in total, more than 550 patients have been treated with the ATEV since December 2012.

Table 4. Clinical Studies of the ATEV Conducted for Other Indications

Study	Indication	Study Details	n=	Status
CLN-PRO-V001	ESRD	Pilot study evaluating safety and efficacy of investigational product for use as a vascular prosthesis for hemodialysis access	40	Ongoing
CLN-PRO-V003	ESRD	Phase I study evaluating safety and efficacy of the investigational product for use as a vascular prosthesis for hemodialysis access	20	Ongoing
CLN-PRO-V006	ESRD	Assessment of the investigational product in patients needing renal replacement therapy: A comparison with ePTFE grafts as conduits for hemodialysis (HUMANITY)	177	Ongoing
CLN-PRO-V007	ESRD	Phase 3 study comparing the efficacy and safety of the investigational product with that of an autologous arteriovenous fistula	240	Ongoing
CLN-PRO-V011	ESRD	Phase 2 assessment of investigational product in patients needing vascular access for dialysis	30	Completed
CLN-PRO-V012	ESRD	Phase 3 randomized study comparing efficacy and safety of investigational product with that of an autogenous arteriovenous fistula in female patients requiring hemodialysis	14	Ongoing
CLN-PRO-V002	PAD	Open-label, single-arm, multicenter pilot study evaluating safety and efficacy of investigational product as an above-knee femoro-popliteal bypass graft	20	Ongoing
CLN-PRO-V004	PAD	Phase 2 evaluation of safety and efficacy of investigational product as a vascular prosthesis for femoropopliteal bypass	15	Completed
CLN-PRO-V005	Vascular Trauma	Phase 2/3 study evaluating safety and efficacy of the investigational product for vascular replacement or reconstruction in patients with life or limb-threatening vascular trauma	72	Ongoing
CLN-PRO-V017	Vascular Trauma	Observational multicenter study evaluating safety and efficacy of the investigational product in a real world setting for arterial replacement or reconstruction in Ukrainian patients with life or limb-threatening vascular trauma.	18	Ongoing

Source: Annual report IND 16746.
Abbreviations: ePTFE = expanded polytetrafluoroethylene, ESRD = End Stage Renal Disease, n = number of patients, PAD = Peripheral Vascular Disease

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

The clinical development of the ATEV for this arterial vascular indication was originally submitted under IND 16746 and has undergone multiple major changes while the study was ongoing. These included major changes to the study design, study population, primary efficacy endpoints, sample size, and the statistical analysis plan. FDA has worked with the Applicant and exercised regulatory flexibility to further product development.

The application received Regenerative Medicine Advanced Therapy designation on May 2, 2023.

Table 5. Key Applicant Regulatory Interactions

Date	Interaction
May 19, 2015	Pre-IND Type B Meeting
June 27, 2016	Original IND Submission
August 01, 2019	**Type C Meeting** proposing conversion of study V005 from a proof-of-concept study to a registrational study. The Applicant proposed to compare ATEV with external controls from the PROspective Observational Vascular Injury Treatment (PROOVIT) database. The FDA expressed concerns about comparability of study patients and external controls and lack of long-term data in the PROOVIT database. The FDA requested adequate prospective clinical and statistical plans.
October 1, 2020	Department of Defense (DoD) designated the ATEV as a Priority Product in accordance with Public Law 115-92.
October 20, 2020	**Informal Meeting**: Applicant proposed study V005 as a Phase 2/3 nonrandomized, open-label, adaptive study in 100 eligible ATEV patients comparing to external controls from PROOVIT who received autologous vein graft. The FDA communicated major concerns about the study design, including study population, sample size, handling of missing data and intercurrent events (IE), noninferiority design, and interim analyses.
December 21, 2020	**Informal Meeting with FDA and DoD**: Applicant proposed to revise the study to compare 120 ATEV patients to matched patients selected from the PROOVIT registry. The FDA communicated major statistical concerns in the study design, including limitations of the PROOVIT registry to serve as external controls, inadequate matching criteria, and inflated Type 1 error rate. FDA recommended noninferiority analysis on the composite endpoint of 3-month or longer assessment of limb salvage, aneurysmal degeneration, and mortality, and superiority analysis on infection rates, compared to synthetic graft.
January 28, 2021	**Informal Meeting with FDA and DoD**: Applicant proposed a revised study V005 as a noninferiority study in which 50 ATEV patients (with lower extremity arterial repair and where autologous vein is not feasible) would be compared to a meta-analysis derived performance goal based on PTFE synthetic graft. The proposed primary efficacy endpoint was amputation free survival (AFS), and the secondary efficacy endpoint was infection. The Applicant proposed to demonstrate noninferiority on AFS and superiority on infection. The FDA requested details on the selection of publications for inclusion and meta-analysis methodology.
December 7, 2021	**Informal Meeting with FDA and DoD**: proposed to revise the primary efficacy endpoint from AFS to infection within 30 days after implantation of ATEV conduit. The FDA did not agree with infection rate as the primary efficacy endpoint and communicated concerns of serious selection bias in introducing multiple changes in the study design while the open-label single-arm trial was on-going. The FDA also communicated that statistical issues remained unresolved, which included Type 1 error control, handling of missing data and IEs, and analysis population. The FDA recommended a new randomized controlled trial with coprimary endpoints be conducted.
March 30, 2022	**Type B Meeting**: proposed two options for a revised study design for CLN-PRO-V005. In Option 1, the Applicant proposed to compare ATEV to synthetic grafts based on the coprimary endpoints of superiority on infection and noninferiority on AFS, both evaluated at 90 days. Performance metrics of

Date	Interaction
	synthetic graft were derived from meta-analysis literature review, and a matching adjusted indirect comparison (MAIC) approach would be used to match patients to external controls. In Option 2, the Applicant proposed to compare ATEV to autologous vein based on the primary endpoint of noninferiority on primary patency rate at 30 days. The PROOVIT registry would serve as external control in the primary analysis. In addition, the Applicant proposed to conduct a supplemental comparison of ATEV to synthetic graft on the functional endpoints of superiority on infection and noninferiority on amputation rates at 3 months. The FDA responded that either proposal was inadequate due to concerns including study population, study duration, choice of endpoints, sample size, handling of missing data and IEs, selection bias, and choice of comparator. The FDA suggested that the Applicant may reconsider an earlier proposal from 12/21/2020 informal meeting, in which the Applicant proposed to pursue an indication for "urgent arterial repair following extremity arterial trauma (b) (4) (b) (4) where autologous vein is not feasible."
October 26, 2022	**Pre-BLA Type B Meeting**: the Applicant presented key new data from the Ukraine Humanitarian Effort real world evidence (RWE) study during the pre-BLA meeting. The FDA did not agree with the Applicant's proposal for BLA submission, the main concerns being insufficient number of study patients, insufficient data in the targeted population, absence of a clearly prespecified comparator and SAP, absence of a clear Phase 4 confirmatory study protocol, and imprecise secondary endpoint selection. Major statistical concerns remained, including the choice of a comparator control group or benchmark and sample size.
March 7, 2023	**Type C Meeting**: Applicant proposed an observational study (V017) in 30 patients with traumatic injury sustained in Ukraine. The FDA did not agree with the Applicant's proposal to combine the efficacy data from Study V017 with study V005 due to heterogeneity between the studies. The FDA agreed with using the while-on-treatment strategy for handling IEs of deaths and amputations for the narrow indication, only in cases where the IE can be "confidently adjudicated to be unrelated to the study intervention." The FDA also recommended that supplemental analyses should be performed to address the IEs using a composite strategy. The FDA communicated concerns with using a mean-based benchmark derived from meta-analysis as the external comparator.
August 11, 2023	**Informal Dispute Resolution**: "clinical efficacy data obtained from V005 study combined with the Ukrainian treatment experience, totaling 50 patients with Day 30 patency data, will be sufficient to support a request for traditional approval of biological license application (BLA) for the proposed indication along with all the safety data relevant to this indication."

Source: Reviewer table
Abbreviations: AFS = amputation free survival, ATEV = acellular tissue engineered vessel, IE = intercurrent events, iPSP = initial pediatric study plan, MAIC=, matching adjusted indirect comparison, OTP = Office of Therapeutic Products, PROOVIT = PROspective Observational Vascular Injury Treatment, PTFE = polytetrafluoroethylene, RMAT = Regenerative Medicine Advanced Therapy, RWE = real world evidence, SAP = statistical analysis plan

2.6 Other Relevant Background Information

This product 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.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was sufficiently organized and integrated to accommodate the conduct of a complete clinical review. It was submitted electronically and formatted as an electronic Common Technical Document according to the FDA Guidance for Electronic Submissions. The submission contained the five modules in the common technical document structure.

3.2 Compliance with Good Clinical Practices and Submission Integrity

The prospective study V005 was performed in accordance with Good Clinical Practice, according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines including the archival of essential documents. This report was prepared according to the ICH E3 clinical study report guidelines.

A summary of the Bioresearch Monitoring (BIMO) inspections conducted at three study V005 sites that participated in support of the clinical review of the BLA is included in Table 6. No violations of the Food, Drug, and Cosmetic Act and other Acts or regulations were identified, however the BIMO inspectors noted the following:

- Site 2: The initial primary investigator at this site, Jonathan Morrison, MD, was replaced due to compliance issues. Informed consent documents were signed at a later date than the patient and there was missing documentation that SAE were reported within 24 hours. To better uphold the study requirements, Dr. Rishi Kundi, MD assumed control of the study and ensured that all issues were addressed.
- Site 6: Charles Fox, MD was removed from the study as the clinical investigator due to study compliance issues and his failure to apply appropriate corrective actions. He was using verbal consent from legally authorized representatives (LARs) to allow patients onto the trial and was receiving verbal consent from LARs over the phone. Additionally, several serious adverse events (SAEs) were reported after the 24-hour period required by the protocol. To better uphold the study requirements, Dr. Ernest Moore, MD assumed control of the study. Dr. Moore reviewed the prior patients' binders to ensure all required information was present and all the issues that occurred were addressed and corrected.

Table 6. Summary of Bioresearch Monitoring Inspections

Site ID	Number of Patients	Investigator and Location	Form 483 Issued	Final Inspection Classification
Site 2	7 (extremity group) 2 (torso/iatrogenic group)	Jonathan Morrison, MD Rishi Kundi, MD Baltimore, MD	No	NAI, Previous PI replaced due to ongoing compliance issues
Site 4	4 (extremity group) 1 (torso/iatrogenic group)	Ravi Rajani, MD Atlanta, GA	No	NAI
Site 6	10 (extremity group) 6 (torso/iatrogenic group)	Charles Fox, MD (04/10/2018-10/25/2019) Ernest Moore, MD (10/25/2019-present) Denver, CO	No	NAI, Previous PI replaced due to ongoing compliance issues
Applicant inspection	–	Humacyte Global, Inc	No	NAI

Source: Reviewer table
Abbreviations: NAI = no action indicated, PI = principal investigator

3.3 Financial Disclosures

Covered clinical study (name and/or number): CLN-PRO-V005
Was a list of clinical investigators provided? ☒ Yes ☐ No (Request list from applicant)
Total number of investigators identified: 32
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0

Significant payments of other sorts: 1

Proprietary interest in the product tested held by investigator: 0

Significant equity interest held by investigator in sponsor of covered study: 0

Is an attachment provided with details of the disclosable financial interests/arrangements? ☒ Yes ☐ No (Request details from Applicant)

Is a description of the steps taken to minimize potential bias provided? ☒ Yes ☐ No (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0

Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

Covered clinical study (name and/or number):

CLN-PRO-V017

Was a list of clinical investigators provided? ☒ Yes ☐ No (Request list from applicant)

Total number of investigators identified: 3

Number of investigators who are sponsor employees (including both full-time and part-time employees): 0

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0 Is an attachment provided with details of the disclosable financial interests/arrangements? ☒ Yes ☐ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? ☒ Yes ☐ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0 Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

Reviewer comment:
No significant issues with financial disclosures were identified that could suggest undue bias in the data submitted in support of this BLA. The disclosed financial interests/arrangements provided for one investigator in study V005 do not affect the approvability of this application. The Applicant has provided a sufficient description of steps taken to minimize potential bias.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

The ATEV is an acellular tissue engineered vessel that is 42 cm in length and 6 mm in inner diameter. It is composed of extracellular matrix proteins which are mostly collagen that are generated from allogeneic smooth muscle cells during (b) (4) The ATEV is manufactured using a tissue engineering process. Human vascular smooth muscle cells that are derived from human aortic tissue deemed suitable for transplant are banked, expanded, and seeded onto a tubular mesh (b) (4) scaffold. The cell-seeded scaffold is cultured in a biomimetic bioreactor system to generate an intermediate tubular construct containing vascular smooth muscle cells and the extracellular matrix the cells deposited. A final decellularization process removes the human cellular and genetic material while maintaining the extracellular matrix structure, mechanical properties, and biological activity. The product has 18 months of shelf-life under 2 to 8°C. The ATEV is packaged in a single unit. Please see Chemistry, Manufacturing and Controls review memo for further details.

Reviewer comment:
The structural integrity of the ATEV has not been evaluated when used in a (b) (4) configuration. It is hypothesized that the ATEV may lack adequate transverse strength when used as a (b) (4)

4.2 Assay Validation

No assays were used to evaluate the ATEV placement and function.

4.3 Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology/toxicology review issues were identified. Please refer to the nonclinical pharmacology/toxicology review for details.

Reviewer comment:
There are no nonclinical data that characterize the behavior of the investigational product after implantation, including its potential to grow after implantation in a patient who has not reached their adult height. This product has both structural and biological components but the mechanism of action isn't entirely clear. Non-clinical histological evidence suggests remodeling in the presence of increased (b) (4) (b) (4) however the Applicant has not conducted any definitive studies that would estimate how long it would take for the cells to migrate and entirely repopulate the ATEV.

4.4 Clinical Pharmacology

The ATEV is an implanted product intended to serve as a mechanical conduit to re-establish blood flow. It is not expected to have any systemic effects and no clinical pharmacology studies were conducted.

4.4.1 Mechanism of Action

The ATEV is an acellular tissue engineered vessel composed of human ECM that allows mechanical and biological activity. In vitro studies have shown that the ATEV can withstand the forces associated with the arterial blood flow and suture during the implantation process and can allow cell binding and proliferation. However, the exact mechanism of action has not been established.

4.4.2 Human Pharmacodynamics

The pharmacodynamic effects of the ATEV are not known.

4.4.3 Human Pharmacokinetics

The pharmacokinetic effects of the ATEV are not known.

4.5 Statistical

The statistical reviewer concluded that the pivotal trial, study V005, was not an adequate and well-controlled trial and identified the following concerns:

- The trial population did not align with the proposed indication.
- The analyses were not prespecified before the outcomes were known.
- The analyses were descriptive without formal hypothesis testing.
- Multiple major changes made while the trial was ongoing introduced high selection bias.
- The study seemed to be poorly conducted with missing data related to evaluation of adverse and intercurrent events and patient follow up.

Reviewer's comment:
Further discussion of these considerations are included in section 6.1 which discusses study V005. Given the objective endpoints, the clinical team concluded that regulatory flexibility can be exercised to accept this single arm trial as an adequate study due to the alternate outcome of imminent limb loss. To address the concerns raised by the statistical team about the trial design and missing data, a conservative approach to primary efficacy analysis was taken and patients with missing data at Day 30 were considered not patent for analysis. The Applicant provided data from both studies V005 and V017 to support safety and efficacy of ATEV; however, both the clinical and statistical teams determined that study V017 offers only limited support of efficacy due to the different study population and settings. Furthermore, the retrospective, observational study design of V017 makes it unsuitable to combine data with that from the prospective study V005.

Please refer to the memo from the statistical reviewer for further details.

4.6 Pharmacovigilance

Enhanced pharmacovigilance will be done following approval and will include periodic reports submitted to the Agency as required as well as expedited reports for three years following the date of product licensure for graft rupture and anastomotic failure. Benefit-Risk Evaluation Reports will be submitted for marketed product as per FDA guidance (i.e., at quarterly intervals, for 3 years from the date of issuance of the biologics license, and then at annual intervals) and DSUR for investigational product(s) as per applicable FDA guidance (e.g., annually).

Additionally, since routine pharmacovigilance was thought to be insufficient to address the risk of graft failure and infection, a long-term observational study comprising of at least 100 patients with extremity vascular injury is to be implemented with a minimum follow up period of 1 year. This study will evaluate the incidence of graft rupture, anastomotic failure, infection and thrombosis, and describe the incidence of limb amputation and death.

The Applicant will also complete study V005 under a post marketing commitment (PMC) in addition to Chemistry, Manufacturing, and Control PMCs recommended for shipping validation, environmental isolates information to support qualification of the sterility test method for product testing, sterilization validation of the bioreactor disposable set, excipient sample suitability for sterility assay, sterility assurance of the (b) (4) and establishment of upper limits for certain final product release testing.

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

5.1 Review Strategy

In this original BLA submission the clinical reviewer evaluated the clinical study report and accompanying datasets for Studies V005 and V017 in addition to the individual case summaries of each patient enrolled in either study. Case summaries for each patient included a longitudinal history of each patient enrolled in the study and were comprised of a medical monitor summary and surgical operative note in addition to clinical notes which may have included: emergency room provider notes, clinical progress notes, imaging reports, histology reports, serious adverse event report forms, and/or autopsy

reports. Summaries were reviewed separately by the clinical reviewer and CDRH vascular surgery consultant prior to compilation of findings into an internal database for use in FDA clinical and statistical reviews. Key outcome measures reviewed included: primary patency, secondary patency, amputation, requirement for repeat surgical intervention, infection of the investigational product, disruption of the ATEV's integrity and comments on the clinical outcome for each patient enrolled in either V005 or V017. In addition to clinical study data and literature references, the Applicant also provided a meta-analysis to provide current efficacy and safety benchmarks for key endpoints in synthetic grafts. The meta-analysis combined both military and civilian studies and therefore was not able to be used for comparison in the civilian studies conducted in this application. Therefore, this reviewer independently evaluated published medical literature about autologous and synthetic grafts to assess outcomes for patency and potential complications (Table3).

For evaluation of safety, the clinical reviewer focused on data from the ongoing study V005, inclusive of patients in both the extremity and torso/iatrogenic treatment arms. Evaluation of efficacy was based on the subset of patients with extremity trauma in V005 consistent with the proposed indication. Data from V017 was used as supportive data due to the retrospective study design and included a different population than that included in study V005.

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

The sources for this review are the data submitted in the licensing application, which includes data from the two ATEV studies (Table 7) and the relevant modules in the BLA submission:

- The administrative and prescribing information in module 1.
- Summary clinical information in modules 2.5 and 2.7
- Clinical study reports in module 5 including the narrative clinical study reports, appendices, tabulation and analysis datasets, case report forms, and literature references submitted by the Applicant.
- 120-day safety update submitted under BLA 125812/19
- Clinical information request (IR) responses received under the following amendments:
  - BLA 125812/36 – imaging compliance table
  - BLA 125812/38 – clinical IR
  - BLA 125812/40 – clinical IR

In addition, the reviewer used publicly available resources including UpToDate and PubMed.

5.3 Table of Studies/Clinical Trials

The BLA includes two studies of the ATEV (Table 7).

Table 7. Clinical Studies Submitted in the Biological License Application

Trial Identifier	Trial Design	Study Primary Endpoints	Study Objective	Study Population	No. of Study Sites, Countries and Patients enrolled
CLN-PRO-V005 NCT#03005418	Phase 2/3 prospective, multicenter, open-label, single-arm, efficacy and safety study	Primary patency at 30 days. Safety and tolerability.	Evaluate the safety and efficacy of the ATEV for use as an interposition replacement or bypass in patients with vascular trauma undergoing surgery for vascular replacement or reconstruction in size-appropriate vessels	≥18 to ≤85 years of age, with life- or limb-threatening traumatic injury to an arterial vessel in the limb or torso, other than the heart, which requires replacement or reconstruction when autologous vein graft is either not feasible in the judgement of the treating surgeon or is not desirable because of the urgency of revascularization	Study sites: 19 Countries: 2 Enrolled: 72 Extremity: 55 Torso/Iatrogenic: 17
CLN-PRO-V017 NCT#05873959	Observational, multicenter, single-arm, open-label, observational study with retrospective data collection	Efficacy: Primary patency at 30 days. Safety and tolerability	Evaluate the efficacy and safety of the ATEV in patients who had an ATEV implanted to repair or reconstruct an arterial vessel following life- or limb-threatening traumatic injury of an extremity	≥18 to ≤85 years of age, with life- or limb-threatening traumatic injury of the extremity suffered during the Ukraine conflict between June 2022 and May 2023	Study sites: 3 Countries: 1 Enrolled: 17 Extremity: 16 Iatrogenic: 1

Source: FDA reviewer
Abbreviations: ATEV = acellular tissue engineered vessel
Data Cut-off: January 15, 2024

5.4 Consultations

Dr. Robert Lee, a vascular surgeon in the Center for Device and Radiological Health (CDRH) was consulted regarding the proper adjudication of clinical outcomes and adverse events of special interest. Throughout the course of this review he provided expert opinion on this product submission evaluation.

