

Application Type	Original BLA
STN	125812/0
CBER Received Date	December 11, 2023
PDUFA Goal Date	August 10, 2024
Division / Office	DCGT/OTP
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Priority Review	Yes
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Review Completion Date / Stamped Date	
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Applicant	Humacyte Global, Inc.
Established Name	Human Acellular Vessel (HAV)
(Proposed) Trade Name	SYMVESS (pending)
Pharmacologic Class	Acellular tissue-engineered vessel

Formulation(s), including Adjuvants, etc	<p>The HAV is a sterile, (b) (4) acellular tubular vessel composed of human collagen (b) (4) along with other extracellular matrix proteins.</p> <p>The product is supplied on a silicone mandrel immersed in sterile phosphate-buffered saline (PBS) in a sealed and labeled plastic container.</p>
Dosage Form(s) and Route(s) of Administration	Implanted using standard vascular surgical techniques that are similar to placement of autologous or synthetic peripheral vascular prostheses
Dosing Regimen	One time implantation
Indication(s) and Intended Population(s)	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.

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GLOSSARY

AE	Adverse Event
AESI	Adverse Event of Special Interest
AFS	Amputation Free Survival
AIC	Akaike Information Criterion
AIS	Abbreviated Injury Scale
AVF	Arteriovenous Fistula
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDRH	Center for Devices and Radiological Health
CI	Confidence Interval
DMC	Data Monitoring Committee
DoD	Department of Defense
ECMO	Extracorporeal Membrane Oxygenation
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration
HAV	Human Acellular Vessel
IE	Intercurrent Event
IED	Improvised Explosive Device
IND	Investigational New Drug
IR	Information Request
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
MAIC	Matching Adjusted Indirect Comparison
MI	Multiple Imputation
PAD	Peripheral Arterial Disease
PDUFA	Prescription Drug User Fee Act
PROOVIT	PROspective Observational Vascular Injury Treatment
PTFE	Polytetrafluoroethylene
RMAT	Regenerative Medicine Advanced Therapy
RWD	Real World Data
RWE	Real World Evidence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SLR	Systematic Literature Review
US	United States

1. Executive Summary

Human acellular vessel (HAV), under the trade name SYMVESS, is an acellular tissue-engineered vessel composed of human extracellular matrix (ECM) proteins typically found in human blood vessels. Humacyte Global Inc. submitted results from two studies, CLN-PRO-V005 and CLN-PRO-V017, in this original Biologics Licensing Application (BLA) to support the indication of HAV's 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. Study CLN-PRO-V005 serves as the primary evidence of efficacy and safety. Study CLN-PRO-V017 serves as supportive evidence.

Study CLN-PRO-V005 was a Phase 2/3, prospective, multicenter, non-randomized, open-label, single-arm study in a total of 72 subjects aged 18 to 85 years old, with life- or limb-threatening traumatic injury to an arterial vessel in the limb or torso, who need replacement or reconstruction. Of the 72 subjects, 54 subjects with non-iatrogenic, extremity arterial injuries who received HAV as a conduit were included in the primary efficacy evaluation. The primary endpoint was primary vessel patency at Day 30. The key secondary endpoints included secondary vessel patency at Day 30, HAV infection at Day 30, and limb-salvage at Day 30. Among the 54 subjects, 13 subjects were not evaluable at Day 30 due to death (n=4), amputation (n=5), intraoperative thrombosis (n=2), or loss to follow up (n=2). Twelve of the thirteen subjects were not evaluable for patency at Day 30, while one subject was determined to be non-patent before Day 30; all thirteen subjects were not evaluable for infection and limb-salvage at Day 30. The Food and Drug Administration (FDA) performed an internal adjudication for these subjects. Results from CLN-PRO-V005 reported in this memo are based on FDA's adjudicated data with a cut-off date of January 15, 2024.

Based on the FDA adjudication, the primary patency rate at Day 30 was 66.7% (95% CI: 53.4%, 77.8%), which was lower than the mean primary patency rate for synthetic grafts of 82.4% (based on a literature search). The secondary patency rate at Day 30 was 72.2% (95% CI: 59.1%, 82.4%), which was lower than that for synthetic grafts of 78.9% (based on literature search). The limb salvage rate at Day 30 was 75.9% (95% CI: 63.1%, 85.4%). The HAV infection rate at Day 30 was 3.7% (95% CI: 1.0%, 12.5%), which was higher than the mean infection rate of 2.5% for synthetic grafts in civilian trauma (based on literature search). The risk of HAV infection was likely underestimated due to the 13 subjects not evaluable for infection at Day 30 but counted as HAV infection-free.

There were six deaths (11.1%) in this extremity group, of which four deaths occurred in the first 30 days, one on Day 42, and one on Day 128. None of the deaths were deemed related to the HAV. Of the 54 subjects, 15 (28%) experienced HAV thrombosis, 5 (9%) developed anastomotic stenosis of the

HAV, 4 (7%) had HAV rupture or anastomotic failure, and 3 (6%) had HAV infection. Other adverse events included fever in 9 (17%) subjects and procedural pain in 8 (15%) subjects.

Study CLN-PRO-V017 was a retrospective, observational, open-label, single-arm study in 17 subjects aged ≥ 18 to ≤ 85 years old, with arterial injury of the extremity, who received the HAV under the Humacyte Humanitarian Aid Program in Ukraine between June 2022 and 15 May 2023. Of the 17 subjects, 16 subjects with non-iatrogenic arterial injury to the limb were included in the primary efficacy evaluation.

Results from CLN-PRO-V017 were based on data with a cut-off date of July 31, 2023. The primary and secondary patency rates at Day 30 were both 93.8% (95% CI: 71.7%, 98.9%). The HAV infection rate was 6.3% (95% CI: 1.1%, 28.3%). None of the subjects were amputated, and no deaths were reported. One subject was reported to have 3 instances of serious adverse event (SAE), due to persistent bleeding caused by a rupture in the HAV which was consequently excised and removed. Another subject was reported to have HAV occlusion and the HAV was abandoned.

The efficacy results in CLN-PRO-V017 appeared to be better than those in CLN-PRO-V005. However, this could be attributed to selection bias, because CLN-PRO-V017 data were skewed to shrapnel injuries and not the more typical devastating severe limb or polytraumatic military injuries that could provide robust data of HAV in terms of infection resistance. Study CLN-PRO-V017 also consisted of less severe injuries compared to CLN-PRO-V005, based on the injury severity score (ISS).

Neither study met the usual criteria for an adequate and well-controlled trial. Study CLN-PRO-V017 was a retrospective observational study, which is prone to selection bias. In Study CLN-PRO-V005, the analyses were not pre-specified before outcomes were already known, and the analyses were all descriptive without formal hypothesis testing planned. Multiple major changes were introduced while the open-label study was ongoing. The study also had conduct issues with poor data quality and questionable trial integrity. For example, several cases were identified in which an implanted HAV subsequently became occluded, but the limb survived without revascularization, which raises the question of whether HAV implantation was necessary in the first place for these subjects. Other subjects treated with the HAV were later identified to have vein available for autologous graft, in which case HAV use would not be mandatory or preferred.

I performed efficacy analyses as specified in the statistical analysis plan (SAP) based on FDA's adjudicated data. There was no clinical evidence submitted that demonstrates HAV's infection resistance. Consequently, there was no evidence to support HAV's use in grossly contaminated wounds. However, the analysis

results did show that HAV may be efficacious, with an unknown long-term safety and efficacy profile, for some adults needing urgent arterial repair following extremity vascular trauma who do have alternative treatment options available (e.g., autologous vein or synthetic graft). In these subjects, there is uncertainty on how HAV compares to other treatment options. It is not apparent from the study data whether there are situations where the benefit of HAV outweighs the risk. Therefore, I defer to the clinical reviewer on the approval recommendation based on the overall benefit risk assessment and aspects of unmet need.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

In the civilian population, traumatic vascular injuries are mainly concentrated to the limbs and torso. In the United States (US), lower extremity vascular injuries are the most common, often due to motor vehicle accidents, gunshot wounds, dog bites, and other situations resulting in blunt or penetrating trauma.

In the military population, combat resulting vascular injuries can occur in all locations of the body, with injuries to the lower extremities being most common, followed by vascular injuries to the upper extremities, neck, and torso. Improvised explosive devices (IEDs) are a major cause of vascular injuries, with over 3,000 casualties per year during recent conflicts.

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

Currently, to salvage injured limbs or end-organs in distal vascular bed and to prevent life threatening hemorrhage, the vascular component of the injuries is treated with interposition or bypass grafting. The gold standard for this type of reconstruction is performed by using an autologous vein from the subject (typically great saphenous vein). Alternatively, synthetic grafts, such as expanded polytetrafluoroethylene (PTFE) or Dacron, may also be used.

However, the use of these grafts is not always possible or without additional risks. For example, the subject may not have adequate autologous vein for harvest. Although synthetic grafts are approved for use in “trauma patients requiring vascular replacement” and are being used to repair vascular trauma in practice, one might say “subjects with massive fecal contamination or crush injuries or necrotic should not have gotten” synthetic grafts, according to Dr. Robert Lee, FDA’s vascular surgeon consult from the Center for Devices and Radiological Health (CDRH).

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

The HAV has been studied in 8 clinical studies in the US, Europe, and Israel, in patients with end-stage renal disease (ESRD), peripheral arterial disease (PAD), and vascular trauma.

Studies CLN-PRO-V001, CLN-PRO-V003, CLN-PRO-V006, CLN-PRO-V011 enrolled ESRD subjects requiring hemodialysis access, who were not suitable for arteriovenous fistula (AVF) creation. Study CLN-PRO-V007 enrolled ESRD subjects requiring hemodialysis access, who were candidates for AVF creation.

CLN-PRO-V002 and CLN-PRO-V004 enrolled subjects with symptomatic PAD requiring femoral-popliteal bypass when autologous vein was not available. CLN-PRO-V002 was a pilot study in Poland in 20 subjects. CLN-PRO-V004 was a Phase 2 single arm uncontrolled study in the US in 15 subjects.

All studies have completed, aside from CLN-PRO-V007 which is still ongoing. An additional 45 expanded-access subjects and 19 Ukraine Humanitarian Aid subjects have been treated. As of the Development Safety Update Report Version 10.0 with a data cutoff date of April 10, 2023, a total of 389 ESRD subjects and 35 PAD subjects have been treated.