Dr. Lee's assessment is that the ATEV had a concerning benefit risk profile, coupled with a catastrophic ATEV failure mode, and less than robust trauma data set. In his consult memo he notes that ATEV blow-outs or disruptions were generally associated with major, life-threatening hemorrhage. He further notes that disrupted ATEVs were associated with infection. Three patients experienced multiple bleeding episodes when attempts were made to salvage the ATEV by treating disrupted anastomoses with covered stents, or when suture repair or buttressing of an ATEV defect was attempted. Following review of the clinical data, the CDRH consultant noted that in his opinion ATEV use has resulted in "catastrophic life-threatening failures" and that the risks "are unacceptable when compared to current alternate treatment options." Based on the outcomes noted, the CDRH consultant stated that ATEV does not have a niche role in potentially saving limbs that would otherwise be lost. In his opinion, for the rare trauma patients who absolutely have no saphenous vein, synthetic graft can be used and does not expose patients to the same level of risks seen with the ATEV.

The CDRH consultant recommends the following:

- No favorable final marketing decision should be made until the Applicant addresses key outstanding clinical questions. For example:
    - presenting follow-up data in a manner to readily identify the extent of missing data
    - outcomes analysis based on key measures including length of ATEV, blunt vs. penetrating trauma
    - providing a data analysis limited to the trauma indication that excludes the iatrogenic injuries and AV access revisions
- There should be external review of the sponsor's adjudications by appropriate experts to resolve discordance in adjudication between the FDA and the Applicant.

- FDA should hold a public panel meeting, engaging members who have the appropriate expertise in vascular surgery, trauma surgery, military medicine and surgical infections to discuss the clinical performance data and provide recommendations whether there is a role for ATEV or what possible role the ATEV might play in managing trauma patients.

Reviewer comment:
As a result of some of the concerns raised by the CDRH consultant, the CBER clinical team took the following actions:

- Sent IR communications to the Applicant who provided follow up data which helped evaluation of missing data.
- Conducted exploratory analyses on key measures including type of trauma and length of ATEV used which did not find any significant changes warranting further evaluation.

- Performed a primary efficacy analysis for the extremity trauma indication which excluded iatrogenic injuries or torso indications.
- Decided on a conservative approach to adjudication of patency. Patients who did not have Day 30 evaluation were considered not patent (discussed further in Section 6.1.11.1 Analyses of Primary Endpoint).
- Conducted a review of the literature which suggests an unmet medical need for the ATEV in the extremities when the autologous vein is not feasible and use of a synthetic graft is not recommended, such as due to location in a joint.

5.4.1 Advisory Committee Meeting

Initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an Advisory Committee discussion. Late in the review cycle, the risk of graft failure was identified. In light of the safety signal identified, the clinical and statistical review teams raised the possibility of an advisory committee review. However, with further internal discussion with the review team and leadership, the decision was made that an advisory committee meeting was not needed.

5.4.2 External Consultations

To further address questions raised by the CDRH consultant and clinical review team and to obtain an independent expert evaluation of the evidence, external consultation was requested from three experienced vascular surgeons who are non-FDA government employees and practicing in academic medical centers.

The external consultants reviewed a summary of FDA and Sponsor data reflected in this review memo and provided their responses to the following questions:

1) Considering the patency rate and infection risk of existing treatment options for extremity arterial injury repair (i.e., autologous vein, synthetic graft), is there a population of patients who would benefit from treatment with ATEV? If so, please define this population and provide your rationale.

2) Provide your assessment of whether ATEV's risks of graft failure and infection are acceptable for the patient population you identify in response to Question #1a when weighed against the benefit of limb salvage.

3) Summarize your assessment of the benefits and risks of treatment with ATEV, based on the data provided to support the biologics license application for ATEV. Discuss if and how ATEV could contribute to the currently available treatment options, such as PTFE grafts, for restoring arterial blood flow to extremities.

All three consultants agreed that vascular trauma patients represent the population who could benefit from treatment with ATEV but that the ATEV did not demonstrate superiority to existing treatment options. Furthermore, they agreed overall that the observed infection rate is acceptable in the context of the observed benefit for the studied patient population.

All three consultants identified graft failure as a serious risk with ATEV use; however, they had different opinions on the acceptability of observed graft failure rates and how best to mitigate the observed risk. Suggestions provided by the consultants include

possible replacement of ATEV with an autologous vein in the setting of post-implantation infection, prolonged antibiotic prophylaxis and additional testing to identify the root cause of graft failure with ATEV use.

Reviewer comment:
The consultants' input aligns with the review team's assessment that the appropriate patient population that would benefit from treatment with ATEV is reflected in the final labeled indication agreed upon with the Applicant during labeling negotiations. The observed serious risk of graft failure, noted by the consultants and identified by the review team, has been incorporated into risk mitigation measures and into the benefit-risk evaluation of the product. The identified risks can be appropriately mitigated through product labeling, routine pharmacovigilance, and an additional longer-term study of graft failure and infection risks in a post-marketing study as part of the agreed-upon PMR.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 – CLN-PRO-V005

Study Title: A Phase 2/3 Study for the Evaluation of Safety and Efficacy of Humacyte's Human Acellular Vessel for Vascular Replacement or Reconstruction in Patients with Life- or Limb-threatening Vascular Trauma.

Clinical Trial Registry Identifiers: NCT03005418, EudraCT 2020-003383-12

Enrollment has completed (First patient enrolled: September 1, 2018; last patient enrolled June 5, 2023) Follow-up evaluation is ongoing.

6.1.1 Objectives (Primary, Secondary, etc.)

Primary Efficacy Objective:

- To determine the primary patency of the ATEV at 30 days in vascular trauma patients following surgery for vascular replacement or reconstruction due to life- or limb-threatening trauma of the extremities.

In the clinical protocol, primary patency is defined as functional access patency until any type of intervention to restore blood flow. Secondary patency is defined as functional patency, with or without preceding successful interventional or surgical procedures to maintain or reestablish patency, until the ATEV is abandoned. Long-term refers to a time point beyond 30 days and includes findings through the end of study at 36 months.

Safety Objective:

- To evaluate the safety and tolerability of the ATEV in vascular trauma patients following surgery for vascular replacement or reconstruction due to life- or limb-threatening trauma of the extremities.

Reviewer comment:
Results for patients who received ATEV in the extremity as a conduit are reported in this review as the primary efficacy endpoint in this study. All patients enrolled in study V005 inclusive of the extremity and torso/iatrogenic group are included in safety reporting.

6.1.2 Design Overview

The study is a prospective, multicenter, non-randomized, open-label Phase 2/Phase 3 study to evaluate the safety and efficacy of the ATEV in patients with life- or limb-threatening vascular trauma. The study was conducted at 19 sites in the United States and Israel.

The protocol was revised during the course of the study with the following major amendments:

- The location of arterial trauma was changed to include non-iatrogenic arterial trauma of the extremities only.
- Eligibility was amended to include adult patients with a MESS ≤7.
- Use was limited to patients with no alternate graft consideration (i.e., Autologous vein graft is either not feasible in the judgment of the treating surgeon (e.g., because of lack of availability of suitable conduit, presence of severe venous insufficiency) or is not desirable because of the urgency of revascularization).
- Study size was modified to include at least 50 patients with non-iatrogenic extremity injury. This value previously ranged from 20 to 100 patients in various versions of the protocol.

A summary of major changes with each revision follows in Table 8. Drafts of version 4.0 of the CLN-PRO-V005 protocol dated October 23, 2019 through May 24, 2023 were discussed between the FDA and the Applicant while the study was open to patient enrollment. During this time period, FDA communicated statistical concerns which would affect analysis of the study data. Agreement was reached on primary and secondary endpoints with the version of the clinical protocol submitted on May 24, 2023.

Table 8. Protocol Revision History, CLN-PRO-V005

Characteristic	Version 1.0 (29 Dec 2015) and Version 2.0 (24 Oct 2016)	Version 3.0 (18 Jul 2018) to version 3.3 (12 Aug 2022)	Draft Version 4.0 (23 Oct 2019)	Draft Version 4.0 (20 April 2020)	Draft Version 4.0 (30 Jul 2021)	Version 4.0 (24 May 2023)
Objective	P2/ Safety and tolerability	P2/ Safety and tolerability	Adaptive P2/3 – Efficacy and Safety using RWE	Adaptive P2/3 – Efficacy and Safety using RWE	Adaptive P2/3 – Efficacy and Safety using RWE	Adaptive P2/3 – Efficacy and Safety using RWE
Location of arterial trauma	Lower Limb	Vessel in the upper or lower limb or torso, other than the heart	Vessel in the upper or lower limb or torso, other than the heart; Iatrogenic Injuries	Vessel in the upper or lower limb or torso, other than the heart; Iatrogenic Injuries	Non-iatrogenic; Arterial Trauma – in limb only	Non-iatrogenic; Arterial Trauma – in limb only
Eligibility	18-85 yrs;	18-85 yrs; MESS ≤ 7 Expanded to include pediatrics 14-17 years of age who have reached Tanner stage 5 in version 3.3	18-85 yrs; MESS ≤ 7	18-85 yrs; MESS ≤ 7	14-85 yrs; MESS ≤ 7	14-85 yrs; MESS ≤ 7
Alternate vascular options	Autologous Vein Graft not feasible or desirable	Autologous Vein Graft not feasible or desirable	Autologous Vein Graft not feasible or desirable	AVG not feasible or desirable	No alternate graft consideration	No alternate graft consideration

Characteristic	Version 1.0 (29 Dec 2015) and Version 2.0 (24 Oct 2016)	Version 3.0 (18 Jul 2018) to version 3.3 (12 Aug 2022)	Draft Version 4.0 (23 Oct 2019)	Draft Version 4.0 (20 April 2020)	Draft Version 4.0 (30 Jul 2021)	Version 4.0 (24 May 2023)
Primary endpoints	Patency (primary, primary assisted and secondary) rate of ATEV at 12 months Rate of limb salvage	Primary patency at 30 days	Primary patency at 30 days.	Primary patency at 30 days	Superiority of early conduit infection (defined as Szilagyi Grade III or higher at 30 days)	Primary unassisted patency at day 30
Secondary endpoints	Patency rate at 3, 6 and 9 months Rates of intervention needed to maintain / restore patency - 12 months	Rate of limb salvage (12m) Patient survival Rate of infections Frequency of AESI	Rate of limb salvage Patient survival Rate of Interventions; Rate of infections Frequency of AESI	Rate of Interventions; Rate of infections; Rate of Limb Salvage Frequency of AESI	Non-inferiority on amputation rates at Day 30; mechanical stability of the ATEV based on freedom from ATEV removal or replacement	Secondary patency at day 30 Limb salvage at day 30 Infection at Day 30
Size	20 patients– 3 sites	40 patients; at least 10 in limb and 10 in torso cohort (10 sites)	60 eligible patients (12 sites)	100 eligible patients; (25 sites – United States +Israel)	50 evaluable patients (35 sites)	50 evaluable patients (35 sites)
Study Enrollment	0	0	22	29	41	63

Characteristic	Version 1.0 (29 Dec 2015) and Version 2.0 (24 Oct 2016)	Version 3.0 (18 Jul 2018) to version 3.3 (12 Aug 2022)	Draft Version 4.0 (23 Oct 2019)	Draft Version 4.0 (20 April 2020)	Draft Version 4.0 (30 Jul 2021)	Version 4.0 (24 May 2023)
Comparator	None	None	An external, non-interventional control group - PROOVIT Registry Autologous Vein Graft	An external, non-interventional control group - PROOVIT Registry	Comparator – Meta-Analysis Data; Synthetic Grafts	Comparator – Meta-Analysis Data; Synthetic Grafts
Stats	No formal hypothesis testing Descriptive Tabulation added in version 2.0	No formal hypothesis testing Descriptive Tabulation	Non-inferiority if Patency > 72%; Futility if patency < 50% at 30 days	Non-Inferiority (margin 10%) to matched PROOVIT comparator	Superiority to Registry infection rate (21%). No statistical comparison for patency.	No statistical comparison for patency.

Source: Table generated by the reviewer

Abbreviations: AESI = Adverse Events of Special Interest, AVG = Autologous Vein Graft, ATEV = acellular tissue engineered vessel, MESS = Mangled Extremity Severity Score, PROOVIT = PROspective Observational Vascular Injury Treatment, RWE = real world evidence, yrs = years

A total of 72 adult patients (≥18 years old) were enrolled and received the ATEV to repair an arterial vessel in the limb or torso, other than the heart. One patient was excluded due to use of the ATEV as a patch instead of a conduit. Among the 71 eligible patients who received the ATEV as a conduit for vascular repair, 54 (76%) were administered the implant to repair an artery in the extremity and 17 (24%) received ATEV for repair of an artery in either the torso or for an iatrogenic injury.

The primary efficacy endpoint was to determine the primary patency of the ATEV at 30 days in vascular trauma patients following surgery for vascular replacement or reconstruction due to life- or limb-threatening trauma of the extremities. Key secondary efficacy endpoints were measured at Day 30 and included secondary patency of the ATEV, infection rate, and the rate of limb salvage.

The study follow-up duration was 36 months.

Reviewer comment:
This study protocol underwent multiple major changes while the study was ongoing, and the clinical outcomes were known due to the open-label single-arm study design. These included major changes to the study design, study population, primary efficacy endpoints, and sample size. The frequent changing of key study elements and the analysis plans while the trial was ongoing limit the total number of evaluable patients for this indication and affect our ability to draw definitive conclusions from the data. Discussions between the agency and Applicant regarding the number of patients evaluated at day 30 and how best to determine Day 30 patency for patients who discontinued prior to this timepoint were ongoing prior to BLA submission and we did not reach agreement.

6.1.3 Population

Patients were considered for enrollment if they sustained life or limb threatening traumatic injury to an arterial vessel in the limb or torso, other than the heart, which required replacement or reconstruction.

Key Inclusion Criteria

Men and women aged 18 to 85 years and adolescents who have achieved Tanner Sexual Maturity Rating Stage V (U.S. sites only)

- Life or limb threatening traumatic injury to an arterial vessel in the limb or torso, other than the heart, which requires replacement or reconstruction
- Damaged vessel with a defect length of ≤38cm and appropriately size matched to the 6 mm ATEV inner diameter
- Autologous vein graft is either not feasible in the judgement of the treating surgeon (e.g., because of lack of availability of suitable conduit, presence of severe venous insufficiency) or is not desirable because of the urgency of revascularization.

Key Exclusion Criteria

- MESS of ≥7
- Limb at high risk of amputation despite vascular reconstruction
- Catastrophic injuries that make survival unlikely (e.g., AIS >5 or Injury Severity Score (ISS) >60)

- Pregnancy
- Unable to continue long-term antiplatelet therapy after resolution of acute injuries.

Reviewer comment:
During the course of development, the study was amended to include adolescent patients who have achieved Tanner sexual maturity stage V, however, due to challenges with recruitment for this subpopulation, no pediatric patients (i.e.,<18 years of age) were enrolled in this study.

The AIS classifies individual injury severity on a scale of 1-6 where 1 is minor and 6 is untreatable. The ISS takes the sum of the squares of the highest AIS from each of the three most severely injured body regions to achieve a score that ranges from 3 (least) to 75 (most) injured. Exclusion of patients with MESS ≥7, AIS >5 or ISS >60 is meant to limit this population to patients in whom limb preservation is possible. However, this also serves to skew the data towards limb salvage by selecting out patients in whom amputation risk is high.

This study enrolled patients with life or limb threatening traumatic injury to an arterial vessel in the limb or torso. During the course of this study, the intended population was reviewed at multiple timepoints in the context of emerging safety signals and the proposed indication was limited to urgent arterial repair following *extremity* vascular trauma when autologous vein is not feasible. Suitability for synthetic graft placement was not discussed in the clinical protocol. Changes made to the study design while the study was ongoing make it difficult to accurately assess the data due to confounders such as type of injury and indication for vascular replacement.

Following the data cutoff date of June 30, 2023, three additional patients were enrolled into study V005 and included in the 120 day safety update.

6.1.4 Study Treatments or Agents Mandated by the Protocol

All patients received an ATEV graft manufactured at either (b) (4) (b) (4) or Humacyte, Durham, North Carolina which was cut to the length required for arterial repair ranging in length from 1 to 40 cm.

Within the protocol, patients were to receive both antibiotic and antithrombotic prophylaxis in conjunction with the ATEV implantation in accordance with local hospital guidelines. All patients must have at least 1 day of antibiotic prophylaxis initiated on the same day as surgery with longer antibiotic prophylaxis administered at the discretion of the investigator based on clinical need.

Antithrombotic prophylaxis was to be commenced intraoperatively with heparin and if not ongoing at the time of surgery, should be commenced as soon as medically appropriate post operatively. The protocol recommended antiplatelet therapy (aspirin 81 to 325 mg and/or clopidogrel 75 mg daily) is at the discretion of the investigator and should continue long term while the ATEV is in place. If the patient is unable to tolerate aspirin and/or clopidogrel the choice of antiplatelet regimen was at the investigator's discretion.

Reviewer comment:

Currently available therapies rely on antibiotic and antithrombotic prophylaxis at the time of vascular graft placement. The Applicant has provided provision for same consistent with standard of care. In their protocol, there is no clear instruction on when antiplatelet therapy may be discontinued. It is understood that antiplatelet therapy should be continued life-long.

6.1.5 Directions for Use

The ATEV is administered by surgical implantation to repair or replace a patient's damaged blood artery after sustaining trauma. The anatomical location and length are decided upon at the discretion of the implanting surgeon and based on appropriate clinical evaluation, vessel mapping and/or imaging.

The ATEV has dimensions of 6 mm in inner diameter and 42 cm in length (approximately 40 cm of usable length). Since the length of the ATEV to be implanted is dependent on the surgical needs, it is trimmed to provide the length required for each vascular replacement by the surgeon in the operating room. Additionally, the ATEV can be cut and used to replace more than one injured artery in the same patient. Each ATEV unit is for use in a single patient only.

6.1.6 Sites and Centers

Study V005 was conducted at 17 sites in the United States and 2 in Israel.

6.1.7 Surveillance/Monitoring

Patients were followed on Days 5 and 30, and every 3 months from Months 3 to 36 with assessments as noted in Table 9:

Table 9. Schedule of Events, Study V005

Event	Pre-Op screening D1	D1	D5 or Prior to d/c	D30 +/- 5 Days	M3 +/- 14 Days	M6 +/- 14 Days	M9 +/- 14 Days	M12/ET† +/- 14 Days	M15-M36† +/- 30 Days
Informed consent	X								
Medical history and nature of trauma	X								
Concomitant medication	X	X	X	X	X	X	X	X	
Physical exam[1]	X	X	X	X	X	X	X	X	X[7]
Pre-op ultrasound or CT angiography[2]	X								
Vital signs			X						
Eligibility (inclusion/exclusion criteria)	X								
ATEV implantation and intraoperative confirmation of patency		X							
Documentation of surgery and any complications		X							

Clinical chemistry	X[3]		X						
Hematology	X[3]		X						
PRA	X[3]			X		X		X	
Duplex ultrasound[4]				X	X	X	X	X	X[4]
CT angiography								X	
AEs		X	X	X	X	X	X	X	X[5]
Documentation of ATEV interventions		X	X	X	X	X	X	X	X[5]

Source: Table 1 Protocol CLN-PRO-V005 v4.0 in 16.1.1.6.
[1]Physical examination includes clinical exam of the operative limb and ATEV at all postoperative visits (incl. patency assessment on D1) and distal vascular bed (extremity injury only)
[2]Pre-op imaging is at the discretion of the investigator based on the clinical condition of the patient.
[3]Measured at preoperative screening when possible; if PRA titer not obtained preoperatively, it must be completed within 12 hours after ATEV implantation.
[4]Visits at Month 24 and Month 36 to be conducted in person with physical exam of the ATEV site and duplex ultrasound imaging of ATEV.
[5]The status of the patient and ATEV will be ascertained every 3 months post Month 12 until 36 months after ATEV implantation by telephone contact with the patient and/or his physician. Only related SAEs and all AESI will be reported after 12 months. If a suspected SAE related to ATEV is discovered an unscheduled visit should be conducted to investigate.
†Patients withdrawn before Month 12 will perform ET visit that correlates with the procedures at Month 12. Patients withdrawn after Month 12 and prior to Month 36 should complete an ET visit that correlates with procedures post Month 12 through Month 36.
Abbreviations: AE = adverse event, CT = computed tomography, D = day, d/c = discharge, ET = early termination, ATEV = acellular tissue engineered vessel, M = month, PRA = panel reactive antibodies

A Data Monitoring Committee was implemented to review safety on an ongoing basis and provide recommendations about stopping, continuing, or modifying the study.