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

Major regulatory history with statistical implications is summarized below:

Pre-submission:

1. On June 27, 2016, the Sponsor proposed Study CLN-PRO-V005 as a Phase 2, single arm, non-randomized study in 20 subjects to evaluate safety and efficacy of HAV for use as a vascular interposition graft in subjects with limb-threatening peripheral arterial trauma.
2. On August 1, 2019, the Sponsor proposed to convert Study CLN-PRO-V005 from a proof-of-concept study to a registrational study. The Sponsor proposed to compare HAV with external controls from the PROspective Observational Vascular Injury Treatment (PROOVIT) database. The FDA expressed concerns about comparability of study subjects and external controls and lack of long-term data in the PROOVIT database. The FDA requested adequate prospective clinical and statistical plans.
3. On October 1, 2020, the Department of Defense (DoD) designated the HAV as a Priority Product in accordance with Public Law 115-92.
4. On October 20, 2020, the Sponsor proposed Study CLN-PRO-V005 as a Phase 2/3 non-randomized, open-label, adaptive study in 100 eligible HAV subjects comparing to external controls from PROOVIT who received

- autologous vein graft. The FDA communicated major statistical concerns about the study design, including study population, sample size, handling of missing data and intercurrent events (IE), non-inferiority design, and interim analyses.
5. On December 21, 2020, the Sponsor proposed to revise the study to compare 120 HAV subjects to matched subjects 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 non-inferiority 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.
 6. On January 28, 2021, the Sponsor proposed a revised Study CLN-PRO-V005 as a non-inferiority study in which 50 HAV subjects (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 rate. The Sponsor proposed to demonstrate non-inferiority on AFS and superiority on infection. The FDA requested details on the selection of publications for inclusion and meta-analysis methodology.
 7. On December 7, 2021, the Sponsor proposed to revise the primary efficacy endpoint from AFS to infection within 30 days after implantation of HAV 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 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 co-primary endpoints be conducted.
 8. On March 30, 2022, the Sponsor proposed two options for a revised study design for CLN-PRO-V005. In Option 1, the Sponsor proposed to compare HAV to synthetic grafts based on the co-primary endpoints of superiority on infection and non-inferiority on AFS, both evaluated at 90 days. Performance metrics of synthetic graft were derived from meta-analysis literature review, and a matching adjusted indirect comparison (MAIC) approach would be used to match subjects to external controls. In Option 2, the Sponsor proposed to compare HAV to autologous vein based on the primary endpoint of non-inferiority on primary patency rate at 30 days. The PROOVIT registry would serve as external control in the primary analysis. In addition, the Sponsor proposed to conduct a supplemental

comparison of HAV to synthetic graft on the functional endpoints of superiority on infection and non-inferiority 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 Sponsor may reconsider an earlier proposal from 12/21/2020 informal meeting, in which the Sponsor proposed to pursue an indication for “urgent arterial repair following extremity arterial trauma (b) (4) [REDACTED] where autologous vein is not feasible.”

9. On October 26, 2022, the Sponsor 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 Sponsor’s proposal for BLA submission targeting accelerated approval, the main concerns being insufficient number of study subjects, insufficient data in the targeted population, absence of a clearly pre-specified 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.
10. On March 7, 2023, the Sponsor proposed an observational study (CLN-PRO-V017) in 30 subjects with traumatic injury sustained in Ukraine. The FDA did not agree with the Sponsor’s proposal to combine the efficacy data from Study CLN-PRO-V017 with CLN-PRO-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.
11. On August 11, 2023, the FDA Center for Biologics Evaluation and Research (CBER) leadership communicated to the Sponsor that “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 [of urgent arterial repair following extremity vascular trauma (b) (4) [REDACTED] (b) (4) [REDACTED] when autologous vein is not feasible] along with all the safety data relevant to this indication.”

12. On December 8, 2023, the Applicant submitted BLA 125812/0.

Post-submission:

1. On April 11, 2024, the Applicant submitted safety and efficacy data for 3 additional subjects in Study CLN-PRO-V005 as part of the 120-day safety update in amendment BLA 125812/19.
2. On May 24, 2024, in response to FDA's clinical information request (IR) #25, the Applicant submitted individual clinical summaries for the 3 additional subjects in the 120-day safety report and an imaging compliance table in amendment BLA 125812/36.
3. On June 7, 2024, in response to FDA clinical IR #27, the Applicant explained that Subject (b) (6) was included in the torso group instead of the extremity group was because this subject was enrolled in 2019 under CLN-PRO-V005 Protocol Version 3.0, which stated that "vascular repair in which any portion originates or terminates in the torso will be considered a patient in the torso cohort even if the other end of the repair resides in an extremity." The IR response was submitted to amendment BLA 125812/38.
4. During the BLA review, the proposed indication of "urgent arterial repair following extremity vascular trauma (b) (4) (b) (4) when autologous vein is not feasible" was changed to the current indication in the package insert of "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." The FDA clinical review team recommended this change because it was thought to be more reflective of the study population.

Reviewer comment: The clinical development of the HAV in CLN-PRO-V005 study involved numerous and complex regulatory, clinical, and statistical issues. Study CLN-PRO-V005 underwent multiple major changes while the study was ongoing, and the ongoing clinical outcomes were known. These included major changes to the study design, study population, primary efficacy endpoints, sample size, and SAP. The performance benchmarks based on literature review were derived while this open label trial was ongoing. The performance benchmarks were finalized when all the primary and key secondary efficacy endpoints in the original submission were known. In a well-controlled study, the performance benchmark should be chosen prior to trial initiation, and used to power the study to meet a pre-specified primary objective. Therefore, the Sponsor's frequent changing of key study elements and the analysis plans while the trial was ongoing introduced selection bias.

The FDA was committed to working with the Sponsor and exercised regulatory flexibility on numerous occasions to further the product development. For example, the FDA review team communicated to the Sponsor that 50 subjects with 30-day primary patency rate within Study CLN-PRO-V005 would be required for adequate efficacy and safety evaluation. CBER leadership later communicated to the Sponsor that a combined 50 subjects with 30-day patency rate from both CLN-PRO-V005 and CLN-PRO-V017 would be adequate to support an application for the narrow indication of (b) (4)

along with adequate and sufficient safety data. This represents a significant degree of flexibility because CLN-PRO-V017 was an observational study where the HAV was given under a Humanitarian Aid Program in Ukraine, and likely to be biased.

The FDA also communicated that a historical mean for a benchmark as the external comparator is generally unacceptable. Substantial evidence of efficacy typically requires an accepted benchmark that is chosen towards the upper bound of the possible range of values, and not simply a mean point estimate, which can bias efficacy assessment in favor of the investigational product. Given the unmet medical need in this narrow indication and DoD Priority Product designation, the FDA exercised regulatory flexibility to allow the use of a mean-based benchmark as external comparator as supportive evidence.

While regulatory flexibilities helped further the product development, the data submitted do not offer the same level of certainty expected from a well-designed clinical study, especially from a randomized trial. On the contrary, these flexibilities introduce many challenges in the interpretation of results, such as presence of selection bias and no Type 1 error control.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

3.2 Compliance With Good Clinical Practices And Data Integrity

There were major issues with data quality. During the BLA review, the FDA clinical review team identified low imaging compliance used to determine patency status (i.e., the use of Duplex versus simple ultrasound or doppler scans) and poor adjudication of patency status in subjects who were not followed up to 30 days post-implantation. As a result of the poor data quality and discrepancy between the datasets and the case report forms, the FDA performed its own internal adjudication of the efficacy data.

The clinical team, including a vascular surgeon consult, Dr. Robert Lee, found that there were several cases where the HAV occluded, and the limb survived without revascularization, raising the question if the HAV was needed in the first place, as well as some subjects for whom HAV use was not mandatory or preferred because they had available vein for transplant.

For further details, refer to the clinical review memo by Dr. Prateek Shukla.

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

5.1 Review Strategy

For this review, Study CLN-PRO-V005 constitutes the primary source of evidence for safety and efficacy of HAV. Study CLN-PRO-V017 serves as supportive evidence. I verified the Applicant's efficacy results based on the Applicant's datasets and conducted the same efficacy analyses based on FDA's adjudicated datasets. Primary efficacy evaluation focused on the set of subjects in the extremity group, as defined in Section 6.1.9.

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

The documents considered for statistical review include:

- Submission in BLA 125812/0 (Original submission)
 - Module 1.2 Cover Letters
 - Module 1.6 Meetings
 - Module 1.14 Labeling
 - Module 2.5 Clinical Overview
 - Module 2.7 Clinical Summary
 - Module 5.3 Clinical Study Reports
 - Module 5 Datasets
- Submission in BLA 125812/19 (Day 120 Safety Update)
 - Module 1.2 Cover Letters
 - Module 2.5 Clinical Overview
 - Module 2.7 Clinical Summary
 - Module 5.3 Clinical Study Reports
 - Module 5 Datasets
- Amendment BLA 125812/36 (Imaging Compliance Table)
 - Module 5.3 Clinical Study Reports
- Amendment BLA 125812/38 (IR Response)
 - Module 1.1.1 Information Amendment

5.3 Table of Studies/Clinical Trials

Table 1 summarizes the overview of clinical studies submitted in BLA 125812.

Table 1. Overview of clinical studies submitted in BLA 125812.

Study Identifier	Objective(s) of the Study	Study Design	Study Population	Number of Subjects
CLN-PRO-V005 (Phase 2/3)	Evaluate the safety and efficacy of the HAV for use as an interposition replacement or bypass in patients with vascular trauma undergoing surgery for vascular replacement or reconstruction in size-appropriate vessels	Prospective multicenter, non-randomized, open-label, single-arm, single dose (implantation)	Adults, ≥ 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	54 subjects received HAV as a conduit to repair non-iatrogenic arterial injuries of the extremities
CLN-PRO-V017 (Observational)	Evaluate the efficacy and safety of the HAV in patients who had an HAV implanted to repair or reconstruct an arterial vessel following life- or limb-threatening traumatic injury of an extremity	Retrospective multicenter (3 sites in Ukraine), non-randomized, open-label, single-arm, single dose (implantation)	Adults, ≥ 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	16 subjects received HAV to repair non-iatrogenic arterial injury of an extremity

Source: FDA reviewer.

5.4 Consultations

5.4.2 External Consults/Collaborations (if applicable)

Dr. Robert Lee from the Center for Devices and Radiological Health (CDRH) was consulted on various review issues. Dr. Lee is a vascular surgeon with 30 years of clinical experience in treating trauma patients, including those with blunt and penetrating vascular trauma due to urban violence, industrial accidents, and multiple freeways converging. Specifically, Dr. Lee provided expert opinion on the proper adjudication of clinical outcomes and adverse events of specific interest.

In Dr. Lee's clinical consult memo, he concluded:

"The observed risks of infection associated HAV blowout and of anastomotic disruption are unacceptable when compared to current alternate treatment options. This observed failure mode of the HAV is unpredictable, catastrophic and life threatening. The risk benefit balance when using the HAV is highly unfavorable, and no suitable niche populations are apparent."