Reviewer comment:
Duplex imaging or alternative appropriate imaging methods (i.e., computed tomography angiography or magnetic resonance imaging are recommended to evaluate patency following vascular graft placement both in the initial few days after placement and then at regular intervals every 3 months for the first year and annually thereafter (Forsyth, Haqqani et al. 2024). Imaging can also be used to identify structural irregularities which would be suggestive of graft infection. The earliest patency assessment included in the clinical protocol was at Day 30, and lack of definitive evaluation of patency prior to study discontinuation made it difficult to impute patency for 12 (21.8%) patients who were not evaluated at Day 30. Patients who did not have definitive evaluation of patency prior to study discontinuation were evaluated as a worse case scenario and included as not patent for FDA analysis. Infection rate during the first 30 days is a key secondary endpoint, however the protocol did not evaluate for structural abnormalities suggestive of infection with imaging as is commonly done in clinical practice.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint:

- Primary ATEV patency at Day 30 after implant

Key Secondary Efficacy Endpoints:

- Secondary patency at Day 30 after implant
- Conduit infection at Day 30 after implant
- Limb salvage rate at Day 30 after implant

Reviewer comment:
For the efficacy assessment, the Applicant evaluated patency, infection and limb salvage rates at 30 days. This time period of 30 days has been cited in the literature following vascular surgery, as there is a higher risk of complications during the first 30 days and reliable follow up beyond 30 days is a known challenge in the civilian trauma population. The Applicant did not predefine a success rate in their statistical analysis plan. They proposed a comparison against a standard of care benchmark after 41 patients had been enrolled and some outcomes were already known; however, agreement on a benchmark was not reached prior to BLA submission.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Study Hypothesis:
This was a nonrandomized, single-arm, open-label study. The Applicant did not provide formal hypothesis testing, prespecified Type 1 error control, or multiplicity adjustment in their statistical analysis plan. Efficacy endpoints were summarized descriptively.

Sample Size:
No formal power calculations were performed as no formal hypothesis testing was planned.

Analysis Population:
The analysis population of the extremity group is defined as any patient who received the ATEV graft and who underwent non-iatrogenic arterial vascular repair with the ATEV in an extremity.

Handling of Intercurrent Events):
The Applicant used a while-on-treatment strategy for imputing patency in patients with intercurrent events (IEs), such as death and amputation; if the IE was determined to be causally unrelated to the ATEV, the last known patency status prior to the IE would be used in the primary efficacy analysis. An independent adjudication committee determined whether the IE may have been related to the ATEV and concluded patency at the time of IE for patients who were not evaluable for the primary endpoint due to IEs. In discussions with the Applicant prior to BLA submission, the FDA recommended that if the IE is deemed causally related to the ATEV, or if causality of the IE could not be determined, or patency status is missing postimplant, patients would be included as patency failure.

Handling of Missing Data:
No missing data handling strategies were provided.

Reviewer comment:
The planned sample size for this study had changed multiple times from 20 patients in the initial study protocol to 100 patients in protocol version 4.0 from April 2020. The Applicant and the FDA discussed the possibility of evaluating non-inferiority to existing standard of care treatments, but no consensus was reached related to establishment of benchmarks for comparison due to a paucity of extremity vascular trauma data.

Comments about missing data handling and imputation strategies were sent to the Applicant during the IND stage but the FDA and the Applicant did not reach agreement prior to this BLA submission and these changes were not implemented in the submitted

Applicant analyses. Based on the Type C meeting on March 7, 2023, FDA agreed that a while-on-treatment strategy can be used to handle intercurrent events only if they can be confidently determined to be unrelated to the ATEV. During review of this BLA, inconsistent and/or inadequate methods to ascertain patency status in different patients by the adjudication committee were identified. In addition, if there was missing data such as no definitive patency assessment or no culture taken for ATEV infection evaluation, the best outcomes (i.e., patency, no infection assumed) were used in the analyses. FDA recommendations during previous discussion were that these should be handled conservatively. As a result, FDA also performed its own internal adjudication of the missing data.

6.1.10 Study Population and Disposition

The study population evaluated for efficacy included 54 patients who had placement of the investigational product to treat extremity vascular trauma. This includes three patients (b) (6) who were enrolled following the initial data cutoff date and were included in the 120-day safety update and one patient who was reclassified from the torso cohort following the most recent protocol revision. All 71 patients who received ATEV as a conduit for vascular replacement in study V005 were included for safety analysis.

87 patients were screened for enrollment in study V005, with 15 (17.2%) screen failures. One patient was excluded from the analysis group due to placement of the ATEV as a patch instead of a conduit. 71 patients received the ATEV as a conduit for either the extremity or a torso/iatrogenic vascular injury. 54 of the 71 received the investigational product as a conduit for an extremity indication and 17 for torso or iatrogenic vascular trauma.

Table 10. Indication Cohorts Within Study V005

Patient Disposition	Patients, n (%)
Total number of patients enrolled and treated	71 (100%)[1]
All ATEV group	71 (100%)
Extremity group (extremity arterial placement as a conduit following non-iatrogenic trauma)	54 (76.1%)[1]
Iatrogenic and torso group	17 (24.0%)

Source: Derived from Table 14.1.1.2 and Table 14.1.5 and clinical dataset
[1]one patient excluded from this group for use of ATEV in a patch configuration.
Abbreviations: ATEV = acellular tissue engineered vessel, n = sample size
Data Cut-off: January 15, 2024

Of the 71 patients in study V005 who received an ATEV as a conduit, 11 patients had completed the study with 36 months of follow-up, 15 patients were ongoing, and 43 patients had discontinued prior to Month 36. Within the group of 54 patients who received an ATEV as as a conduit for an extremity indication, 7 patients had completed the study with 36 months of follow-up, 10 patients were ongoing, and 37 patients discontinued from the study prior to Month 36 due to loss to follow up, death, ATEV abandonment or withdrawal of consent. Further details about patient disposition are provided in 6.1.10.1.3 Patient Disposition.

Reviewer comment:
Patients (b) (6) were enrolled in this study between July 5 and August 19, 2023, after the original data cutoff date of June 30, 2023. FDA included these patients in the efficacy analysis to maximize data for analysis from this small trial and to reduce selection bias, as poor outcomes for at least one of the patients may have been known to the Applicant at the time of selection of the data cutoff date. The data cutoff date of June 30, 2023, was selected after the official CBER response to the Applicant's request for of the informal dispute resolution finalized on August 11, 2023.

6.1.10.1 Populations Enrolled/Analyzed

The safety population consisted of all study patients who received any amount of the ATEV, regardless of follow-up status. Sub analysis was performed to further evaluate risk within the extremity and torso/iatrogenic groups.

Reviewer comment:
FDA review of the patient narratives revealed that one patient (b) (6) was erroneously assigned to the torso and iatrogenic group by the Applicant based on an earlier version of the protocol. Following IR communication, the Applicant clarified that patient (b) (6) had been assigned to the torso/iatrogenic group based on a previous version of the protocol in which any patient with any portion of the ATEV graft originating in the torso would be classified to the torso cohort. Within the case summary, it is noted that this patient presented with a gunshot wound to the left upper chest which required the ATEV placement as an interposition graft from the left subclavian artery to the left axillary artery. Per the most recent version of the clinical protocol (version 4), this patient meets the definition for classification within the extremity cohort based on the termination of the graft within the extremity. This patient was reassigned to the extremity group for analysis based on criteria in the most recent version of study V005 (version 4).

FDA also identified one patient (b) (6) in the extremity group where the ATEV was used as a patch instead of a conduit. This patient was removed from safety and efficacy analyses. The efficacy analysis relied on a study population of 54 patients and the safety analysis relied on a study population of 71.

6.1.10.1.1 Demographics

Patient demographics are presented in Table 11. The extremity group population is predominantly male (74.1%) and made up of primarily Black or African American (48.2%) and White (42.6%) patients. The age of patients ranged from 18 to 72 years with a median of 30.0 years and a mean of 33.4 years.

Table 11. Patient Demographics for Study V005

Characteristic	Extremity Group n=54	Torso/Iatrogenic Group n=17	Total n=71
Sex, n (%)			
Male	40 (74.1%)	11 (64.7%)	51 (71.8%)
Female	14 (25.9%)	6 (35.3%)	20 (28.2%)
Age, years			
Mean (SD)	33.4 (13.6)	48.1 (20.7)	36.9 (16.7)
Median (min, max)	30.0 (18,72)	54.0 (18,81)	30.0 (18,81)
Race, n (%)			
Black or African American	26 (48.2%)	8 (47.1%)	34 (47.9%)
Native Hawaiian or other Pacific Islander	0 (0)	1 (5.9%)	1 (1.4%)
White	23 (42.6%)	8 (47.1%)	31 (43.7%)
Other	5 (9.3%)	0 (0)	5 (7.0%)
Ethnicity, n (%)			
Hispanic or Latino	12 (22.2%)	2 (11.8%)	14 (19.7%)
Not Hispanic or Latino	42 (77.8%)	15 (88.2%)	57 (80.3%)
Country of participation, n (%)			
United States	50 (92.6%)	17 (100%)	67 (93.1%)
Israel	4 (7.4%)	0 (0%)	4 (5.6%)

Source: Derived from BLA 125812/0; Module 5.3.5.2, Clinical Study Report, p.75.
Abbreviations: max = maximum, min = minimum, n = sample size
Data Cut-off: January 15, 2024

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

In the extremity group, 26 (48.2%) patients had an AIS of severe and 14 (25.9%) patients had an AIS of critical (Table 12). Table 13 demonstrates injury characteristics within the study population. The median ISS in the extremity group was 17, with a minimum score of 9 and a maximum score of 50. 31 patients (57.4%) presented with penetrating trauma and 23 patients (42.6%) presented with blunt trauma. Gunshot wounds were the most common type of injury followed by motor vehicle accidents.

Table 12. Injury Severity Classification for Patients, Study V005

Parameter	Extremity Group n=54	Torso/Iatrogenic Group n=17	Total n=71
Abbreviated injury scale (AIS), n (%)			
Moderate	0 (0%)	2 (11.8%)	2 (2.8%)
Serious	14 (25.9%)	1 (5.9%)	15 (21.1%)
Severe	26 (48.2%)	4 (23.5%)	30 (41.7%)
Critical	14 (25.9%)	6 (35.3%)	20 (28.2%)
Missing	0 (0%)	4 (23.5%)	4 (5.6%)

Source: Derived from BLA 125812/0; Module 5.3.5.2, Clinical Study Report.
Abbreviations: AIS = abbreviated injury scale, n = sample size
Data Cut-off: January 15, 2024

Reviewer comment:
The AIS scores were calculated by the investigator at the time of patient enrollment. This scale is a measurement tool for single injuries that allows for comparison of specific injuries and their relative severity. Overall, the distribution is as expected for this study population.

Table 13. Injury Characteristics, Study V005

Parameter	Extremity Group n=54	Torso/Iatrogenic Group n=17	Total n=71
Injury location, n (%)			
Abdomen	0 (0%)	1 (5.9%)	1 (1.4%)
Chest	0 (0%)	3 (17.7%)	3 (4.2%)
Pelvis	0 (0%)	1 (5.9%)	1 (1.4%)
Lower extremity	42 (77.8%)	8 (47.1%)	50 (70.4%)
Upper extremity	12 (22.2%)	4 (23.5%)	16 (22.5%)
Artery category, n (%)			
Femoral artery	21 (38.9%)	7 (41.2%)	28 (39.4%)
Popliteal artery	21 (38.9%)	1 (5.9%)	22 (31.0%)
Brachial artery	7 (13.0%)	4 (23.5%)	11 (15.5%)
Axillary artery	5 (9.3%)	1 (5.9%)	6 (8.5%)
Other[1]	0 (0%)	4 (23.5%)	4 (5.6%)
Mangled Extremity Severity Score, n (%)			
8	4 (7.4%)	0 (0%)	4 (5.6%)
7	2 (3.7%)	0 (0%)	2 (2.8%)
6	14 (25.9%)	0 (0%)	14 (19.7%)
5	11 (20.4%)	4 (23.5%)	15 (21.1%)
4	12 (22.2%)	2 (11.8%)	14 (19.7%)
3	7 (13.0%)	5 (29.4%)	12 (16.9%)
2	2 (3.7%)	3 (17.6%)	5 (7.0%)
Missing	3 (0%)	3 (17.6%)	6 (5.6%)
Cause of trauma, n (%)			
Arteriovenous fistula	0 (0%)	4 (23.5%)	4 (5.6%)
Crush	2 (3.7%)	0 (0%)	2 (2.8%)
Fall	3 (5.6%)	0 (0%)	3 (4.2%)
Gunshot injury	29 (53.7%)	4 (23.5%)	33 (46.5%)
Iatrogenic injury	0 (0%)	8 (47.1%)	8 (11.3%)
Industrial accident	3 (5.6%)	0 (0%)	3 (4.2%)
Motor vehicle accident	14 (25.9%)	1 (5.9%)	15 (21.1%)
Other	3 (5.6%)	0 (0%)	3 (4.2%)
Nature of trauma, n (%)			
Blunt trauma	23 (42.6%)	1 (5.9%)	24 (33.8%)
Penetrating trauma	31 (57.4%)	16 (94.1%)	47 (66.2%)
Deep tissue injury	53 (98.1%)	5 (29.4%)	57 (80.3%)
Open fracture injury	32 (59.3%)	5 (29.4%)	36 (50.7%)
Contaminated wound[2]	51 (94.4%)	9 (52.9%)	59 (83.1%)

Source: FDA reviewer. Derived from clinical study report and case summaries.
[1]other includes subclavian, common iliac, and external iliac arteries.
[2]Includes penetrating wounds, open wounds, wounds where a foreign body is present or added (example external fixators), degloving injuries, puncture wounds, and wounds in areas of the body with high concentrations of commensal flora (e.g., oral mucosa, genitals, armpits).
Abbreviations: n = sample size
Data Cut-off: January 15, 2024

Autologous vein is the primary source of repair for vascular trauma due to better long-term safety and patency. Table 14 lists the reasons for not using the autologous vein when enrolling patients into this study as provided by the Applicant.

Reviewer comment:
The injury characteristics of patients enrolled in study V005 are consistent with the types of injuries reported in the literature for extremity vascular trauma.

Table 14. Reasons for Not Using Autologous Vein in Vascular Repair

Reason	Extremity Group n=54	Torso/Iatrogenic Group n=17	Total n=71
Concomitant injury to the vein	13 (24.1%)	1 (5.9%)	14 (19.7%)
Poor quality or size of the vein	16 (29.6%)	8 (47.1%)	24 (33.8%)
Previously removed	4 (7.4%)	0 (0%)	4 (5.6%)
Time limitation	17 (31.5%)	6 (35.3%)	23 (32.4%)
Other[1]	7 (13.0%)	2 (11.8%)	9 (12.7%)

Source: CLN-PRO-V005 CSR Listing 16.2.4.4; BLA 125812/SN0000
Note that more than one reason may have been reported for a given patient, thus patients may be counted in more than one category.
[1]Other includes body habitus; both legs with external fixation made harvesting problematic; complexity of global care; contralateral limb trauma; heavy contamination, obesity resulting in difficult saphenous vein harvest; and prone positioning.
Abbreviations: n = sample size
Data Cut-off: January 15, 2024

Reviewer comment:
The Applicant has provided reasons for not using the autologous vein which include use of the ATEV to save time and for technical reasons. The Applicant notes poor quality or size of the autologous vein as a reason for not using this option during vascular reconstruction. During review of individual cases, we noted that many of the patients presented to the OR following significant bleeding and were hypovolemic due to traumatic injury. This may have contributed to the high number of patients who did not receive autologous vein due to poor quality or size of the vein at the time of placement. Time limitation for autologous vein harvesting was included in earlier protocol versions when use of the autologous vein was considered “not desirable.” In the original BLA submission, the Applicant included patient preference as a possible reason for the ATEV use for several patients. These patients are included in the “Other” category in Table 14. During BIMO inspection, the primary investigator clarified that time limitation and poor vein quality were the reasons for the ATEV use in three patients who consented to ATEV use from this site.

6.1.10.1.3 Patient Disposition

A total of 72 patients were enrolled. 71 patients received the ATEV as a conduit and one patient (b) (6) received the ATEV as a patch and was excluded from the safety and efficacy analysis. 54 patients were included in the extremity group. 17 patients received the ATEV for a torso or iatrogenic injury.

Of the 54 patients in the extremity group who received the ATEV as a conduit, 13 (24.1%) were not evaluated at Day 30 due to death (n=4), amputation (n=5), ATEV explant (n=2) and loss to follow up (n=2). The ATEV was confirmed to be not patent at the time of loss to follow up for one of these patients.

Table 15. Patients Evaluated at Different Timepoints, Study V005

Patient Disposition	Patients, n (%)
Total number of patients in the extremity group	54 (100%)
Patients evaluated at Day 30	41 (75.9%)
Patients evaluated at Month 6	30 (55.6%)
Patients evaluated 1 year	18 (33.3%)
Patients evaluated 3 years / end of study	7 (13.0%)

Source: Updated from Table 14.1.1.2 and Table 14.1.5 and clinical dataset
Abbreviations: n = sample size
Data Cut-off: January 15, 2024

Evaluation of long-term patency is limited by the large number of patients who discontinued from the study prior to completion at Month 36 (Table 16). 37 (68.5%) patients discontinued from the study due to lost to follow up, death, ATEV abandonment, or withdrawal of consent. Seven patients completed the study with 36 months of follow-up. At the time of this review, study V005 is ongoing with 10 patients who have received an ATEV still in follow-up and have not completed the per-protocol 36-month follow up.

Table 16. Reasons for Early Discontinuation, Study V005

Reason for Study Discontinuation (<36 months)	Patients, n (%)
Total number of patients in the extremity group	54 (100%)
Completed study	7 (13.0%)
Evaluation ongoing	10 (18.5%)
Early study discontinuation	37 (68.5%)
Loss to follow up	15 (27.8%)
ATEV abandoned/explanted	9 (16.7%)
Amputation	6 (11.1%)
Death	6 (11.1%)
Withdrew consent	1 (1.9%)

Source: Updated from Table 14.1.1.2 and Table 14.1.5 and clinical dataset
Abbreviations: ATEV = acellular tissue engineered vessel, n = sample size
Data Cut-off: January 15, 2024

Reviewer comment:
There is significant uncertainty regarding the safety and effectiveness of this product beyond 30 days due to the limited number of patients who have completed the expected follow up. The data in Table 16 is inclusive of updates received at the 120-day safety update. In the interim between the original data cutoff and the 120-day safety update, three patients were enrolled, one patient completed the study, and four patients were lost to follow up.

6.1.11 Efficacy Analyses

Efficacy analyses was conducted in the cohort of 54 patients who received ATEV as a conduit for non-iatrogenic extremity trauma.

6.1.11.1 Analyses of Primary Endpoint(s)

The primary efficacy endpoint was the rate of primary patency at 30 days. Twelve of the 54 patients enrolled in the extremity group who were not evaluated at Day 30 (Table 17).