It is important to acknowledge that the Department of Defense has identified the need for an off the shelf vascular graft that could be used to treat America's wounded warriors. Although the sponsor's desire to market their device for this use is clear, data has NOT been provided to support that the HAV is safe or effective in this setting and the available data raises major concerns that the HAV would result in worse outcomes than alternative options available to American soldiers and other trauma patients."

Based on the concerning benefit risk profile for the HAV, Dr. Lee recommended that *"no favorable final marketing decision should be made until the sponsor addresses key outstanding clinical questions."* These include providing follow-up data to identify the extent of missing data, conduct outcome analyses on key measures including length of HAV and blunt versus penetrating trauma, and perform analysis limited to the trauma indication excluding iatrogenic injuries and arteriovenous access revisions. Dr. Lee also recommended that there should be an external review of the Sponsor's adjudications by appropriate experts due to data discrepancies identified during the BLA review. For further details, refer to the clinical consult memo by Dr. Robert Lee.

5.5 Literature Reviewed (if applicable)

Literature reviewed for synthetic graft systematic literature review (Search 1):

- Chong VE, Lee WS, Miraflor E, Victorino GP, Applying peripheral vascular injury guidelines to penetrating trauma. J Surg Res. 2014 Jul;190(1):300-4.
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- Ramdass MJ, Harnarayan P. A decade of major vascular trauma: Lessons learned from gang and civilian warfare. Ann R Coll Surg Engl. 2017 Jan;99(1):70-75.
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- 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.
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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study #1: CLN-PRO-V005

The protocol for Study CLN-PRO-V005 was titled “A Phase 2/3 Study for the Evaluation of Safety and Efficacy of Humacyte’s Human Accellular Vessel for Vascular Replacement or Reconstruction in Patients with Life or Limb-threatening Vascular Trauma”. Here, I reviewed the protocol Version 4.0 dated May 24, 2023, and the statistical analysis plan (SAP) Version 8.0 dated May 25, 2023. Substantial statistical changes to the protocol and SAP are summarized in Section 2.5. CLN-PRO-V005 was the first-in-human study in which HAV was used to repair vascular injuries in the limb or torso, other than the heart.

6.1.1 Objectives (Primary, Secondary, etc)

Primary efficacy objective:

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

Key secondary efficacy objectives:

- To determine the patency of the HAV at least 30 days, regardless of interventions
- To determine the ability of the HAV to remain infection-free for 30 days
- To determine the rate of limb salvage for 30 days

Secondary objectives:

- To determine the long-term primary patency of the HAV
- To determine the long-term patency of the HAV, regardless of interventions
- To determine the long-term ability of HAV to stay infection-free
- To determine the long-term rate of limb salvage
- To determine the rates of interventions needed to maintain/restore patency in the HAV
- To determine patient survival
- To evaluate remodeling of the HAV

6.1.2 Design Overview

CLN-PRO-V005 was a Phase 2/3, prospective, multicenter, non-randomized, open-label, single-arm study to evaluate the safety and efficacy of HAV in subjects with vascular trauma to size appropriate vessels in the limb or torso, requiring replacement or reconstruction. The study planned up to 100 subjects. All subjects were to be followed for the initial 12 months, and beyond 12 months, only subjects with a patent HAV were to be followed out to a total of 36 months from the date of HAV implantation.

6.1.3 Population

Key eligibility criteria are described below.

Selected inclusion criteria:

- 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.
- Preoperative imaging or clinical examination indicates the damaged vessel has a defect length of ≤ 38 cm and is appropriately size matched to the 6 mm diameter of the HAV per the judgment of the treating surgeon, taking into account vasoconstriction and situational inflow and outflow considerations.
- 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.
- Aged 18 to 85 inclusive (all sites) and adolescents who have achieved Tanner Stage V Sexual Maturity Rating (US sites only). As in adults, vascular injuries in this pediatric population can be treated with the HAV only if the vascular trauma involves size-appropriate vessels, per the judgment of the treating surgeon.
- Life expectancy of at least 1 year.

Selected exclusion criteria:

- Mangled Extremity Severity Score (MESS) of ≥ 7 .
- Affected limb is at high risk of amputation despite vascular reconstruction (e.g., because of crush injury).
- Catastrophic injuries that make survival unlikely (e.g., Abbreviated Injury Scale (AIS) > 5 or Injury Severity Score (ISS) > 60).
- HAV may not be used for coronary artery repair.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Investigational product: HAV

Route of administration: Implanted (single time) using standard vascular surgical techniques that are similar to the placement of autologous or synthetic peripheral vascular prostheses.

Additional medications: Essential medications include both antibiotic and antithrombotic prophylaxis in conjunction with HAV implantation in accordance with local hospital guidelines. Concomitant medications may include systemic anti-infective medications, non-steroidal anti-inflammatory drugs, systemic glucocorticoids, immunomodulatory drugs, blood products, chemotherapy or radiation used to treat malignancy, and lipid lowering agent. Particular attention was made to identify the use of antithrombotic or antiplatelet agents.

6.1.6 Sites and Centers

The study was conducted at 19 centers, including 17 in the US and 2 in Israel.

6.1.7 Surveillance/Monitoring

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

6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint:

- Primary HAV patency for at least 30 days after implant
 - Primary patency is defined as functional access patency until any type of intervention.

Key secondary efficacy endpoints:

- Secondary patency for at least 30 days after implant
 - Secondary patency is defined as functional HAV patency, with or without preceding successful interventional or surgical procedures to maintain or reestablish patency, until the HAV is abandoned.
- Conduit infection at Day 30 after implant
- Limb salvage rate at Day 30 after implant

Other secondary endpoints:

- Primary patency (long term)
- Secondary patency (long term)
- HAV infection (long term)
- Amputation (long term)
- HAV interventions to maintain/restore patency
- Death
- Histopathology of any clinical explants

Reviewer comment: The FDA and the Applicant had numerous discussions and interactions regarding the efficacy endpoints throughout the pre-BLA phase and after study initiation. Section 2.5 summarizes the key regulatory history and major changes to the endpoints.

6.1.9 Statistical Considerations & Statistical Analysis Plan

This was a non-randomized, single-arm, open-label study. There was no formal hypothesis testing, no pre-specified Type 1 error control, and no multiplicity adjustment. Efficacy endpoints were summarized descriptively.

Analysis Population:

The analysis populations are summarized as follows:

- All HAV set (AHS): All subjects who received HAV, regardless of the location of the vessel repaired and the type of injury.
- Extremity set (ES): All subjects in the AHS who underwent non-iatrogenic arterial vascular repair with HAV in an extremity.
- Torso+Iatrogenic set (TIS): All subjects in the AHS who received HAV in torso as well as subjects who received HAV to repair an iatrogenic injury. Some subjects may belong to both ES and TIS if multiple HAVs were implanted.

Sample Size:

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

Reviewer comment: The planned sample size for this study had changed multiple times. On August 11, 2023, CBER leadership communicated to the Sponsor that “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 [of urgent arterial repair following extremity vascular trauma (b) (4)] when autologous vein is not feasible] along with all the safety data relevant to this indication.”

Statistical methodology:

Primary patency at Day 30 after implantation: The proportion of subjects who had 30-day patency was estimated along with a 2-sided 95% score confidence interval without continuity correction.

Secondary patency for at least 30 days after implantation: The proportion of subjects who maintained secondary patency for at least 30 days was estimated along with an associated 2-sided 95% score confidence interval.

Conduit infection at Day 30 after implant: The proportion of subjects whose HAV remained infection-free for at least 30 days was estimated along with a 2-sided 95% score interval.

Limb salvage rate at Day 30 days after implant: The proportion of subjects who remain amputation-free for at least 30 days was estimated along with a 2-sided 95% score interval.

Reviewer comment: The FDA also computed exact binomial 95% CIs for these endpoints. The exact intervals were slightly wider than the score intervals, but produced similar results and did not change the statistical interpretations of the results.

Handling of intercurrent events:

Death and amputation are two frequent IEs that occur in trauma subjects. The Applicant proposed to use the while-on-treatment strategy for handling these IEs for patency, where if the IE was determined to be causally unrelated to the HAV, the last known post-implant patency status at the time of IE would be used in the primary efficacy analysis. The Applicant created an independent adjudication committee to adjudicate patency status for subjects who were not evaluable due to IEs.

- If the IE is deemed causally related to the HAV, subjects would be included as patency failure
- If causality of the IE cannot be determined, or where patency status is missing post-implant, subjects would be included as patency failure

Reviewer Comment: The FDA agreed to the use of while-on-treatment strategy for handling of deaths and amputations for primary and secondary patency. Based on the Type C meeting on March 7, 2023, a while-on-treatment strategy can be used to handle these IEs only if they can be confidently determined to be unrelated to HAV. During review of the BLA, the FDA clinical review team expressed concerns that inconsistent and/or inadequate methods may have been used to ascertain patency status in different subjects by the adjudication committee (e.g., Applicant's use of ultrasound imaging instead of Duplex scans to determine patency rate, where the Duplex scan is the preferred method). As a result, FDA also performed its own internal adjudication. For further details, refer to the clinical review memo by Dr. Prateek Shukla.

Handling of missing data:

No missing data handling strategies was provided.

Reviewer's comment: Comments about missing data handling approaches were communicated to the Sponsor during the IND stage but the comments were not incorporated. The Sponsor used the same while-on-treatment strategy for missing data due to loss to follow up. In addition, if there was no definitive patency assessment such as Duplex imaging or no culture taken for HAV infection evaluation, the best outcomes (i.e., patency, no infection assumed) were used in the Sponsor's analyses.

Supplementary analysis:

- The main analyses were repeated in AHS and TIS.
- Complete case analysis, where the main estimator will be repeated excluding all missing 30-day patency cases.

Reviewer comment: Supplementary analyses in the AHS and TIS were not performed since the results would not inform regulatory decision on HAV's efficacy and safety for the proposed indication. The Applicant also referred to the complete case analysis as 'Sensitivity Estimator 3' in the SAP, but this is a misnomer and is in fact a supplementary analysis.

Sensitivity analysis:

The main estimator was supported by sensitivity estimators as follows:

- Sensitivity Estimator 1: The main estimator will be repeated, after imputing all unadjudicated causality and missing patency cases as patent.
- Sensitivity Estimator 2: Complete adjudicated case analysis, where the main estimator will be repeated excluding unadjudicated causality and missing patency cases.
- Sensitivity Estimator 4: Best-case scenario, the main estimator will be repeated after inputting all missing 30-day patency cases as patent.
- Sensitivity Estimator 5: Worst-case scenario, the main estimator will be repeated after imputing all missing 30-day patency cases as not patent. This corresponds to the composite strategy where all IEs were counted as failures events.
- Sensitivity Estimator 6: Using multiple imputation (MI) for all missing 30-day patency assuming missingness depends on covariates but not on HAV patency. Logistic regression will be used including age, sex, ISS, and location (lower vs upper) as potential covariates. Additional covariates may be added if they reduce the model Akaike information criterion (AIC).