Table 17. Reason For Not Having 30 Day Patency Data In the Extremity Group (n=54)

Reason for Early Termination (< 30 days)	n (%)
Total	12 (22.2%)[1]
Amputation	5 (9.3%)
Death	4 (7.4%)
Intraoperative thrombus/abandoned	2 (3.7%)
Loss to follow up	1 (1.9%)

Source: Adapted from clinical dataset and case summaries
Abbreviations: n = sample size
[1]13 patients were not evaluated at day 30. One patient lost to follow up following thrombosis at Day 20 counted as not patent.
Data Cut-off: January 15, 2024

All major amputations, deaths, loss to follow up and/or any other events that prevented assessment of primary patency were adjudicated by the Applicant's adjudication committee (AAC). For the purpose of imputing 30-day patency, the committee provided an assessment of the patency status of each patient who did not have 30-day patency data. One patient who deemed not patent on Day 20 was lost to follow up and not evaluated on Day 30. 12 patients were not evaluable at Day 30 and did not have evaluation of patency. The committee categorized three of these patients as nonpatent due to thrombus and ATEV explant. The remaining nine patients were adjudicated as patent by the AAC for purposes of calculating primary patency at day 30.

FDA similarly evaluated the patients without 30-day patency data to determine whether ATEV patency at 30 days would have been likely. Table 18 provides results of Humacyte and FDA adjudication for patients who were not evaluated at Day 30.

Table 18. Adjudication of Patients Who Were Not Evaluated at Day 30, Study V005 (n=13)

Patient ID	Day of Study Exit	Summary
		FDA and Applicant Agree on Patency at Day 30
(b) (6)	1	**Explanted** – intraoperative thrombosis, ATEV replaced by autologous vein.
(b) (6)	1	**Explanted** – intraoperative thrombosis, ATEV replaced by autologous vein.
(b) (6)	17	**Amputation** – infected ATEV explanted and replaced with PTFE following three thrombectomy procedures.
(b) (6)	20	**Loss to Follow Up** – Occlusion of ATEV on day 4 and considered not patent
		Patients who FDA Considered Non-Patent and Applicant Considered Patent
(b) (6)	4	**Amputation** – 2 ATEV grafts used (artery/vein). Vein repair disrupted day 4. Muscle necrosis and crush injury progression led to amputation. Pulse in graft palpated at time of amputation. No duplex scan done. Non-occlusive thrombus identified on explant histology
(b) (6)	4	**Death** – ischemic bowel 2° to initial injuries. ATEV patency last confirmed on day 2 by Duplex.
(b) (6)	4	**Death** – asystole while on ECMO. Radial pulse detected by Doppler ultrasound, with capillary refill time < 2 seconds just prior to the time of death. No ATEV evaluation.
(b) (6)	5	**Loss to follow up –** Pulse and/or doppler signals proximal and distal to injury on day 5.

(b) (6)	6	**Amputation** – Above knee amputation on Day 6 for nerve and soft tissue trauma. Intraluminal thrombi present on explant histology
(b) (6)	8	**Death** – sepsis, no ATEV evaluation
(b) (6)	9	**Amputation –** 2º to bone injury. No ATEV evaluation
(b) (6)	9	**Death** – sepsis, no ATEV evaluation
(b) (6)	19	**Amputation** – due to insensate, paretic foot. Dorsalis pedis, posterior tibialis pulse assessed prior to amputation. No ATEV evaluation

Source: Adapted from clinical dataset and case summaries
Data Cut-off: January 15, 2024
Abbreviations: ATEV = acellular tissue engineered vessel, ECMO = extracorporeal membrane oxygenation, n = sample size, PTFE = Polytetrafluoroethylene graft

Reviewer comment:
In discussion prior to BLA submission, FDA agreed to adjudication committee review of patients who underwent amputation or died prior to Day 30 to assess relationship to the ATEV. In all cases, the adjudication committee found that the ATEV was not the cause of amputation or death. The Applicant and the FDA discussed an imputation strategy to determine how best to evaluate subjects who were not evaluated at Day 30. No formal agreement was reached prior to BLA submission. In review of the 13 patients who were not evaluated at Day 30, FDA disagreed with imputation of Day 30 patency as the majority of patients discontinued from the study within the first week and all patients discontinued from the study by day 20. FDA findings in relation the Applicants are noted below:

- FDA agrees with non-patency for the three patients (b) (6) who were not patent due to thrombus and ATEV explant.
- FDA disagrees with the Applicant's conclusion of patency for one patient (b) (6) because the patient was amputated on Day 4 with worrisome explant histology including bacteria and thrombus present within the graft.
- FDA found no definitive assessment of patency prior to death or limb amputation to support the Applicant's conclusion of patency in seven patients.
- One patient was lost to follow up on Day 5 without imaging to support patency of the ATEV. The Applicant adjudicated this patient as patent. FDA statistical team advises that a patient who is lost to follow up should be considered a treatment failure and should not have patency imputed based on ATEV status before the patient was lost to follow up.

Table 19 summarizes the FDA analysis of primary patency at Day 30 for the primary efficacy analysis population (n=54).

Table 19. FDA Results for Primary Patency at Day 30 in the Extremity Group

Analysis	Patency Rate % (n/N)	95% CI
Primary efficacy analysis: Primary patency rate at Day 30 (While-on-treatment)[1]	66.7% (36/54)	53.4%, 77.8%
Supplementary analysis: Primary patency rate at Day 30 (Composite)[2]	66.7% (36/54)	53.4%, 77.8%
Supplementary analysis: Primary patency rate at Day 30 (Complete case)[3]	78.3% (36/46)	64.4%, 87.7%

Source: FDA statistical reviewer.
[1]les were handled using while-on-treatment strategy, corresponding to the 'Main Estimator'.
[2]les were handled using composite strategy, where missing 30-day patency due to IE was considered not patent, corresponding to 'Sensitivity Estimator 5'.
[3]les were excluded as a complete case analysis, corresponding to the 'Sensitivity Estimator 3'.
Abbreviations: N = study population, n = sample size
Data Cut-off: January 15, 2024

FDA's final determination of the rate of primary patency at Day 30 after FDA adjudication was 66.7% (95% CI: 53.4%, 77.8%). This patency rate was the same using either the while-on-treatment strategy (primary efficacy analysis) and the composite strategy (supplementary analysis). The same result is explained by many of the patients not having data to support patency. An additional supplementary analysis, the complete case approach, resulted in a primary patency rate of 78.3% (95% CI: 64.4%, 87.7%), which is likely inflated due to selection bias.

Reviewer comment:
The Applicant concluded a primary patency rate at Day 30, using the while-on-treatment strategy, of 84.3% (95% CI: 72.0%, 91.8%) which FDA did not agree with. The Applicant's while-on-treatment strategy overestimated the primary patency rate as the adjudicated patients were assumed as patent for Day 30 despite the fact many died or were amputated within the first 10 days after implant and had no definitive imaging assessments (i.e., doppler ultrasound, computed tomography angiography or magnetic resonance imaging) prior to death or amputation to confirm patency of the ATEV. One patient was also lost to follow up on Day 5 without any ATEV patency assessment. The FDA and the Applicant had previously discussed an imputation strategy on how best to characterize these intercurrent events in the assessment of patency, but no consensus was reached prior to BLA submission.

6.1.11.2 Analyses of Secondary Endpoints

Key Secondary Endpoints:

- Secondary patency at Day 30 after implant
- Conduit infection at Day 30 after implant
- Limb salvage rate at Day 30 after implant

Secondary Patency at Day 30

Secondary patency is defined as functional patency, with or without preceding successful interventional or surgical procedures to maintain or reestablish patency, until the ATEV is abandoned. Three patients were identified with secondary patency at Day

30 (b) (6) Adjudication for the 12 patients who were not evaluable at Day 30 in analyses of secondary patency remained consistent with adjudication of primary patency noted in section 6.1.11.1.

Table 20. Secondary Patency Rate at Day 30 in the Extremity Group, Study V005

Analysis	Patency Rate % (n/N)	95% CI
Key secondary efficacy endpoint: Secondary patency rate at Day 30 (While-on-treatment)[1]	72.2% (39/54)	59.1%, 82.4%
Supplementary analysis: Secondary patency rate at Day 30 (Composite)[2]	72.2% (39/54)	59.1%, 82.4%
Supplementary analysis: Secondary patency rate at Day 30 (Complete case)[3]	84.8% (39/46)	71.8%, 92.4%

Source: FDA statistical reviewer.
[1]Ies were handled using while-on-treatment strategy, corresponding to the 'Main Estimator'.
[2]Ies were handled using composite strategy, where missing 30-day patency due to IE was considered not patent, corresponding to 'Sensitivity Estimator 5'.
[3]Ies were excluded as a complete case analysis, corresponding to the 'Sensitivity Estimator 3'.
Abbreviations: N = study population, n = sample size
Data Cut-off: January 15, 2024

Reviewer comment:
The Applicant' concluded a secondary patency rate at Day 30, using the while-on-treatment strategy, of 90.2% (95% CI: 79.0%, 95.7%). As noted in the analyses of the primary patency endpoint, the Applicant's while-on-treatment strategy appears to overestimate the secondary patency rate as all patients with intercurrent events were adjudicated by the Applicant as patent for Day 30 despite the fact many died or were amputated within the first 10 days after implant and had no definitive imaging assessments prior to death or amputation.

When evaluating secondary patency using FDA's conservative adjudication of patency, the secondary patency rate of 72.2% would be considered clinically meaningful especially when taken in the context of patients who do not have alternative options for limb preservation.

Infection Rate at Day 30

In the BLA submission, the applicant identified one patient (1.9%) with infection in the 30 days following ATEV implantation. Infection was confirmed by positive culture on day 7. This patient (b) (6) underwent graftotomy on day 6 to remove a thrombus from the lumen of the ATEV and was taken back to the OR on day 7 following an episode of bleeding from the surgical site. In the OR, the surgeon reported that "sutures that had been placed at the graftotomy and puncture sites had pulled through." Histology from the excised ATEV indicated an infectious process starting in the surrounding tissues and eventually compromising the structural integrity of the ATEV.

Upon review of the case summaries, FDA identified a second patient who presented with bleeding from the surgical site on day 30 (b) (6) On Day 35, the ATEV was excised due to continued bleeding and the investigator noted that the infected wound had eroded into the ATEV graft. This infection was not counted toward the incidence of infection by

the Applicant. The relevant AE verbatim term "Erosion of proximal ATEV secondary to infected wound" was coded as "Vascular graft complication."

Reviewer comment:
The Applicant provided an infection rate at 30 days of 1.9%. Upon review of the case summaries, we found an additional patient who presented with bleeding from the surgical site on day 30 and was subsequently found to have clinical signs of ATEV infection and loss of ATEC integrity during surgical evaluation on day 35. Inclusion of the second patient yields an infection rate at day 30 of 3.7%. In both cases infection was only identified when the ATEV failed and revision was required. Additional infections were noted after day 30. Further discussion regarding infections noted after day 30 are included in section 6.1.12.5. We are concerned that identification of ATEV infection in this manner underestimates the true incidence of ATEV infection but note that there was no prespecified evaluation of infection included in the clinical protocol. Further evaluation of ATEV infection is recommended during the PMR observational study which will further characterize the risk of graft failure.

Amputation and Limb Salvage

There were eight amputations (14.8%) in the primary analysis population of 54 patients, five patients (9.3%) underwent amputation of the treated limb within the first 30 days and an additional three who underwent amputation of the treated limb by Month 36. The Applicant calculated a While-on-Treatment limb salvage rate of 90.2% at Day 30. Use of a while-on-treatment strategy does not take into consideration patients who are no longer at risk of amputation as a result of death. FDA therefore evaluated a limb salvage rate where patients who died, had ATEV 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.

Reviewer comment:
The amputation rate for synthetic graft patients derived from a meta-analysis pool was 24.3% (95% CI: 8.7%, 43.7%). Taking into consideration limitations of interpreting the amputation rate, the amputation rate throughout the study was similar to the rate reported in the literature and suggests a potential benefit for the non-vein, non-synthetic graft population which is equal to available therapies.

6.1.11.3 Subpopulation Analyses

The type of injury and length of vascular graft used have previously been evaluated in existing therapies (i.e., autologous vein and synthetic graft). Literature suggests that these factors may contribute to patency following implantation. Therefore, FDA conducted post hoc exploratory subgroup analyses to assess the patency rate by the ATEV length and blunt versus penetrating trauma.

Primary Patency at Day 30 by Graft Length

The length of the ATEV used is dictated by the vascular injury being repaired. A review of the literature did not identify an accepted graft length that would suggest a threshold for subgroup analysis. Based on the median length of the ATEV used in all patients, FDA conducted subgroup analyses by length, <15 cm versus ≥15 cm. One patient (b) (6)

(b) (6) did not have length recorded. Twenty-seven (69.2%) patients were patent at Day 30 for those with the ATEV <15 cm, compared to 9 (60.0%) with the ATEV ≥15 cm.

Reviewer comment:
A subgroup analysis was performed evaluating graft length effect on patency at day 30. Patients with grafts less than 15 cm had 9% higher patency at day 30, but confounders such as the small population analyzed and differences in underlying injury which contribute to different graft lengths make it difficult to conclusively comment on the effects of graft length on patency at 30 days.

Primary Patency at Day 30 by Trauma Type
A subgroup analysis by blunt or penetrating trauma was performed and demonstrated similar rates of patency between the two groups. The primary patency rate at Day 30 among patients with penetrating trauma was 67.7% (95% CI: 50.1%, 81.4%) compared to 65.2% (95% CI: 44.9%, 81.2%) in patients presenting with blunt trauma.

Reviewer comment:
Penetrating and blunt trauma require different approach to management and are associated with different rates of complications such as the incidence of compartment syndrome. A subgroup analysis of primary patency did not demonstrate a meaningful difference between these two trauma populations.

Infection by location of ATEV implantation
A subgroup analysis evaluating infection by location of ATEV graft in the upper or lower limb was performed and found that 2 patients of the patients who had ATEV placed in the lower limb and one of the patients who had ATEV placed in the upper limb developed graft infection.

Reviewer comment:
It is difficult to derive a meaningful conclusion regarding risk of infection as attributed to placement of ATEV in the upper or lower limb due to the small number of patients identified with infection. The findings are consistent with the general trends seen in the literature where vascular grafts placed in the lower limb are at higher risk of graft infection.

6.1.11.4 Dropouts and/or Discontinuations

Table 21 characterizes the number of patients treated by duration of follow up and provides reason for study discontinuation at any point during the 36-month follow up. 7 patients have completed the study and 37 discontinued prior to evaluation at 36 months. An additional 10 patients are ongoing at the time of data cut-off for 120-day safety report on January 15, 2024.

Table 21. Follow Up for Extremity Patients, Study V005 (n=54)

Parameter	n (%)
Duration of follow up, days	
Mean	334.6
Median (min, max)	188.5 (1, 1134)

Parameter	n (%)
Reason for early study discontinuation, n (%)	
Total	37 (68.5%)
Death	6 (11.1%)
Limb amputation	6 (11.1%)
Lost to follow up	15 (27.8%)
ATEV abandoned/explanted following loss of patency	9 (16.7%)
Withdrew consent	1 (1.9%)

Source: Applicant dataset and case summaries
Abbreviations: max = maximum, min = minimum, n = sample size
Data Cut-off: January 15, 2024

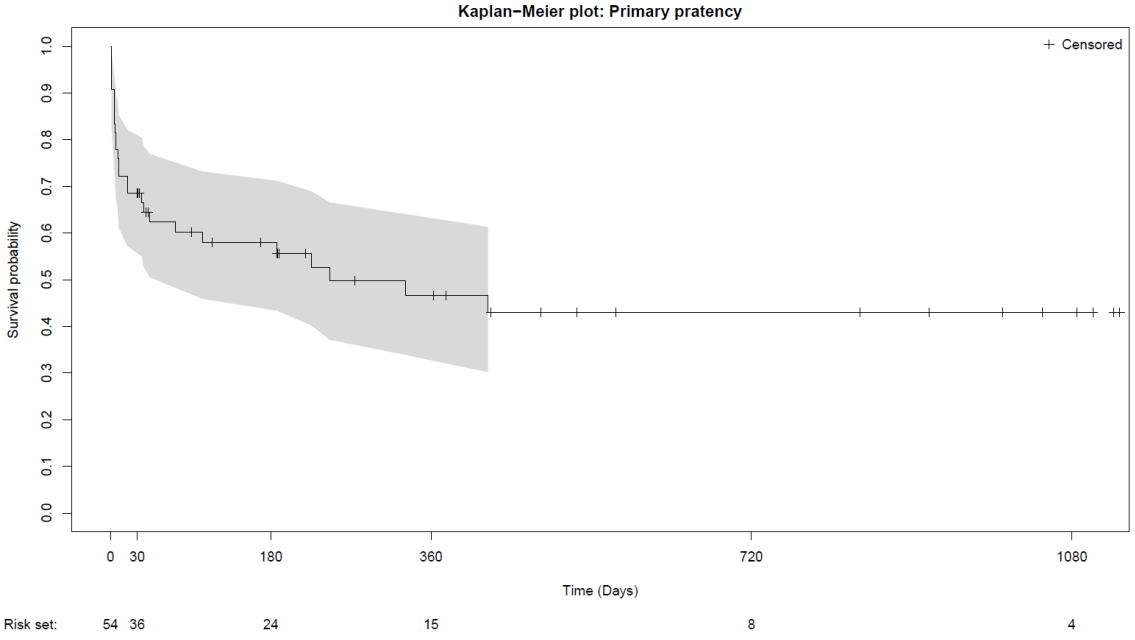
Reviewer comment:
Roughly one third of patients were lost to follow up in this clinical study. The high number poses serious threat to the validity of the results of this study. However, a review of the literature for extremity vascular trauma repair identifies this as a common problem within this patient population. It is expected that the Applicant will complete 36-month follow up for the 10 patients currently enrolled in this study and provide updated data on those patients following study completion.

6.1.11.5 Exploratory and Post Hoc Analyses

Long-Term Primary Patency Rate

The 30-day primary patency Kaplan-Meier (KM) estimate was 68.5% (95% CI: 57.2%, 82.1%) and the 6-month estimate was 58.0% (95% CI: 45.9%, 73.2%). The KM plot for the primary patency rate is illustrated in Figure 1.

Figure 1 Kaplan-Meier Plot for Primary Patency

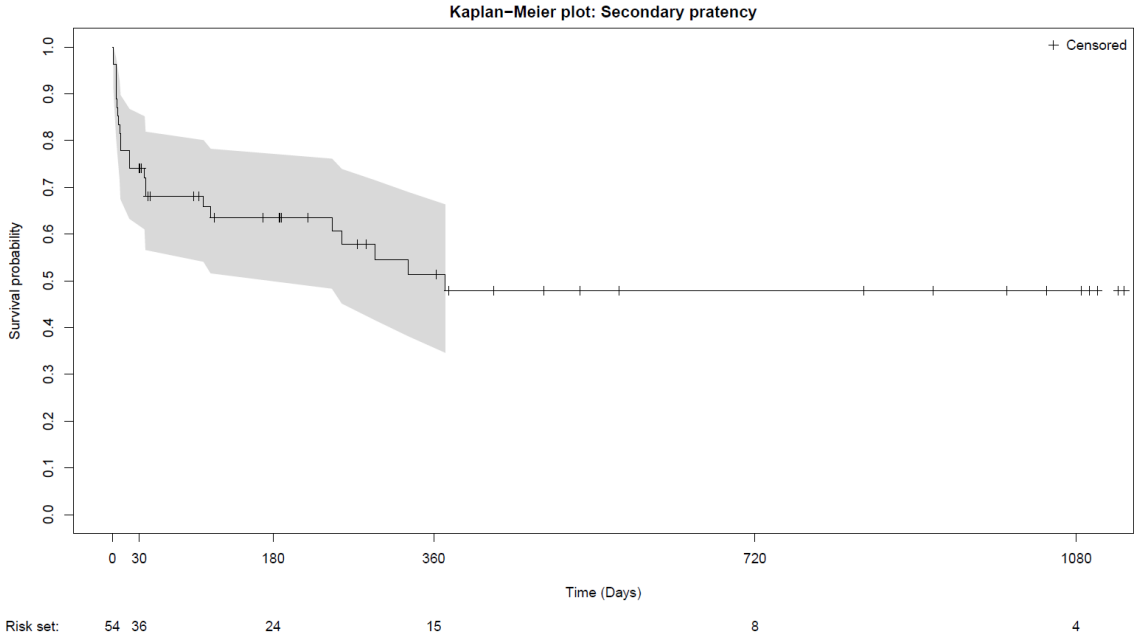


Source: FDA statistical reviewer.