Reviewer comment: The numbering for 'Sensitivity Estimator' corresponds to the Applicant's numbering in the SAP. Sensitivity Estimator 3 corresponds to the complete case analysis, which is a supplementary analysis.

Subgroup Analyses:

Exploratory analyses of efficacy endpoints may be performed on the following subgroups, contingent on adequate enrollment: upper versus lower extremity, severity of injury, degree of ischemia, location of injury, mechanism of injury, and interval between injury and repair.

Benchmark and Literature review:

The Applicant performed a systematic literature review (SLR) of studies of subjects with traumatic arterial injury or injury to the upper or lower extremity. Studies included randomized controlled trials, single-arm trials, observational prospective cohort or registry studies, observational retrospective studies, and registry or case control studies, published between 2002 and through May 2023.

The Applicant performed two searches: one for vascular reconstruction via synthetic graft (Search 1), and one for non-autologous vein non-synthetic vascular graft (Search 2). Only papers with a score of 4 on the Murad scale (Murad 2018) were included in the meta-analysis for benchmark calculation.

Search 1 screened a total of 6,215 papers of synthetic grafts used in the repair of traumatic arterial injury to the extremities. Search 2 screened a total of 1,582 papers in non-vein non-synthetic grafts and ligation in the same population as in Search 1.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

In the original BLA submission (125812/0), 69 subjects who received the HAV were included, with 51 subjects in the ES group and 18 subjects in the TIS group, with a data cut-off date of June 30, 2023. In the Day 120 safety update (125812/19), the Applicant submitted the safety and efficacy data for 3 additional subjects (b) (6) with a data cut-off date of January 15, 2024. These 3 subjects were all in the ES group. To reduce selection bias and maximize information in this small trial, the FDA included them in the analysis population. The FDA also determined that one subject (b) (6) who was initially assigned to the TIS group, should belong to the ES group. Furthermore, the HAV was used as a patch instead of a conduit in another subject (b) (6) in the ES group, so was removed from analyses. In total, 54 subjects who received the HAV as a conduit were included the ES group and 17 in the TIS group.

Reviewer comment: On August 11, 2023, the Applicant received the informal dispute resolution letter from CBER leadership that “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 [of urgent arterial repair following extremity vascular trauma (b) (4) autologous vein is not feasible]

along with all the safety data relevant to this indication.” However, the Applicant retrospectively made a data cutoff on June 30, 2023, for the V005 study. Consequently, 3 ES subjects were excluded, although outcomes for two of the subjects were already known at the time of informational dispute resolution letter.

- Subject (b) (6) was enrolled on July 5, 2023*
- Subject (b) (6) was enrolled on July 13, 2023, and died on (b) (6)*
- Subject (b) (6) was enrolled on August 19, 2023, and died on (b) (6)*

These 3 subjects were all in the ES group. To reduce selection bias and maximize information in this small trial, the FDA included them in the efficacy analyses.

On June 7, 2024, in response to a clinical IR, the Applicant clarified that one subject (b) (6) was included in the torso group instead of the extremity group because this subject was enrolled under CLN-PRO-V005 Protocol Version 3.0. The enrollment criteria under this protocol stated that “vascular repair in which any portion originates or terminates in the torso will be considered a patient in the torso cohort even if the other end of the repair resides in an extremity.” Based on the FDA clinical reviewer’s assessments, although this subject was presented with a gunshot wound to the left upper chest (torso), the HAV was implanted as an interposition graft from the left subclavian artery to the left axillary artery. Thus, this subject met the definition of ES and the FDA included this subject in the ES group for analysis.

6.1.10.1.1 Demographics

Subjects in the ES group had a median age of 30 years old, with a minimum age of 18 and maximum age of 72 years old, were mostly male (74.1%), either white (42.6%) or black/African American (48.1%) race, and non-Hispanic or Latino ethnicity (77.8%). Subjects in the TIS group were older, with a median age of 54 years old, but otherwise had similar baseline demographics. Baseline demographics in CLN-PRO-V005 are summarized in Table 2.

Table 2. Baseline demographics in Study CLN-PRO-V005.

Parameter	ES (N = 54)	TIS (N = 17)	Total HAV (N = 71)
Age (years)	-	-	-
n	54	17	71
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)
Sex, n (%)	-	-	-
Male	40 (74.1%)	11 (64.7%)	51 (71.8%)
Female	14 (25.9%)	6 (35.3%)	20 (28.2%)
Race, n (%)	-	-	-
Black or African American	26 (48.1%)	8 (47.1%)	34 (47.9%)
White	23 (42.6%)	8 (47.1%)	31 (43.7%)
Other	5 (9.3%)	1 (5.9%)	6 (8.5%)
Ethnicity: Hispanic or Latino, n (%)	-	-	-
Yes	12 (22.2%)	2 (11.8%)	14 (19.7%)
No	42 (77.8%)	15 (88.2%)	57 (80.3%)

Abbreviations: SD = Standard Deviation; Min = Minimum; Max = Maximum

Source: Adapted from BLA125812/0; Module 5.3.5.2, Clinical Study Report, p.75.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

In the ES group, 26 (48.2%) subjects had an Abbreviated Injury Scale (AIS) of severe and 14 (25.9%) subjects an AIS of critical. The median Injury Severity Score (ISS) in the ES group was 17, with a minimum score of 9 and a maximum score of 50. The two most common types of injuries in the ES group were gunshot wounds (53.7%) and motor vehicle accidents (25.9%). Penetrating trauma was more common than blunt trauma, with 31 (57.4%) extremity subjects compared to 23 (42.6%), respectively. Comorbid conditions and medical history issues were infrequent in this population. The baseline disease and medical characteristics in CLN-PRO-V005 are summarized in Table 3.