Long-Term Secondary Patency Rate

The 30-day secondary patency KM estimate was 74.1% (95% CI: 63.3%, 86.7%) and the 6-month estimate was 63.5% (95% CI: 51.6%, 78.2%). The KM plot for secondary patency rate is illustrated in Figure 2.

Figure 2. Kaplan-Meier Plot for Secondary Patency



Source: FDA statistical reviewer

The KM analysis of primary and secondary patency are limited by the availability of long-term patency data after one year.

Reviewer comment:
The long-term patency rate was estimated by Kaplan-Meier Plot evaluate whether existing data could provide meaningful results regarding the long term patency of ATEV following implantation. These data suggest that further loss of patency can be expected beyond the Day 30 endpoint. However, due to the small number of patients enrolled and the high rate of patients who did not complete the 36 months of follow up, these estimates provide limited clinically meaningful conclusions.

6.1.12 Safety Analyses

6.1.12.1 Methods

Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities Version 26.0.

The Safety Population included all patients who received the ATEV in the study in both the extremity and torso/iatrogenic groups. Sub analysis of the safety population as either extremity group or torso/iatrogenic group is provided where applicable.

All AEs presented in the safety database were treatment-emergent adverse events (TEAEs), defined as any AEs that occur after the initiation of the surgical procedures to implant the ATEV or, if the AE was present at baseline, that the AE increased in severity after implantation of the ATEV.

The severity of AEs was graded according to the following definitions:

- Mild: Events require minimal or no treatment and do not interfere with the patient's daily activities.
- Moderate: Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: Events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.
- Life-threatening: Any adverse event that places the patient or participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
- Death: Death was related to the AE.

6.1.12.2 Overview of Adverse Events

Adverse event severity is classified in Table 22.

Table 22. Adverse Event Severity for Patients Enrolled in Study V005

Assessment	Extremity Group n=54	Torso/Iatrogenic Group n=17
Any AEs	53 (98.1%)[1]	17 (100%)
Any mild AEs	38 (70.4%)	15 (88.2%)
Any moderate AEs	34 (63.0%)	14 (82.4%)
Any severe AEs	27 (50.0%)	11 (64.7%)
Any life-threatening AEs	10 (18.5%)	3 (17.6%)
Any deaths	6 (11.1%)	6 (35.3%)
Any SAEs	28 (51.9%)	15 (88.2%)
Any AEs leading to premature ATEV removal	4 (7.4%)	1 (5.9%)
Any AEs leading to death	5 (9.3%)	6 (35.3%)

Source: Reviewer table derived from clinical data set, JMP 17.0
[1]one patient did not have any AEs reported
Abbreviations: AE = adverse event, n = sample size
Data Cut-off: January 15, 2024

Reviewer comment:
Severity of adverse events are similar to that seen with existing grafts, however a direct comparison cannot be made due to a paucity of data for current standard of care therapies. The reporting of adverse events is limited by the number of patients who discontinued from the study prior to the 36 month endpoint. Only 55.6% of patients were evaluated at Month 6 and 33.3% of patients were evaluated at 1 year. Therefore, late adverse events may not be accurately captured in the study data.

One patient in the extremity group died from an overdose and had two AEs reported. He recovered from a pseudomonas infection on day 24 prior to death on day 114. Adverse events appear to be underreported for this individual.

Adverse Reactions:
The subset of AEs that FDA determined to be reasonably associated with use of the investigational product are defined as adverse reactions. The most frequently occurring adverse reactions (≥3% of patients) reported following extremity implantation of the ATEV were thrombosis, pyrexia (fever), pain, anastomotic stenosis, rupture/anastomotic failure and ATEV infection (Table 23). Out of the five cases of anastomotic stenosis, two cases (3%) were assessed as serious adverse reactions.

Table 23. Adverse Reactions With a Frequency of ≥3% Following Implantation With the ATEV in Study V005*

Adverse Reaction	Extremity Patients, (n=54)**	Torso + Iatrogenic Patients, (n=17)
ATEV thrombosis	15 (27.8%)	5 (29.4%)
Pyrexia (fever)	9 (16.7%)	2 (11.8%)
Pain	8 (14.8%)	1 (5.9%)
Anastomotic stenosis	5 (9.3%)	1 (5.9%)
ATEV rupture	4 (7.4%)	3 (17.6%)
ATEV infection	3 (5.6%)	3 (17.6%)

Source: Reviewer table derived from clinical dataset and case summaries
*Adverse reaction frequency based on limited long-term data within the study population
**Extremity patients are with arterial repair in upper or lower limbs
Abbreviation(s): ATEV = acellular tissue engineered vessel, n = sample size
Data Cut-off: January 15, 2024

6.1.12.3 Deaths

A total of 12 patients died during the study. Six deaths occurred in the extremity group representing 10.9% of patients in this cohort. Of these six deaths in the extremity group, four patients died before their Day 30 visit. Two additional patients in this group died 42 days and 114 days after the ATEV implantation. A subgroup analysis evaluating type of trauma demonstrated no difference in number of deaths between patients presenting with penetrating or blunt trauma. All deaths were adjudicated as not related to the ATEV.

Table 24. Deaths on-Study for V005

Characteristic	Extremity Group (n=54)	All ATEV Group (n=71)
Death on-study[1]	6 (11.1%)	12 (16.9%)
Cause of death reported as an AE[2]	5 (9.3%)	9 (12.7%)
Time to death (days)		
N	6	12
Mean	29.7	224.3
Median	8.5	17.5
Min, Max	4, 114	4, 1119

Source: Adapted from clinical study report
[1] Values shown are cumulative over time; percentages for patient counts are calculated using the number of patients in the indicated patient group.
[2] Per protocol, fatal AEs were reported through Month 36, but only SAEs related to the ATEV were to be reported after Month 12; the death of 2 of the 10 patients in the All ATEV Group that happened after Month 12 were not reported as related AEs but are included in the total deaths
Abbreviations: AE = adverse event, ATEV = human acellular vessel, Max = maximum value, Min = minimum value, n = sample size, SAE, serious adverse event
Data Cut-off: January 15, 2024

Table 25. Deaths Within Study V005

Patient ID	Study Group	Day of Death	Cause of Death
(b) (6)	Extremity	4	Asystole despite ventilator and maximum pressor support for multiple injuries related to motorcycle accident.
(b) (6)	Extremity	4	Multiorgan failure and ischemic bowel as a result of initial injuries.
(b) (6)	Extremity	8	Shock, hypoxia and MRSA sepsis related to multiple gunshot wounds in the left chest, flank and bilateral extremities.
(b) (6)	Extremity	9	Septic shock and liver failure in setting of ischemic bowel related to MOI (multi rollover MVC).
(b) (6)	Extremity	39	Diffuse brain injury following second gunshot wound to head on Day 39 after the HAV placement.
(b) (6)	Extremity	114	Drug overdose.
(b) (6)	Torso/iatrogenic	11	Cardiac arrest in setting of active bleeding from the proximal ATEV anastomosis and common iliac artery.
(b) (6)	Torso/iatrogenic	12	Respiratory failure due to influenza A and acute encephalopathy
(b) (6)	Torso/iatrogenic	29	Cardiac arrest.
(b) (6)	Torso/iatrogenic	285	Cardiac arrest in setting of COVID-19 acute respiratory distress syndrome
(b) (6)	Torso/iatrogenic	1055	Unknown causes unrelated to ATEV
(b) (6)	Torso/iatrogenic	1119	Malignant neoplasm of middle lobe of right lung.

Source: Reviewer table derived from case summaries
Abbreviations: ATEV = acellular tissue engineered vessel, MOI = mechanism of injury, MRSA = Methicillin-resistant Staphylococcus aureus, MVC = motor vehicle crash

Narratives of Deaths in Study V005:

There were six deaths within the extremity group:

- *Patient* (b) (6) – 28-year-old male received the ATEV graft to the left superficial femoral artery to repair a worsening pseudoaneurysm approximately 1 month after a gunshot wound to affected area. The ATEV used due to concomitant injury to vein and poor quality or size of vein, and 1.5-centimeter superficial femoral artery (SFA) defect thought to be too large for primary repair. On Day 39 after the ATEV implant, the patient sustained multiple gunshots to the head, left upper extremity and proximal right lower extremity with obvious deformity and extensive bleeding. Supportive care withdrawn on Day 40 due to brain death.

- *Patient* (b) (6) – 41-year-old male sustained thoracoabdominal trauma (Grade 3 liver laceration and bilateral hemopneumothoraxes), brain injury and left upper extremity injuries in a motorcycle accident. Due to time limitations an autologous venous harvest was not possible and the ATEV was placed as a left brachial interposition graft. Patient remained hemodynamically unstable and on extracorporeal membrane oxygenation until he developed asystole on Day 4.

- *Patient* (b) (6) – 48-year-old male experienced a motor vehicle crush injury of the right lower extremity with subsequent occlusion of the right popliteal artery without reconstitution, open fracture of the right proximal tibia, traumatic compartment syndrome of right lower extremity, and closed fracture of upper end of right tibia. The ATEV was used as an interposition bypass graft from the right SFA proximally to tibioperoneal trunk distally. Recovery complicated by Pseudomonas infection of the surgical site, an abscess of the right lower

extremity, and acute kidney injury. Patient recovered and was discharged home before death on Day 128 due to a drug overdose.

- *Patient* (b) (6) – 19-year-old man who sustained multiple gunshot wounds to the right forearm, right thigh, and left and right buttocks. Two days after injury, the ATEV was placed in the superficial femoral artery. The following day continuous renal replacement therapy was initiated. The patient was returned to the operating room for bowel resection as a result of ischemic bowel secondary to the initial injuries. The following day the patient experienced the SAEs of acute respiratory distress syndrome and multiple organ failure on the day of death (Day 4).

- *Patient* (b) (6) – 72-year-old female with multiple injuries following a motor vehicle accident including bilateral rib fractures, displaced sternal manubrial fracture with small retrosternal hematoma, nondisplaced lumbar transverse process fractures right femoral intertrochanteric and diaphyseal fractures, displaced left distal femoral fracture, left lateral tibial plateau and inferior patellar pole fractures with a large joint effusion, and laceration of the left SFA at the level of the femoral fracture. Due to the bilateral injuries and length of ischemia time, it was decided to use the ATEV for repair of the left superficial femoral artery. Post operative course complicated by septic shock/necrotic distal small bowel, right colon, and gall bladder on Day 3, and a recurrence of septic shock on Day 8. She developed liver failure on Day 9 and became hemodynamically unstable. Despite increased pressor support, she died on Day 9.

- *Patient* (b) (6) – 30-year-old male who experienced multiple gunshot wounds to the bilateral upper extremities, left chest and flank. The ATEV was placed as an interposition graft in the brachial artery due to the complexity of global care. Patient developed necrotizing pneumonia and an acute pulmonary embolus on Day 5. On Day 8, the patient experienced worsening hypoxia and became increasingly hemodynamically unstable. Despite all interventions, including stress-dose steroids, vasopressors, neuromuscular blockade, and high-dose pressors, the patient's respiratory and hemodynamic status continued to worsen. The patient went into cardiac arrest and died on Day 8.

There were six deaths within the torso/iatrogenic group:

- *Patient* (b) (6) – 18-year-old man sustained gunshot wounds to the left hip and forearm. He sustained extensive venous injury to the right iliac vein and distal inferior vena cava was discovered and serially ligated. There was also a complete transection of the right external iliac artery at the level of the bifurcation and an incomplete transection of the left external iliac artery. He received a right iliac bypass with the ATEV. Second ATEV placed the next day from the common iliac to the external iliac. On Day 25 the patient developed a thrombosis of the left iliac artery ATEV graft. The thrombosis was attributed to the patient's hypercoagulable state secondary to critical illness. The patient experienced a cardiac arrest on Day 29 for which he was unable to recover.

- *Patient* (b) (6) – 61-year-old male with medical history that included Li-Fraumeni syndrome, prostate cancer, bladder cancer and lung adenocarcinoma metastatic to the brain, which was resected and treated with radiation in (b) (6) Treated

for sarcoma of the left thigh, due to concerns of seeding normal tissue with tumor cells the saphenous vein was not harvested and instead the ATEV was implanted as a left superficial femoral artery. The ATEV was documented as functional on Day 841. Study participation ended on Day 1119 due the patient's demise. Cause of death was malignant neoplasm of middle lobe of right lung.

- *Patient* (b) (6) – 24-year-old male sustained gunshot wounds to the abdomen. Due to concomitant vein injury, and time limitation, an autologous venous harvest was not possible. The ATEV was implanted from right mid common iliac artery to right external iliac artery. Sepsis of unknown origin on Day 8 and treated empirically. During hospitalization, the patient developed a pulmonary embolism. Cardiac arrest on Day 11 in setting of active bleeding from the proximal anastomosis of the ATEV and common iliac artery, and an infected hematoma. There was no return of spontaneous circulation, and the patient was pronounced dead. The graft was noted to be intact without mechanical defect other than failure of the suture line. The surgeon reported that there were signs of localized infection at the graft area however cultures or histological analysis of the ATEV were not performed.

- *Patient* (b) (6) – 73-year-old female with ESRD, who developed delayed onset dialysis access steal syndrome. Patient had the ATEV implanted to resolve a severe steal syndrome from her AV access, and dialysis was performed twice after implantation. One week after implantation on Day 12, the patient presented with sepsis, and died from respiratory failure due to influenza A and acute encephalopathy.

- *Patient* (b) (6) – 58-year-old male with ESRD received a ATEV Graft to remedy a steal syndrome on their arteriovenous fistula (AVF), which resulted in better flow after the procedure. Before the patient's Month 18 visit, a serious stenosis of the ATEV bypass was diagnosed and was subsequently treated with angioplasty, thus considered resolved. The patient's digits, hand and arm were salvaged. The patient continued on study until Month 33, and no other interventions were performed. Before the patient could complete the scheduled End-of-Study visit, the study site received a report that the patient had died of unknown causes that were unrelated to the ATEV.

- *Patient* (b) (6) – 54-year-old female with ESRD who developed symptomatic vascular steal syndrome from a left brachio-basilic AVF, due to a stenosis on the brachial artery. History notable for hypertension, asthma, anxiety and bipolar I disorder, obesity, anemia, agoraphobia, steal syndrome, keloid formation, osteoarthritis, cervical radiculopathy, herpetic gingivostomatitis, yeast infection, surgical decompression of cervical spine, gastroesophageal reflux disease, arteriovenous fistula surgery, gastric bypass, moderate mitral valve incompetence, and left ventricular hypertrophy. Inadequate size and quality of available veins led to the use of the ATEV to bypass the stenosis of her brachial artery for an iatrogenic indication. Primary patency at the Day 30 visit confirmed by Doppler Ultrasound. Day 169 – stenosis at the anastomosis. Day 285 – cardiac arrest in setting of COVID-19 acute respiratory distress syndrome.

Reviewer comment:
Review of the case summaries for the patients who died during study V005 reveals death often related to the initial mechanism of injury for most patients. Within the extremity group, no deaths were assessed as related to the ATEV.

Patient (b) (6) died following failure of the proximal ATEV anastomosis with the common iliac artery. While the graft was noted to be intact without mechanical defect other than failure of the suture line, the surgeon reported signs of localized infection at the graft during resuscitation however this was never confirmed. This death was adjudicated by the Applicant's adjudication committee as not related to the HAV, however this was done without evaluation of the graft and the segment with suture failure.

6.1.12.4 Nonfatal Serious Adverse Events (SAE)

A total of 43 out of 71 patients experienced 135 nonfatal SAEs during the study. Within the extremity group, 28 out of 54 patients experienced 78 SAEs during the study. Nonfatal SAEs are categorized in Table 27.

Table 26. Other Nonfatal Serious Adverse Events in Study V005

SAE Preferred Term	Extremity Group (n=54)	Torso+Iatrogenic Group (n=17)	All ATEV Group (n=71)
Any severe AEs	27 (50.0%)	11 (61.1%)	38 (53.5%)
Any nonfatal SAEs	28 (51.9%)	15 (83.3%)	43 (60.6%)
Vascular graft thrombosis	11 (20.4%)	1 (5.6%)	12 (16.9%)
Vascular graft complication[1]	2 (3.7%)	3 (16.7%)	5 (7.0%)
Anastomotic stenosis	3 (5.6%)	1 (5.6%)	4 (5.6%)
Wound infection	4 (7.4%)	0	4 (5.6%)
Muscle necrosis	3 (5.6%)	1 (5.6%)	4 (5.6%)
Postoperative wound infection	3 (5.6%)	0	3 (4.2%)
Shock hemorrhagic	3 (5.6%)	0	3 (4.2%)
Cardiac arrest	1 (1.9%)	2 (11.1%)	3 (4.2%)
Respiratory failure	1 (1.9%)	2 (11.1%)	3 (4.2%)
Acute kidney injury	2 (3.7%)	1 (5.6%)	3 (4.2%)
Vascular graft haemorrhage[2]	2 (3.7%)	0	2 (2.8%)
Vascular graft occlusion	2 (3.7%)	0	2 (2.8%)
Vascular pseudoaneurysm ruptured	0	2 (11.1%)	2 (2.8%)
Sepsis	0	2 (11.1%)	2 (2.8%)
Soft tissue infection	1 (1.9%)	1 (5.6%)	2 (2.8%)
Hypervolemia	0	2 (11.1%)	2 (2.8%)
Muscle necrosis	3 (5.6%)	1 (5.6%)	4 (5.6%)
Cardiac arrest	1 (1.9%)	2 (11.1%)	3 (4.2%)
Respiratory Failure	1 (1.9%)	2 (11.1%)	3 (4.2%)
Anemia	1 (1.9%)	1 (5.6%)	2 (2.8%)
Hypervolemia	0	2 (11.1%)	2 (2.8%)
Anemia	1 (1.9%)	1 (5.6%)	2 (2.8%)
Abscess limb	1 (1.9%)	0	1 (1.4%)
Acute hepatic failure	1 (1.9%)	0	1 (1.4%)
Arterial hemorrhage	0	0	0 (0%)

Source: Clinical study report
[1]Vascular graft complication includes patients who had anastomotic breakdown following ATEV placement.
[2]Vascular graft hemorrhage includes patients who had bleeding from a mid-graft rupture or loss of ATEV integrity
Data Cut-off: January 15, 2024
Abbreviations: AE = adverse event, ATEV = acellular tissue engineered vessel, n = sample size, SAE = serious adverse event

Reviewer comment:

Vascular graft thrombosis is the most common nonfatal serious adverse event in study V005 consistent with expected findings from existing vascular graft options (i.e., autologous vein or synthetic graft). Vascular graft hemorrhage and vascular graft complications both include events where patients experienced bleeding from the ATEV following loss of integrity due to either mid-graft rupture or anastomotic failure. These events are discussed further in section 6.1.12.5.

6.1.12.5 Adverse Events of Special Interest

Adverse events of special interest (AESI) were defined in the statistical analysis plan as AEs of anastomotic failure or rupture of the ATEV, ATEV infection, thrombosis, pseudoaneurysm formation, and aneurysm formation. The frequency of the various AESI in the different patient groups is shown in Table 27. In the extremity group, 15 out of 54 patients (27.8%) experienced a thrombotic event involving the ATEV, and 5 out of 54 extremity patients (9.3%) developed anastomotic stenosis of the ATEV. Other complications of the ATEV include anastomotic failure or rupture (n=4, 7.3%), pseudoaneurysm (n=2, 3.7%), and aneurysm (n=1, 1.9%). These numbers reflect identification of AESI based on review of the clinical case summaries.

Table 27. Adverse Events of Special Interest, Study V005

AESI Assessment	Extremity Group n=54	Torso/Iatrogenic Group n=17
AESI		
Any Infection	23 (42.6%)	12 (70.6%)
Wound infection	16 (29.6%)	5 (27.8%)
ATEV Infection	3 (5.6%)	3 (17.6%)
ATEV anastomotic failure or rupture	4 (7.4%)	3 (17.6%)
ATEV pseudoaneurysm	2 (3.7%)	1 (5.9%)
ATEV aneurysm	1 (1.9%)	0 (0%)
ATEV occlusion/thrombosis	15 (27.8%)	5 (29.4%)

Source: Reviewer table derived from individual case summaries of patients
Abbreviations: AESI = adverse event of special interest, n = sample size
Data Cut-off: January 15, 2024

Reviewer comment:
Following FDA review, the values for ATEV infection and ATEV rupture were found to be different.

- The applicant had identified two ATEV infections based on positive cultures. Following review of case summaries for enrolled patients, we identified an additional case in which the surgeon reported clinical signs of ATEV infection at the time of surgical revision.
- The Applicant classified one rupture as vascular graft complication which was reclassified to rupture for the purposes of analysis. The four patients in the extremity group listed as anastomotic failure or rupture in Table 28 include this reclassification.

Infection

All patients received prophylactic antibiotics. Two patients (3.7%) out of 54 in the extremity vascular group had evidence of ATEV infection in the 30 days following ATEV implant as discussed in section 6.1.11.2. One additional patient had evidence of ATEV infection on day 35, yielding an ATEV infection rate of 5.6% (95% CI: 3.0%, 17.9%) in

the 54 patients over the course of the study. Three additional cases, based on FDA review of the case summaries for each patient were identified. Table 28 demonstrates the confirmed ATEV infection rates in study V005. ATEV infection in the study V005 was only noted in cases where culture, histology or surgical evaluation of the ATEV was possible at the time of surgical reintervention. Narratives for the three infections in the extremity group and three patients with infection in the torso/iatrogenic group are included below.

Table 28. Identified Infections for Patients, Study V005

Patient ID	Study Group	Day of ATEV Infection	Comment
(b) (6)	Extremity	7	infection identified by graft cultures taken on Day 7 following mid-graft rupture of the ATEV at site of previous thrombectomy. ATEV explanted and infection confirmed on histopathology.
(b) (6)	Extremity	35	infection identified by graft cultures taken on Day 35 following mid-graft rupture of the ATEV in the setting of overlying wound infection and subsequent graft air exposure.
(b) (6)	Extremity	36	infection identified on Day 36 when the investigator noted erosion of proximal ATEV secondary to infected wound during reintervention required due to bleeding from ATEV proximal anastomosis failure.
(b) (6)	Torso/iatrogenic	11	Clinical signs of graft infection noted by the surgeon in setting of active bleeding from the proximal ATEV anastomosis and common iliac artery.
(b) (6)	Torso/iatrogenic	11	ATEV explanted following mid-graft rupture on day 10. Histology report states “it is likely that the graft disruption was caused by a severe infectious process that extended into the graft from the surrounding infected and necrotic host tissues”
(b) (6)	Torso/iatrogenic	40	Infection identified by histology demonstrating gram positive cocci in the adventitia and abluminal surface of the graft following ATEV explant due to ruptured pseudoaneurysm and bleeding.

Source: Reviewer table derived from case summaries
Abbreviations: ATEV = acellular tissue engineered vessel

Narratives of Infections in Study V005:

There were three infections within the extremity group:

- *Patient* (b) (6) – 65-year-old male received 28.0 cm ATEV to repair the right popliteal artery due to poor quality and size of veins following motor vehicle accident. Patient underwent subsequent open thrombectomy on Day 6. Mid-graft suture failure on Day 7. “Sutures that had been placed at the graftotomy, and puncture sites had pulled through” as per the case summary. 80% of distal ATEV excised and replaced with polytetrafluoroethylene (PTFE) graft. Subsequent right above knee amputation on Day 17.
  Culture: Day 7 ATEV culture positive for pseudomonas aeruginosa and Enterobacter cloacae
  Histology: Rod-shaped Gram-negative bacteria were observed in the thrombus, adventitia, and along the abluminal surface of the graft. In one section, rare rod-

shaped Gram-positive bacteria also were present in the thrombus. “Appearance of inflammatory cells and gram-negative bacteria in the adventitia and extending to the abluminal surface of the graft indicated an infectious process starting in the surrounding tissues and eventually compromising the structural integrity of the ATEV [Investigational product].”
Clinical: No comment from investigator

- *Patient* (b) (6) – 18-year-old male received 7.0 cm ATEV to repair the right axillobrachial artery due to size mismatch of autologous vein following machinery accident. The patient experienced a mid-graft rupture on Day 35 following overlying wound breakdown and subsequent air exposure. The patient ultimately required amputation on Day 43.
  Culture: Positive culture from graft segment explanted on Day 35
  Histology: Bacteria were not observed with Gram stain.
  Clinical: no comment from investigator
  Additional notes: This infection was not counted toward incidence of infection by the Applicant because the onset was after Day 30.

- *Patient* (b) (6) – 20-year-old male received 35.0 cm ATEV to repair right popliteal artery following motor vehicle accident. The native saphenous vein could not be used due to pre-existing stenosis. The patient developed graft thrombosis 5 days after surgery and again on Day 19 which required thrombectomy. On Day 30, the patient had bleeding from the surgical site with no source identified. On Day 35, the patient had significant bleeding with accompanied cognitive decline requiring resuscitation code and intubation. Angiography on Day 36 demonstrated active bleeding from the proximal anastomosis. ATEV replaced with autologous vein.
  Culture: None provided
  Histology: None
  Clinical: Investigator noted that the infected wound had eroded into the ATEV graft.
  Additional note: This infection was not counted toward the incidence of infection by the Applicant. The relevant AE verbatim term “Erosion of proximal ATEV secondary to infected wound” was coded as “Vascular graft complication.”

There were three infections within the torso/iatrogenic group:

- *Patient* (b) (6) – 62-year-old male received 8.5 cm ATEV to repair right superficial femoral artery due to concomitant venous injury following iatrogenic injury during tumor resection. Contained rupture of distal pseudoaneurysm on Day 30 with subsequent abscess formation and bleeding on Day 40. Graft replaced with interposition graft.
  Culture: None provided
  Histology: Gram-positive cocci observed in the adventitia and abluminal surface
  Clinical: No comment from investigator.

- *Patient* (b) (6) – 24-year-old male received 4.0 cm ATEV implanted from right mid common iliac artery to right external iliac artery due to concomitant vein injury and time limitation following gunshot wounds to the abdomen. Sepsis of unknown source was diagnosed on Day 8 and treated empirically. During

hospitalization, the patient also developed a pulmonary embolism. Cardiac arrest occurred on Day 11 in setting of active bleeding from the proximal anastomosis of the investigational graft and common iliac artery, and an infected hematoma in the area of the previously closed retroperitoneum. The graft was noted to be intact without mechanical defect other than failure of the suture line. The surgeon reported signs of localized infection at the graft area. There was no return of spontaneous circulation, and the patient was pronounced dead.
Culture: Fecal contaminant in abdominal cavity
Histology: None available. Graft reportedly explanted and sent for analysis but specimen never received in histology lab.
Clinical: Signs of localized infection at graft area noted by surgeon

- *Patient* (b) (6) – 20-year-old male received 31 cm ATEV to repair left subclavian artery due to time limitations following a motorcycle accident. Midgraft rupture of the subclavian artery on Day 10 with amputation and excision of graft on Day 11.
  Culture: none provided
  Histology: The histology report states "It is likely that the graft disruption was caused by a severe infectious process that extended into the graft from the surrounding infected and necrotic host tissues, ultimately causing degradation and disruption of the graft."
  Clinical: no comment by the investigator

Reviewer comment:
The ATEV infection rate includes patients who had graft infection confirmed by either positive graft culture, histology demonstrating bacteria in the graft or signs of graft infection noted by the surgeon. In all three cases, the identification of infection requires exposure of the ATEV through surgical reintervention. Despite infection being an AESI, there were no protocol specified evaluation of infection before Day 30 and all patients received prophylactic antibiotics. Therefore, the observed ATEV infection rate in the extremity group of 5.6% may not be an accurate assessment of the true ATEV infection rate.

There were three cases of ATEV infection that contribute to the 5.6% incidence of infection in the extremity group. However, there were two additional cases where ATEV infection in the extremity was plausible, but definitive data were not provided.

- Patient (b) (6) had an overlying wound infection positive for Acinetobacter treated with debridement, wound vacuum-assisted closure placement, and broad-spectrum antibiotics (cefepime). He subsequently developed pseudoaneurysm rupture on Day 19 leading to ATEV ligation and oversewing of the distal stump. There was no evaluation to see if erosion of the underlying graft due to infection may have contributed to the loss of ATEV integrity.
- Patient (b) (6) "developed ATEV infection secondary to surrounding infected necrotic tissue" and subsequent mid-graft rupture. The location of the ATEV infection is not further specified and could have occurred in the torso or the extremity or spanned both. This patient was classified as a torso injury in the absence of knowledge that the infection occurred in the axillary portion of the repair, the patient was included in the torso group for the purpose of safety analysis and the infection did not count toward infections in the extremity group.

Also contributing to uncertainty regarding the incidence of infection is the assumption that patients leaving the study within the first week after placement of the ATEV would remain infection free. This is corroborated by two patients with ATEV infection (b) (6) and (b) (6) who became symptomatic on Day 30 and 36 and who were confirmed to have infection when the ATEV was ultimately explanted.

One paper that enrolled civilian trauma patients with an injury severity score (mean: 21.1, median, 17.5) very similar to patients in study V005 (mean: 20.8, median, 17.0), did not report any graft infections following implantation of autologous vein graft (Stonko et al. 2022). Civilian trauma literature describes a synthetic graft infection rate of 2.5% which may provide an appropriate benchmark for interpreting the observed infection rate in study V005. Cross study comparisons do not identify better or worse outcomes between the HAV and synthetic grafts; nonetheless, the data do not support the Applicant's claim that the ATEV is infection resistant.

Rupture/Anastomotic Failure

In the provided case summaries, the Applicant has included any loss of integrity of the ATEV due to either anastomotic failure or a disruption in the continuity of the graft as a rupture. Four patients out of 54 in the Extremity Group implanted with the ATEV placed as a conduit in study V005 had post transplantation loss of ATEV integrity which resulted in bleeding from the ATEV site. One patient developed mid-graft rupture in the presence of overlying wound infection which eroded the overlying tissue and led to exposure of the ATEV to air. One patient had failure of sutures placed mid-graft following thrombectomy procedure. An additional two patients in the extremity group had loss of ATEV integrity at either the proximal or distal anastomosis site. Details of an additional four patients who developed mid-graft rupture or anastomotic failure from the ATEV in the torso/iatrogenic group or from study V017 are included in Table 29.

Table 29. Patients With Rupture or Anastomotic Failure Within Study V005 or V017

Group, Study	Patient ID	Day of Rupture/ Failure	Length of ATEV Used (cm)	Summary
Extremity, V005	(b) (6)	10	28.0	Repair of popliteal artery with subsequent open thrombectomy on Day 6. Mid-graft suture failure on Day 10 with positive explant culture. Subsequent amputation Day 17.
Extremity, V005	(b) (6)	19	6.5	Distal anastomosis pseudoaneurysm rupture of axillary artery on Day 19. Graft oversewn with sufficient collateral circulation.
Extremity, V005	(b) (6)	35	7.0	Mid-graft rupture of axillobrachial graft on Day 35 following overlying eschar and air exposure. Subsequent amputation on Day 43.
Extremity, V005	(b) (6)	30	35.0	Proximal anastomosis rupture of popliteal artery on Day 36. Replaced with autologous vein.
Torso/iatrogenic, V005	(b) (6)	10	31.0	Mid-graft rupture of the subclavian artery on Day 10 with amputation and excision of graft on Day 11.
Torso/iatrogenic, V005	(b) (6)	11	4.0	Proximal anastomosis failure on Day 11 in setting of infected hematoma secondary to fecal contaminant. Patient death on Day 11.
Torso/iatrogenic, V005	(b) (6)	30	8.5	Contained rupture of distal pseudoaneurysm on Day 30 with subsequent abscess formation and bleeding on Day 40. Graft replaced with interposition graft.
Extremity, V017	(b) (6)	8	34.0	Mid-graft rupture of the superficial femoral artery on Day 8 and removed on Day 13. Signs of graft infection noted by surgeon during reintervention on Day 12.

Source: Clinical case summaries

Reviewer comment:
The term rupture is used to include both instances of mid-graft loss of ATEV integrity as well as anastomotic failure consistent with the term used in the Applicant's case summaries. There is conflicting data on the true incidence of ruptures when using autologous vein or synthetic grafts, however the literature suggests a range of 0-6%. It is generally accepted that overlying wound infection can spread into an adjacent vessel increasing risk of graft rupture. Based on the data provided in this BLA, the rate of graft rupture is 7.4% within the 54 patients in the extremity group and 9.9% for all patients treated with ATEV as a conduit in study V005.

6.1.12.6 Clinical Test Results

Duplex ultrasound examinations were performed to detect ATEV stenosis and aneurysm development and evaluate patency. For the primary efficacy endpoint evaluated at Day 30, 35 out of 42 patients (83.3%) had evaluation with duplex imaging. At Month 6, 23 of 32 (71.9%) evaluable patients had duplex imaging evaluation of the ATEV.

Reviewer comment:

Accurate evaluation with Duplex imaging is limited as the imaging studies varied across institutions. Complete evaluation of the ATEV inclusive of doppler flow and evaluation of structural abnormalities following transplantation (i.e., pseudoaneurysms, aneurysms) was not conducted across all study sites. Central review of imaging did not occur during this study. Incomplete evaluation of blood flow and potential structural abnormalities may overrepresent patency of the ATEV and underrepresent the incidence of structural abnormalities.

6.1.12.7 Dropouts and/or Discontinuations

37 patients discontinued prior to study completion in the extremity group:

- 15 lost to follow up
- 6 deaths
- 6 Limb amputation with ATEV removal
- 9 ATEV thrombosis with collateral flow
- 1 withdrew consent

6.1.13 Study Summary and Conclusions

Evaluation of primary and secondary efficacy endpoints for study V005 demonstrates effectiveness of this product with rates of 66.7% and 72.2% at Day 30, respectively. Data from this study also provides evidence of a clinically meaningful benefit in the indicated population with a limb salvage rate of 75.9% at Day 30. The complexity lies in the safety profile of this product. The Applicant has provided data from a small cohort of 54 patients who have had the ATEV placed in the extremities. The observed rate for anastomotic failure and rupture in the extremity group (7.4%) and across all patients in both the extremity and torso/iatrogenic group (9.9%) represents a significant risk which requires further characterization.

6.2 Study #2 – CLN-PRO-V017

Study Title: An Observational Multicenter Study to Evaluate the Safety and Efficacy of Humacyte Human Acellular Vessel [ATEV] in a Real World Setting for Arterial Replacement or Reconstruction in Ukrainian Patients with Life or Limb-threatening Vascular Trauma."

Clinical Trial Registry Identifiers: NCT05873959

The study V017 provides data analysis from a real world evidence study evaluating the use of ATEV administered as Humanitarian aid in Ukraine. In June of 2022, Humacyte shipped 30 ATEV units to 5 hospitals in Ukraine. 19 ATEVs have been implanted between June 2022 and July 31, 2023 under the Humacyte Humanitarian Aid Program.

Reviewer comment:
This study serves as supportive evidence of safety and efficacy of the ATEV. However, this study does not provide substantial evidence of safety and efficacy which can be combined with the previous study due to the evaluation of this product in a different population comprised of lower severity injuries often treated in a not urgent manner. While data for 30-day patency was collected for enrolled patients, lack of active monitoring underestimates the incidence of adverse events and safety signals in this retrospective evaluation.

6.2.1 Objectives (Primary, Secondary, etc)

Primary Efficacy Objective:

- To determine the rate of primary patency at 30 days after the ATEV implantation.

Secondary Efficacy Objectives:

- To determine the rate of affected limb salvage/amputations up to 6 months after the ATEV implantation
- To determine the patency of the ATEV (primary, primary assisted and secondary) up to 6 months after implantation

6.2.2 Design Overview

This study is a retrospective, observational, multicenter study to evaluate the safety and efficacy of the ATEV in a real-world setting, for arterial replacement or reconstruction in patients with life- or limb-threatening vascular trauma sustained during the Ukraine-Russia conflict. The study was conducted at three sites across Ukraine.

A total of 19 patients (≥18 to ≤85 years old) received the ATEV for arterial replacement or reconstruction following vascular trauma.

6.2.3 Population

The inclusion and exclusion criteria are the same as those used in study V005 and included in section 6.1.3.

6.2.4 Study Treatments or Agents Mandated by the Protocol

All patients received a ATEV graft manufactured at Humacyte, Durham, North Carolina which was cut to the length required for arterial repair ranging in length from 1 to 40 cm.

6.2.5 Directions for Use

The directions for use are the same as those used in study V005 and included in section 6.1.5.

6.2.6 Sites and Centers

Thirty ATEV units were shipped to five hospitals in Ukraine for Humanitarian use. The Applicant states that 19 ATEV units have been used in three sites located in Ukraine in study results for study V017.

6.2.7 Surveillance/Monitoring

This was a retrospective observational study. No active monitoring was included. Patients who had vascular injury and received the ATEV are appropriate for inclusion into the study; they were informed about the study and invited to sign an informed consent to allow retrospective access to their data. Following informed consent provided by the patient already implanted with the ATEV, a retrospective review of their data was completed, as applicable and available.

Table 30. Schedule of Events, Study V017

	Visit 1	Post-implantation D30	Post implantation after D30 and/or at M6	Post implantation after M6 and/or until end of study
Informed consent	X			
Medical history and nature of trauma	X			
Concomitant medication	X	X	X	X
Physical examination [1]	X	X	X	X
Pre-op Ultrasound or CT angiography	X			
Eligibility (inclusion/exclusion criteria)	X			
Documentation on HAV implantation and intraoperative confirmation of patency [2]	X			
Documentation of surgery and any complications	X			
Duplex ultrasound [3]		X	X	X
CT angiography		X	X	X
SAEs and AESI	X	X	X	X
Documentation of HAV interventions (if available)	X	X	X	X

Abbreviations: AEs, adverse events; ET, early termination; HAV, human acellular vessel; M, month

1. Physical examination may include clinical exam of the operative limb and HAV at all post-operative visits (incl. patency assessment) and physical exam to evaluate AEs; include distal vascular bed at the discretion of the investigator in the best interest of the patient.
2. Determination of intraoperative HAV patency by physical exam, Doppler, angiography or ultrasound at the discretion of the investigator in the best interest of the patient.
3. An alternative imaging method (CTA, MRI, etc.) may have been substituted for duplex ultrasound at the discretion of the investigator in the best interest of the patient.

Source: Appendix 1 Protocol CLN-PRO-V017 v1.0 in 16.1.1
Abbreviations: AESI = adverse event of special interest, CT = computed tomography, SAE = serious adverse event

Reviewer comment:
As this was a retrospective observational study, no active monitoring was included. The Applicant has provided 6 months of data for most patients, however, there remains a high possibility of missing data which can result from a patient presenting to another medical institution for treatment during this time period. Review of case summaries provides documentation of this occurring after day 30 in two patients.

6.2.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint:

- Primary ATEV patency at Day 30 after implant

Key Secondary Efficacy Endpoints:

- Secondary patency at Day 30 days after implant
- Conduit infection at Day 30 after implant
- Limb salvage rate at Day 30 after implant

Other Secondary Endpoints:

- ATEV interventions to maintain/restore patency
- Long-term primary patency
- Long-term secondary patency
- Long-term limb salvage

6.2.9 Statistical Considerations & Statistical Analysis Plan

Study Hypothesis:
This was a retrospective, observational study in which patients received the ATEV. There was no formal hypothesis testing, no prespecified significance level and Type 1 error control, and no multiplicity adjustment. Descriptive statistical analysis was performed for safety and efficacy data.

Sample Size:
No formal power calculations were performed. The sample size was determined by the number of patients available who consented to the study at each site. Analyses of the primary and key secondary efficacy endpoints were the same as described in Section 6.1.9 for study V005. Missing data and intercurrent event handling strategies were also the same as study V005.

Analysis Population:
The analysis population included all patients who underwent non-iatrogenic arterial vascular repair with a ATEV in an extremity. One patient who underwent ATEV placement as a patch for iatrogenic repair was excluded from analysis.

6.2.10 Study Population and Disposition

Insert text here

6.2.10.1 Populations Enrolled/Analyzed

In total, 19 patients received the ATEV in Ukraine under the Humanitarian program. Two patients were lost to follow up and could not be contacted for informed consent and inclusion in this study.

Among the remaining 17 patients, 16 patients were included in the extremity group for primary analysis. One patient had iatrogenic injury to the limb and was excluded.

6.2.10.1.1 Demographics

All 16 patients (100.0%) in the extremity group were White males. The median age was 30.5 years, with a range of 22 to 54 years, and a mean age of 34.2 (SD 9.0). All patients were non-Hispanic.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Distribution of type of trauma in the extremity group was 87.8% penetrating trauma and 12.5% blunt trauma. Blasts and shrapnel injury represented the most frequent cause for vascular trauma in this study, involving 12 out of 16 patients (75%), followed by gunshot wounds in 2 patients (12.5%). Data from this study is limited by retrospective collection of data from patients who were treated with the ATEV on a humanitarian basis. The majority of patients had sustained traumatic injuries and were relatively young. Comorbid conditions were infrequent in this population.

Injury severity and baseline medical characteristics for the 16 patients in the extremity group are summarized in Injury Characteristics, Study V017, respectively. The majority of patients sustained injury to the femoral artery (68.8%) in the lower extremity (87.5%). The majority of patients were categorized severe (31.3%) on the AIS, followed by

serious (18.8%) and critical (12.5%). Four patients had missing AIS. The median ISS was 16, with a minimum score of 1 and a maximum score of 73.

Table 31. Injury Severity, Study V017

Parameter	Extremity Group n=16
Abbreviated Injury Scale (AIS), n (%)	
Minor	2 (12.5%)
Serious	3 (18.8%)
Severe	5 (31.3%)
Critical	2 (12.5%)
Missing	4 (25.0%)

Source: FDA reviewer.
Abbreviations: AIS = abbreviated injury scale, n = sample size

Table 32. Injury Characteristics, Study V017

Parameter	Extremity Group n=16
Injury severity score (ISS), n	13
Mean (SD)	20.1 (18.9)
Median (minimum, maximum)	16 (1, 73)
Injury location, n (%)	-
Lower extremity	14 (87.5%)
Upper extremity	2 (12.5%)
Artery category, n (%)	-
Femoral artery	11 (68.8%)
Popliteal artery	3 (18.8%)
Other	2 (12.5%)
Cause of trauma, n (%)	-
Blast shrapnel injury	12 (75.0%)
Gunshot injury	2 (12.5%)
Industrial accident	1 (6.3%)
Motor vehicle accident	1 (6.3%)
Nature of trauma, n (%)	-
Blunt trauma	2 (12.5%)
Penetrating trauma	14 (87.8%)
Open fracture injury	13 (81.3%)

Source: FDA reviewer. Derived from clinical case summaries
Abbreviations: ISS = Injury Severity Score, n = sample size, SD = standard deviation

Reasons for not using autologous vein included: 4 (23.5%) for concomitant injury to the vein, 12 (70.6%) for poor quality or size of vein, 7 (41.2%) for time limitation-harvest not possible, and 3 (17.6%) for other.

Table 33. Reasons for Not Using Autologous Vein, Study V017

Reason	Extremity Group (n=16)
Concomitant injury to the vein	6 (37.5%)
Significant tissue defect	1 (6.3%)
Estimated risk of injury to the vein due to adjacent injuries to the area (blast or crush injury)	2 (12.5%)
Poor quality or size of the vein	3 (18.8%)
Previously used for stenting	2 (12.5%)
Time limitation	1 (6.3%)
Thrombosis, sclerosis, ablation	1 (6.3%)

Source: CLN-PRO-V017 CSR Listing 16.2.4.4; BLA 125812/SN0000
Abbreviations: n = sample size

Reviewer comment:
43.8% of patients in this study had severe or critical injuries. By comparison the clinical trial conducted in the civilian population for study V005 had a 74% of patients being classified as severe or critical injuries as measured by the AIS. Differences in injury severity may have contributed to differences seen in adverse events within this group. Noteworthy is that some patients in this study were treated weeks after the initial injury and not in an urgent manner as per the indication. MESS scores were only available for 2 patients in this study as retrospective evaluation and thus cannot be used as a basis of comparison.

6.2.10.1.3 Patient Disposition

Seventeen patients provided informed consent for study V017, with a data cutoff date of July 31, 2023. Sixteen of the 17 patients, received the ATEV to repair non-iatrogenic vascular injuries to an extremity. The ATEV length ranged from 3.5 to 40 cm (mean =18.3 cm). The mean follow-up duration in study V017 was 139.5 days (range 13 to 180 days). All 16 patients in the extremity group were evaluated at Day 30. 3 patients (18.8%) did not have follow up past 30 days and 7 patients (43.8%) did not have follow up past 6 months. No patients died or underwent limb amputation.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint

In the Extremity Group, primary patency was confirmed with Duplex imaging in 15 out of 16 patients (93.8%; 95% CI: 71.7%, 98.9%) at Day 30. One patient had the ATEV replaced on Day 13 following rupture and was categorized as not patent for the 30-day endpoint.

6.2.11.2 Analyses of Secondary Endpoints

Secondary Patency at Day 30
The secondary patency rate at Day 30 was 93.8%, with one patient deemed not patent at 30 days due to ATEV explant on Day 13.

Infection Rate at Day 30
The ATEV infection rate in the extremity group was 6.3% (95% CI: 1.1%, 28.3%). One patient (b) (6) underwent the ATEV explant following repeated interventions for graft rupture and bleeding from the graft site on days 8, 12 and 13. Following explant,

histology identified the presence of bacteria along the abluminal surface, suggestive of extension of infection from the surrounding tissues.

Amputation and Limb Salvage
No patients required amputation of the limbs during the study period. All patients were included as having successful limb salvage at Day 30. Limb Salvage rate was 100%.

Reviewer comment:
The primary and secondary patency of the ATEV at Day 30 was 93.8%. This suggests a clinically meaningful benefit for the use of ATEV as an arterial graft in the extremities.

6.2.11.3 Subpopulation Analyses

None

6.2.11.4 Dropouts and/or Discontinuations

The ATEV was abandoned in two patients (12.5%) and three patients were lost to follow up (18.8%). Eleven (68.8%) patients have completed 6 months follow up.

6.2.11.5 Exploratory and Post Hoc Analyses

None

6.2.12 Safety Analyses

6.2.12.1 Methods

Method for analysis of AEs was consistent with those defined in study V005 and included in section 6.2.12.

The Safety Population consists of 16 patients who received the ATEV in the study, regardless of follow-up status.

6.2.12.2 Overview of Adverse Events
Table 34 summarizes the treatment-related AEs observed in study V017. Complications observed for the patients with extremity trauma repair within this study included thrombosis or occlusion in one patient (6.3%), infection in one patient (6.3%) and ATEV rupture in one patient (6.3%). No deaths or amputations were reported for patients in this study.

Table 34. Adverse Events by System Organ Class and Preferred Term, Study V017

System Organ Class[1] Preferred Term	Extremity Group (n=16)
Any AEs	4 (25.0%)
Infections and infestations	4 (25.0%)
Wound infection	3 (18.8%)
Coronavirus infection	1 (6.3%)
Postoperative wound infection	1 (6.3%)
Injury, poisoning and procedural complications	2 (12.5%)
Vascular graft complication	1 (6.3%)
Vascular graft occlusion	1 (6.3%)
Vascular graft thrombus	1 (6.3%)
Vascular disorders	2 (12.5%)
Arterial hemorrhage	1 (6.3%)
Peripheral ischemia	1 (6.3%)
Metabolism and nutrition disorders	1 (6.3%)
Diabetes mellitus	1 (6.3%)
Hyperhomocysteinemia	1 (6.3%)

Source: Table 14.3.2.1 clinical study report
[1]Adverse events were coded using MedDRA version 26.0
Abbreviations: AE = adverse event, n = sample size

6.2.12.3 Deaths

No deaths were reported in this study.

6.2.12.4 Nonfatal Serious Adverse Events

Only one patient had an SAE. Patient (b) (6) underwent a mid superficial femoral artery to distal popliteal artery bypass using the ATEV. On Day 8, bleeding from the surgical site led to the discovery of a 2 mm rupture that was repaired with sutures. On Day 12, the patient was operated on again for bleeding from the sutured ATEV site. The ATEV was removed on Day 13 due to persistent bleeding and replaced with autologous saphenous vein. Histology analysis noted “the presence of bacteria along the abluminal surface [which] was suggestive of extension [of infection] from the surrounding tissues.” There were reportedly no clear signs of ATEV infection at time of first bleed on Day 8, but the “ATEV was thought to be too soft” to repair at the time of evaluation on Day 9 following second bleeding event. No cultures were taken from the ATEV. No further long-term information is provided for this patient following explant of the ATEV.

Table 35. Serious Adverse Events by System Organ Class and Preferred Term, Study V017

System Organ Class Preferred Term	Extremity Group (n=16)
Any SAE, n(%)	1 (6.3%)
Injury, poisoning and procedural complications	1 (6.3%)
Vascular rupture	1 (6.3%)
Vascular disorders	1 (6.3%)
Arterial hemorrhage	1 (6.3%)

Source: Derived from clinical dataset
Abbreviations: n = sample size, SAE = serious adverse event

6.2.12.5 Adverse Events of Special Interest

ATEV infection and rupture were seen in one patient (b) (6) who underwent three interventions prior to Day 30 before the ATEV was explanted. A second patient (b) (6)

(b) (6) presented after Month 6 with a thrombosis of the ATEV which could not be resolved and resulted in abandonment of the graft.

No amputations, aneurysms or pseudoaneurysms were reported in this study.

Table 36. Adverse Events of Special Interest, Study V017

AESI Assessment	Extremity Group n=16
Any Infection	5 (31.2%)
Wound infection	4 (25.0%)
ATEV infection	1 (6.3%)[1]
ATEV rupture	1 (6.3%)[1]
ATEV occlusion/thrombosis	1 (6.3%)

Source: Derived from clinical study report and case summaries
Abbreviations: AESI = adverse event of special interest, n = sample size
[1]patient (b) (6)

Reviewer comment:
No amputations, aneurysms or pseudoaneurysms were reported in this study. Safety cannot be accurately characterized. The absence of active monitoring of emerging safety signals following ATEV implantation likely underestimate the true rate of adverse events. Therefore, it is difficult to make a comparison of safety results from this retrospective study to the prospective study discussed previously (V005).

6.2.12.6 Clinical Test Results

Data from clinical tests was obtained retrospectively from the medical record. 6.2.12.7 Dropouts and/or Discontinuations

Table 37. Follow up for Extremity Patients, Study V017

Parameter	Study V017 n=16
Duration of follow up, days	
Mean	333
Median (min, max)	188 (1, 1134)
Patients treated, by duration of follow up, n (%)	
≥1 day	16 (100%)
≥30 days	15 (93.8%)
≥6 months	10 (62.5%)
Reason for study discontinuation, n (%)	
Lost to follow up	3 (18.8%)
ATEV rupture/explant	1 (6.3%)
ATEV thrombosis	1 (6.3%)

Source: Derived from clinical case summaries
Abbreviations: AESI = adverse event of special interest, max = maximum, min = minimum, n = sample size

6.2.13 Study Summary and Conclusions

Evaluation of primary and secondary efficacy endpoints for study V017 demonstrates effectiveness of this product with rate of 93.8% for both endpoints. Data from this study also provides evidence of a clinically meaningful benefit in the indicated population with a limb salvage rate of 100% at Day 30. The evaluation of safety is challenging due to the limitations of the retrospective study design which does not accurately capture emerging

safety signals following ATEV implantation in the absence of active monitoring. This has the potential to underestimate the true rate of adverse events.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

The clinical reviewer does not recommend an integrated overview of efficacy (i.e., an analysis using pooled data from all patients treated with the ATEV) because study V017 offers only limited supportive evidence due to the different study population and settings, which makes comparing the two studies difficult. Efficacy of the ATEV is reviewed primarily in section Efficacy Analyses (Section 6.2.11)

7.1.8 Persistence of Efficacy

Long-term efficacy of this product has not been adequately evaluated due to the high number of patients who terminated the study early. Study V017 evaluated patients through at least 6 months in the protocol. The Applicant has provided some data beyond 180 days for patients from this study, but interpretation is limited by the lack of a standard assessment timeline which can reliably evaluate the investigational product. Evaluation of the ATEV at one year is limited to only 27.1% of all patients who received this investigational product as a conduit in an extremity (Table 38).

Table 38. Follow Up for Extremity Patients, Study V005 and Study V017

Parameter	V005 n=54	V017 n=16	Total n=70
Duration of follow up, days			
Mean	334.6	141.4	294.3
Median (min, max)	188.5 (1, 1134)	180 (13, 180)	180 (1,1134)
Patients treated, by duration of follow up, n (%)			
≥1 day	54 (100%)	16 (100%)	70 (100%)
≥30 days	41 (75.9%)	15 (93.8%)	56 (80.0%)
≥3 months	34 (63.0%)	12 (75%)	46 (65.7%)
≥6 months	30 (55.6%)	12 (75%)	43 (61.4%)
≥12 months	19 (35.2%)	0	19 (27.1%)
36 months/end of study	7 (13.0%)*	0	7 (10.0%)
Reason for early study discontinuation, n (%)			
Total	37 (68.5%)	5 (31.3%)	42 (60%)
Death	6 (11.1%)	0	6 (8.6%)
Limb amputation	6 (11.1%)	0	6 (8.6%)
Lost to follow-up	15 (27.8%)	3 (18.8%)	18 (25.7%)
ATEV abandoned/explanted	9 (16.7%)	2 (12.5%)	11 (15.7%)
Withdrew consent	1 (1.9%)	0	1 (1.4%)

Source: Applicant dataset and case summaries
Abbreviations: max = maximum, min = minimum, n = sample size

Review of the seven patients who completed study V005 is included in Table 39. Of the seven patients who completed 36 month follow up, all retained ATEV patency at Month 36 and none developed graft infection. One patient underwent below knee amputation following thrombosis of the ATEV due to development of forefoot gangrene.

Table 39. Clinical Summary for Extremity Patients Completing 36 Months, Study V005

Patient ID	Days Followed	Narrative
(b) (6)	1047	22-year-old male received ATEV for superficial femoral artery interposition graft following MVA. Primary patency of the ATEV was confirmed at all clinical visits. No interventions or procedures were performed on the ATEV, and no amputation of the affected limb was performed.
(b) (6)	1086	37-year-old female received ATEV for popliteal artery injury following fall. Follow up complicated by infection, hematoma, and an abscess adjacent to the postsurgical site.. Primary patency of the ATEV was confirmed at all clinical visits. No interventions or procedures were performed on the ATEV, and no amputation of the affected limb was performed.
(b) (6)	1095	39-year-old male received ATEV for popliteal artery injury following GSW. Patency of the ATEV was confirmed at day 30. Follow up complicated by aneurysm of ATEV noted on day 195 with distal pain and paresthesia. Aneurysm stable until Day 424 when patient developed worsening lower extremity pain and discoloration and found to have occluded SFA and complete thrombosis of the ATEV which was thrombolysed. On day 475 and 482 patient underwent forefoot and below knee amputation below the level of the ATEV. Second thrombus noted on day 760 but resolved without intervention. Patency at month 36 visit confirmed.
(b) (6)	1104	45-year-old female received ATEV for popliteal artery injury following an occupational crush injury. Follow up complicated by wound and orthopedic hardware infection. Despite surrounding infection, primary patency of the ATEV was confirmed at all clinical visits. No interventions or procedures were performed on the ATEV, and no amputation of the affected limb was performed.
(b) (6)	1111	31-year-old male received ATEV for superficial femoral artery injury following fall. Despite follow up complicated by wound infection primary patency maintained until Month 9 when anastomotic stenoses was diagnosed and successfully treated. ATEV confirmed patent at 36 months and limb retained.
(b) (6)	1127	25-year-old male received ATEV as a right superficial femoral artery to right popliteal artery interposition bypass graft following GSW. Primary patency of the ATEV was confirmed at all clinical visits. No interventions or procedures were performed on the ATEV, and no amputation of the affected limb was performed.
(b) (6)	1134	34 year old female received ATEV for superficial femoral artery injury following occupational crush injury. Follow up complicated by infections in the joint and surrounding soft tissue without definitive evaluation of the ATEV.. Primary patency of the ATEV was confirmed at all clinical visits. No interventions or procedures were performed on the ATEV, and no amputation of the affected limb was performed.

Source: Applicant case summaries
Abbreviations: ATEV = acellular tissue engineered vessel, GSW = gunshot wound, MVA = motor vehicle accident, SFA = superficial femoral artery

Reviewer comment:
Long-term efficacy of ATEV has not been established as only 7 subjects completed the trial at the time of this review. Literature suggests that thrombosis and graft failure are known complications of autologous vein and synthetic grafts even more than one year after implantation. It is noteworthy that while an aneurysm and an anastomotic stenosis were observed in one patient each, patients retained the patency of the graft at 36 months. The cohort of patients who completed 36 month include patients who had no complications with the ATEV throughout the follow up period as well as patients with serious adjacent infections providing some evidence of benefit in the setting of comorbidities.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

No clinical studies were conducted in pregnant patients, and no data are available to indicate whether the ATEV can cause fetal harm when administered to pregnant women or can affect reproductive capacity.

In study V005, there was one patient who became pregnant during study follow up. The 21-year-old woman received a left interposition brachial artery ATEV graft due to inadequate size of the great saphenous vein following a gunshot wound. During Month 6 visit, imaging demonstrated stenosis of the distal anastomosis. She was 11 weeks pregnant at the time and deferred angiography with intervention. The patient miscarried at 13 weeks gestation and was reported to have discontinued anticoagulation at some point thereafter. During the Month 9 visit (Day 331), primary patency was lost and occlusion was confirmed by duplex ultrasound. The ATEV was considered abandoned, and the patient was terminated from the study. Patient subsequently had a successful pregnancy with live birth 19 months after the ATEV placement. The draft labeling indicates that the ATEV should be used in pregnant women if clinically indicated.

9.1.2 Use During Lactation

The ATEV has not been evaluated in lactating patients.

9.1.3 Pediatric Use and PREA Considerations

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 clinical study 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 groups for which a waiver is being requested due to uncertainty regarding the ability of this product to grow with the patient.

CBER 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. A partial waiver was also granted for the remainder of the pediatric population.

Based on discussion with the PeRC team, we recommend the following approach to labeling and PREA fulfillment:

1. The indication statement will include the qualifier “adults” since the product will not be approved for pediatric patients.
2. 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.”
3. 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 safety in patients less than Tanner Maturity Rating Stage V is valid but there is no clinical, nonclinical or product data to support this safety concern.
4. The approval will include a PREA PMR for evaluation of adolescent patients who have reached Tanner Maturity Rating Stage V.

Reviewer comment:
No animal studies evaluated whether the ATEV will grow in length once implanted. The Applicant has previously conducted studies in adult baboons and swine which were not designed to study whether the ATEV remodels and grows with the patient. The capacity of the ATEV to remodel has also not been evaluated at a sufficient duration to definitively say that the ATEV can completely repopulate with vascular cells and remodel like a normal blood vessel.

Prior discussions with the FDA included the possibility of evaluating the ATEV in a juvenile baboon, and challenges that were acknowledged included diameter mismatch in the baboons and issues with the surgical procedure (thrombosis, occlusion, loss of patency), which would be technically challenging to conduct in smaller, lower weight animal models. FDA and the Applicant did not reach agreement on studies in a juvenile animal to support safety of studying the ATEV in children who have not reached their adult height, and none were ultimately required in concert with BLA submission because of the informal dispute resolution.

9.1.4 Immunocompromised Patients

The safety and effectiveness of the ATEV in immunocompromised patients have not been established.

9.1.5 Geriatric Use

Six adults ≥65 years of age (2 in extremity group) were enrolled and treated in the study. Sample size is too small to derive any definitive conclusions; however, findings appeared to be similar in this subpopulation compared to the overall population.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Trauma patients in general and young men especially are known to have poor compliance with long-term follow up. This is reflected both in existing literature for extremity vascular trauma and in the submitted data for study V005.

10. CONCLUSIONS

There is an unmet medical need for an alternative vascular graft to preserve the limb when the autologous vein is not feasible following extremity vascular injury. Available alternatives include synthetic graft materials but their use is limited in the extremities due to the higher risk of complications including graft occlusion, infection, and graft failure due to repetitive motion in joint spaces (Desai, 2011). There remains a population for whom the absence of a suitable option to restore adequate blood flow to the effected limb will result in limb amputation.

The primary evidence of effectiveness is based on primary patency at 30 days following use of the ATEV graft for vascular repair in extremity trauma. The Trial V005 in 54 patients with extremity trauma demonstrated a primary patency rate at Day 30 of 66.7% (95% CI: 53.4%, 77.8%) and a secondary patency rate of 72.2% (95% CI: 59.1%, 82.4%). The limb salvage rate at Day 30 was 75.5% (95% CI: 62.4%, 85.1%). The ATEV infection rate was 1.9% in the first 30 days. Supporting data from Humanitarian use in the Ukraine provides a 30-day patency rate of 93.8%. No patients in study V017 required amputation. Day 30 outcomes in this acute trauma population is considered clinically meaningful, as this 30 day period of restoration of blood flow provides an opportunity to save a limb in clinical situations of imminent limb loss. Additionally, this period provides an opportunity for the establishment of the collateral circulation which would make later interventions possible, if needed. Based on these findings from both studies, the ATEV demonstrates a clinically meaningful benefit in restoring blood flow in the affected limb and ultimately limb salvage.

The safety database included 71 adult patients from study V005 and was supported by safety evaluation of 16 patients in the observational study V017. The primary potential serious risk with vascular placement of the ATEV was the risk of mid-graft rupture or anastomotic failure. While this is a known complication of autologous vein and synthetic vein grafts, it is considered to be relatively rare in the civilian population (Table 3). The observed rate of anastomotic failure or rupture of 9.1% in all patients from studies V005 and V017 is worrisome and requires further characterization.

When evaluating infection as a safety outcome, six (8.5%) of the 71 patients developed ATEV infection between days 7 and 40. Because there was no protocol specified evaluation of infection prior to Day 30, identified infections were limited to instances when reintervention to the graft was required due to bleeding from the ATEV. Definitive identification of adverse events including infection in the retrospective study V017 is further limited by the absence of active monitoring.

The provided data from both studies V005 and V017 support the conclusion that ATEV can provide meaningful clinical benefit in terms of patency and associated limb salvage when an autologous vein is not feasible. To address the identified risks, changes have been made to the indication to limit use of this product to the population who would have the greatest benefit from its use. We have also revised the USPI to highlight the

observed risks to the provider so that they may make an informed decision. For the indicated population, it is my assessment that the benefits outweigh the risks based on my review of the study data.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Risk-benefit considerations are listed in Table 40.

Table 40. Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Extremity vascular trauma can lead to limb loss or death. Repair is essential for bleeding control and limb preservation. • Autologous veins are the primary choice for extremity vascular trauma repair • Synthetic grafts may be used when autologous veins are not available	Arterial trauma is a serious condition. An alternative to synthetic grafts is needed for instances when the autologous vein is not a viable option.
Unmet Medical Need	• There are patients who do not have an available autologous vein • Synthetic graft is not suitable for grossly contaminated wounds due to their propensity for infection. They also have lower long-term patency rates than autologous veins. • Use of existing synthetic graft materials is limited in the extremities due to the higher risk of complications including graft occlusion, infection, and graft failure due to repetitive motion in joint spaces.	• Currently approved therapies are reasonably well tolerated and have demonstrated efficacy. There is an unmet medical need for a safe and effective alternative when the autologous vein is not feasible
Clinical Benefit	• Two studies in adults were submitted. Primary evidence of effectiveness was demonstrated in Study V005, which was primary patency at 30 days. Long-term data evaluation was limited by missing data and loss to follow up. • Primary patency at 30 days: 66.7%, secondary patency at 30 days: 72.2% • Limb amputation rate: 9.1% at 30 days, 14.5% overall. • Limb salvage rate taking into consideration patients who died or had their graft explanted during the study period was 75.9%. • Supporting data from Study V017 further supports the observed benefit through Day 30 primary and secondary patency rates of 93.8%. Additionally, all patients in study V017 had limb salvaged at Day 30.	• The evidence for clinical benefit is based on 66.7% primary patency and 72.2% secondary patency at 30 days in patients for whom autologous vein was not feasible. • The clinical meaningfulness of the observed patency rate was supported by the limb salvage rate.
Risk	• Risk of mid-graft rupture and anastomotic failure is 9.1% across all patients in both studies. Graft failure resulted in life threatening bleeding requiring immediate attention to preserve life in seven out of 71 patients from study V005. There was one death in the setting of proximal anastomotic failure following placement in the torso. • ATEV infection was only identified following graft failure when there was confirmation either by culture, histology or examination of the graft by the surgeon during graft reintervention. There was no protocol specified evaluation of infection before Day 30. • The long term risks of this product have not been characterized. • The perceived time saving convenience of using this product over existing therapies may place patients at undue risk.	• The long-term risk of the ATEV has not been adequately characterized. Patients receiving vascular grafts are known to be difficult to follow clinically. The Applicant has agreed to conduct a post marketing study to further characterize identified risks with ATEV placement. • The known risk of anastomotic failure or rupture is 9.1%. This is higher than expected for available therapies and requires further characterization.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• The most substantial risks with implantation of the ATEV is either rupture or anastomotic failure which can result in serious arterial bleeding. • Post marketing studies would provide sufficient data to evaluate safety especially in the military setting, as the civilian population would have the same challenges with follow up seen both in this study and in the literature. • Further characterization of infection will be included in the post marketing study which will include a larger population and provide the opportunity for better evaluation.	• Limiting the indication to the extremity population helps to mitigate risk in the event of graft failure. • Providers have also been advised of the risk of graft failure through inclusion of a box warning in the USPI. • The Applicant has agreed to conduct a post marketing study to further characterize the risk of graft failure and infection with ATEV placement.

11.2 Risk-Benefit Summary and Assessment

There is an unmet medical need for an alternative vascular graft to preserve the limb when the autologous vein is not feasible following extremity vascular injury. Use of existing synthetic graft materials is limited in the extremities due to the higher risk of complications including graft occlusion, infection, and graft failure due to repetitive motion in joint spaces. This product would address the unmet need in the population for whom the absence of a suitable option to restore adequate blood flow to the effected limb will result in limb amputation.

The benefit of ATEV 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. Furthermore, ATEV's effects on the key secondary endpoint of limb salvage provides supportive evidence of benefit with a rate of 75.9% at Day 30. Study V017 further supports the observed benefit through Day 30 primary and secondary patency rates of 93.8%. Additionally, all patients in study V017 had limb salvaged at Day 30. ATEV 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. Data submitted to the BLA suggest a benefit in terms of limb preservation for patients who receive the ATEV under this indication.

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. SYMVESS infection was also identified as a risk in the setting of overlying wound infection during this study and is consistent with the risk seen in existing vascular grafts. More concerning is the risk of mid-graft rupture or anastomotic failure of SYMVESS. Characterization of this risk is incomplete due to the limited number of patients enrolled and the limited follow up. 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 a paucity of data in the literature to identify a benchmark by which to compare the rates seen following ATEV implantation. Limited literature suggests that the rate of graft failure seen in Study V005 is higher than reported with existing vascular graft options. Therefore, we have limited use of this product to patients with an extremity arterial injury when urgent revascularization is needed to avoid imminent limb loss, and autologous vein graft is not feasible in order to ensure that the benefit outweighs the risk. Revisions to the USPI via the Boxed Warning for graft failure and Warnings and Precautions section for graft rupture or anastomotic failure have also been included to inform providers of the risks identified in the clinical study. Furthermore, the Applicant has agreed to a postmarketing requirement to further characterize the risk of graft failure and infection in patients with extremity vascular injury who have received SYMVESS for the approved indication. Based on the totality of presented data and the unmet need, the benefit outweighs the risks for this product.

11.3 Discussion of Regulatory Options

The regulatory options include: (1) traditional approval; or (2) Complete Response.

The Applicant submitted a package that has provided evidence of safety and effectiveness from an open label prospective study supported by a retrospective observational study which shows patency at 30 days and subsequent limb preservation.

Identified safety concerns related to the use of this investigational product have been adequately mitigated. Approval action is recommended.

11.4 Recommendations on Regulatory Actions

The Applicant has provided evidence of effectiveness based on patency at Day 30 from a prospective open label study and supportive data from a retrospective study. ATEV is indicated for a population in which the autologous vein is not feasible for urgent revascularization to avoid imminent limb loss. The observed safety risks of graft failure will be further evaluated in a postmarketing study and mitigated with safety measures including a boxed warning identifying the risk of mid-graft rupture or anastomotic failure. Based on the totality of presented data demonstrating limb preservation when the autologous vein is not feasible and in consideration of the added safety measures described, the benefits outweigh the risks for this product. This reviewer therefore recommends traditional approval.

11.5 Labeling Review and Recommendations

The review team made substantial changes to each section of the prescribing information, based on available clinical trial data and FDA guidance on product labeling to suitably convey known information regarding safety and efficacy results shown in clinical studies of the ATEV. A narrow indication was identified where it would be used 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.

11.6 Recommendations on Postmarketing Actions

The following postmarketing studies have been discussed and agreed upon mutually between FDA and the Applicant for this submission:

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.

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.

PMC#10: 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.

There are seven supplemental CMC PMC studies related to product manufacturing and shipping. Please see CMC review for additional details.

12. LITERATURE REVIEWED

During review of the BLA, this reviewer consulted FDA regulatory guidance documents, as well as academic literature, for background and context regarding the targeted disease and the mechanism of action of the product. The literature consulted follows below.

Akingba, AG, EA Robinson, AL Jester, BM Rapp, A Tsai, RL Motaganahalli, MC Dalsing, and MP Murphy, 2013, Management of vascular trauma from dog bites, Journal of vascular surgery, 58(5):1346-1352.

Biancari, F, M Railo, J Lundin, A Albäck, I Kantonen, A Lehtola, and M Lepäntalo, 2001, Redo bypass surgery to the infrapopliteal arteries for critical leg ischaemia, European Journal of Vascular and Endovascular Surgery, 21(2):137-142.

Clouse, WD, TE Rasmussen, MA Peck, JL Eliason, MW Cox, AN Bowser, DH Jenkins, DL Smith, and NM Rich, 2007, In-theater management of vascular injury: 2 years of the Balad Vascular Registry, Journal of the American College of Surgeons, 204(4):625-632.

DeRose, G and J Provan, 1984, Infected arterial grafts: clinical manifestations and surgical management, The Journal of Cardiovascular Surgery, 25(1):51-57.

Desai M, Hamilton G. Graft Materials Past and Future. In: Fitridge R, Thompson M, editors. Mechanisms of Vascular Disease: A Reference Book for Vascular Specialists [Internet]. Adelaide (AU): University of Adelaide Press; 2011. 28. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534281/

DV, F, 1985, Five-year experience with PTFE grafts in vascular wounds, J Trauma, 25:71-82.

Eastridge, BJ, M Hardin, J Cantrell, L Oetjen-Gerdes, T Zubko, C Mallak, CE Wade, J Simmons, J Mace, and R Mabry, 2011, Died of wounds on the battlefield: causation and implications for improving combat casualty care, Journal of Trauma and Acute Care Surgery, 71(1):S4-S8.

Faulconer, ER, BC Branco, MN Loja, K Grayson, J Sampson, TC Fabian, JB Holcomb, T Scalea, D Skarupa, and K Inaba, 2018, Use of open and endovascular surgical techniques to manage vascular injuries in the trauma setting: a review of the American Association for the Surgery of Trauma PROspective Observational Vascular Injury Trial registry, Journal of Trauma and Acute Care Surgery, 84(3):411-417.

Feliciano DV, Mattox KL, Graham JM, Bitondo CG. Five-year experience with PTFE grafts in vascular wounds. J Trauma. 1985 Jan;25(1):71-82.

Forsyth, A, MH Haqqani, DB Alfson, SP Shaikh, F Brea, A Richman, JJ Siracuse, D Rybin, A Farber, and TS Brahmbhatt, 2024, Long-term outcomes of autologous vein bypass for repair of upper and lower extremity major arterial trauma, Journal of Vascular Surgery, 79(6):1339-1346.

Fox CJ, Gillespie DL, O'Donnell SD, Rasmussen TE, Goff JM, Johnson CA, Galgon RE, Sarac TP, Rich NM. Contemporary management of wartime vascular trauma. J Vasc Surg. 2005 Apr;41(4):638-44.

Frech, A, L Pellegrini, G Fraedrich, G Goebel, and J Klocker, 2016, Long-term clinical outcome and functional status after arterial reconstruction in upper extremity injury, European Journal of Vascular and Endovascular Surgery, 52(1):119-123.

Gennarelli, TA and E Wodzin, 2006, AIS 2005: a contemporary injury scale, Injury, 37(12):1083-1091.

Greer, LT, B Patel, KC Via, JN Bowman, MA Weber, and CJ Fox, 2012, Management of secondary hemorrhage from early graft failure in military extremity wounds, Journal of Trauma and Acute Care Surgery, 73(4):818-824.

Helfet, D, T Howey, R Sanders, and K Johansen, 1990, Limb Salvage Versus Amputation: Preliminary Results of the Mangled Extremity Severity Score, Clinical Orthopaedics and Related Research (1976-2007), 256:80-86.

Holcomb, JB, NR McMullin, L Pearse, J Caruso, CE Wade, L Oetjen-Gerdes, HR Champion, M Lawnick, W Farr, and S Rodriguez, 2007, Causes of death in US Special Operations Forces in the global war on terrorism: 2001–2004, Annals of surgery, 245(6):986-991.

Huber TS, Carter JW, Carter RL, Seeger JM. Patency of autogenous and polytetrafluoroethylene upper extremity arteriovenous hemodialysis accesses: a systematic review. J Vasc Surg. 2003 Nov;38(5):1005-11.

Johansen, K, M DAINES, T HOWEY, D HELFET, and ST HANSEN Jr, 1990, Objective criteria accurately predict amputation following lower extremity trauma, Journal of Trauma and Acute Care Surgery, 30(5):568-573.

Kelly, JF, AE Ritenour, DF McLaughlin, KA Bagg, AN Apodaca, CT Mallak, L Pearse, MM Lawnick, HR Champion, and CE Wade, 2008, Injury severity and causes of death from Operation Iraqi Freedom and Operation Enduring Freedom: 2003–2004 versus 2006, Journal of trauma and acute care surgery, 64(2):S21-S27.

Laverty RB, Brock SG, Walters TJ, Kauvar DS. Outcomes of Arterial Grafts for the Reconstruction of Military Lower Extremity Arterial Injuries. Ann Vasc Surg. 2021 Oct;76:59-65. doi: 10.1016/j.avsg.2021.03.006.

Lin CH, Consuegra MDL, Lin TS. Revisiting Management Strategies for Popliteal Artery Injuries. Ann Plast Surg. 2022 Mar 1;88(1s Suppl 1):S44-S49. Nelson, JA, JP Fischer, R Grover, SJ Kovach, DW Low, SK Kanchwala, LS Levin, JM Serletti, and LC Wu, 2015, Vein grafting your way out of trouble: Examining the utility and efficacy of vein grafts in microsurgery, Journal of Plastic, Reconstructive & Aesthetic Surgery, 68(6):830-836.

Perler, B, C Vander Kolk, C Dufresne, and G Williams, 1991, Can infected prosthetic grafts be salvaged with rotational muscle flaps?, Surgery, 110(1):30-34.

Rasmussen T, Stockinger Z, Antevil J, White C, Fernandez N, White J, White P. Joint Trauma System Clinical Practice Guideline: Vascular Injury. 12 August 2016. https://jts.health.mil/assets/docs/cpgs/Vascular_Injury_12_Aug_2016_ID46.pdf

Rayamajhi S, Murugan N, Nicol A, Edu S, Klopper J, Naidoo N, Navsaria P. Penetrating femoral artery injuries: an urban trauma centre experience. Eur J Trauma Emerg Surg. 2019 Oct;45(5):909-917.

Rehman ZU. Outcomes of Popliteal Artery Injuries Repair: Autologous Vein versus Prosthetic Interposition Grafts. Ann Vasc Surg. 2020 Nov;69:141-145.

Reilly B, Khan S, Dosluoglu H, Harris L, O'Brien-Irr M, Lukan J, Dryjski M, Blochle R. Comparison of Autologous Vein and Bovine Carotid Artery Graft as a Bypass Conduit in Arterial Trauma. Ann Vasc Surg. 2019 Nov;61:246-253.

Rudström H, Bergqvist D, Ogren M, Björck M. Iatrogenic vascular injuries in Sweden. A nationwide study 1987-2005. Eur J Vasc Endovasc Surg. 2008 Feb;35(2):131-8.

Seeger, JM, 2000, Management of patients with prosthetic vascular graft infection, The American Surgeon, 66(2):166-177.

Sharrock AE, Tai N, Perkins Z, White JM, Remick KN, Rickard RF, Rasmussen TE. Management and outcome of 597 wartime penetrating lower extremity arterial injuries from an international military cohort. J Vasc Surg. 2019 Jul;70(1):224-232.

Stonko DP, Betzold RD, Abdou H, Edwards J, Azar FK, Elansary NN, Treffalls RN, Savidge SG, DuBose JJ, Feliciano DV, Morrison JJ; AAST PROOVIT Study Group. In-hospital outcomes in autogenous vein versus synthetic graft interposition for traumatic arterial injury: A propensity-matched cohort from PROOVIT. J Trauma Acute Care Surg. 2022 Feb 1;92(2):407-412.

Urrechaga E, Jabori S, Kang N, Kenel-Pierre S, Lopez A, Rattan R, Rey J, Bornak A. Traumatic Lower Extremity Vascular Injuries and Limb Salvage in a Civilian Urban Trauma Center. Ann Vasc Surg. 2022 May;82:30-40.

Vertrees A, Fox CJ, Quan RW, Cox MW, Adams ED, Gillespie DL. The use of prosthetic grafts in complex military vascular trauma: a limb salvage strategy for patients with severely limited autologous conduit. J Trauma. 2009 Apr;66(4):980-3.

Watson JD, Houston R 4th, Morrison JJ, Gifford SM, Rasmussen TE. A retrospective cohort comparison of expanded polytetrafluorethylene to autologous vein for vascular reconstruction in modern combat casualty care. Ann Vasc Surg. 2015;29(4):822-9. doi: 10.1016/j.avsg.2014.12.026.Wilson, SE, 2001, New alternatives in management of the infected vascular prosthesis, Surgical infections, 2(2):171-177.

Zeltsman, D, CD Tzarnas, and MD Kerstein, 1999, Management of vascular prosthetic infections: results of long-term follow-up, The American surgeon, 65(4):331-333.

13. APPENDICES

13.1 Appendix 1. Mangled Extremity Severity Score (MESS)

Table 40. Mangled Extremity Severity Score (MESS)

Characteristic	Points
Skeletal/soft tissue injury	
Low energy (stab; simple fracture; "civilian" GSW)	1
Medium energy (open or multiple fractures, dislocation)	2
High energy (close-range shotgun or "military" GSW, crush injury)	3
Very high energy (above+ gross contamination, soft-tissue avulsion)	4
Limb ischemia	
Pulse reduced or absent but perfusion normal	1*
Pulseless; paresthesia, diminished capillary refill	2*
Cool, paralyzed, insensate, numb	3*
Shock	
Systolic BP always > 90 mm Hg	0
Hypotensive transiently	1
Persistent hypotension	2
Age (years)	
< 30	0
30 – 50	1
> 50	2

Source: JOHANSEN, KAJ M.D., Ph.D.; DAINES, MICHAEL M.D.; HOWEY, THOMAS M.D.; HELFET, DAVID M.D.; HANSEN, SIGVARD T. Jr. M.D.. Objective Criteria Accurately Predict Amputation following Lower Extremity Trauma. The Journal of Trauma: Injury, Infection, and Critical Care 30(5):p 568-573, May 1990. [Table 2]
*Score doubled for ischemia > 6 hours
Abbreviations: BP = blood pressure, GSW = gunshot wound, mm Hg = millimeters mercury

13.2 Appendix 2. Abbreviated Injury Score (AIS)

Table 41. Abbreviated Injury Score (AIS)

AIS Severity Score	Injury Severity Description
1	Minor
2	Moderate
3	Serious, not life threatening
4	Severe, life-threatening
5	Critical, survival uncertain
6	Maximum (untreatable)

Source: Gennarelli, TA; Wodzin, E. AIS 2005: A contemporary injury scale. Injury 37(12):pp 1083-1091, 2006.
Abbreviations: AIS = abbreviated injury score