Table 3. Baseline disease and medical characteristics in Study CLN-PRO-V005.

Parameter	ES (N = 54)	TIS (N = 17)	Total HAV (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 (42.3%)
Critical	14 (25.9%)	6 (35.3%)	20 (28.2%)
Missing	0 (0%)	4 (23.5%)	4 (5.6%)
Injury Severity Score (ISS)	-	-	-
n	54	13	67
Mean (SD)	21.1 (10.2)	21.8 (13.4)	21.2 (10.8)
Median (Min, Max)	17.0 (9, 50)	24.0 (4, 50)	17.0 (4, 50)
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 ¹	12 (22.2%)	4 (23.5%)	16 (22.5%)
Artery Category, n (%)	-	-	-
Femoral artery	18 (33.3%)	7 (41.2%)	25 (35.2%)
Popliteal artery	22 (40.7%)	1 (5.9%)	23 (32.4%)
Other	14 (25.9%)	9 (52.9%)	23 (32.4%)
Cause of Trauma, n (%)	-	-	-
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%)	12 (70.6%)	12 (16.9%)
Industrial accident	3 (5.6%)	0 (0%)	3 (4.2%)
Motor vehicle accident	14 (25.9%)	1 (5.9%)	15 (21.1%)
Other ²	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	52 (96.3%)	5 (29.4%)	57 (80.3%)
Open fracture injury	31 (57.4%)	5 (29.4%)	36 (50.7%)
Contaminated wound	50 (92.6%)	9 (52.9%)	59 (83.1%)

Abbreviations: SD = Standard Deviation; Min = Minimum; Max = Maximum

¹One subject (b) (6) presented with a gunshot wound to the left upper chest (torso) but received the HAV as an interposition graft from the left subclavian artery to the left axillary artery. This subject was included in the upper extremity category of the ES group.

²Other causes of trauma in the ES group include laceration from broken glass, rotary saw injury, and skateboard accident.

Source: FDA reviewer.

Autologous vein is the gold standard for repair of vascular trauma. The reasons for not using autologous vein included 3 (5.6%) for patient's preference, 8 (14.8%) for concomitant injury to the vein, 19 (35.2%) for poor quality or size of vein, and 22 (40.7%) for time limitation so harvest not possible. There were 14 (25.9%) instances for other reasons, including body habitus; both legs with external fixation made harvesting problematic; complexity of global care; contralateral limb trauma; saphenous vein transposition was performed initially but failed; saphenous vein harvest not possible; saphenous vein previously removed; heavy contamination; risk of injury to vein due to adjacent injuries to the area; subject on extracorporeal membrane oxygenation (ECMO) did not want to create another wound; obesity resulting in difficult saphenous vein harvest; and prone positioning.

Reviewer's comment: FDA's vascular surgeon consult from CDRH, Dr. Robert Lee, said that "there were several cases where the HAV occluded, and the limb survived without revascularization, raising the question if the HAV was needed in the first place." The clinical reviewer identified four "potential subjects who had HAV abandoned without replacement: (b) (6)

Furthermore, one subject (b) (6) was treated with HAV but had HAV removed on Day 1 due to thrombosis; subsequently, this subject received autologous vein graft. Based on the operative note, "the patient had been consented for Humacyte conduit bypass as part of a clinical trial and therefore we elected to use this conduit and not harvest the saphenous vein." These cases represent situations in which HAV use was not mandatory and raise concerns about trial conduct.

6.1.10.1.3 Subject Disposition

A total of 87 subjects were screened, of whom 15 were screen failures and 72 subjects received HAV. One subject (b) (6) received the HAV as a "patch" instead of as a conduit and was excluded from the efficacy analysis sets. Fifty-four (54) subjects who received the HAV as a conduit were included in the ES group for FDA's efficacy analyses.

Of the 54 subjects in the ES group, 13 subjects were not evaluable at Day 30 for some or all efficacy endpoints. These subjects included 4 deaths, 5 amputations, 2 HAV explantations on Day 1 due to immediate thrombosis, and 2 lost to follow-up. Twelve of the 54 (22.2%) subjects did not have patency data at Day 30.

Reviewer comment: Of these 13 subjects, one subject (b) (6) was lost to follow up on Day 19, but was determined to be non-patent on Day 4. Thus, this subject was evaluable for patency, but not for infection or limb salvage.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Adjudication of subjects not evaluable for Day 30

Of the 54 subjects in the ES group, 12 subjects were not evaluable for primary patency at Day 30 due to amputation (n=5), death (n=4), intraoperative thrombosis (n=2), and loss to follow-up (n=1). The Applicant adjudicated only 3 subjects as non-patent due to thrombosis and HAV explant and adjudicated the remaining 9 subjects as patent despite lack of definitive imaging assessment of patency and presence of histology evidence of non-patency.

The FDA's clinical review team performed an internal re-adjudication of the 12 subjects based on the subjects' case reports. The FDA agreed with the Applicant on 3 subjects (b) (6) who were not patent due to thrombosis and HAV explant. The FDA disagreed with the Applicant and determined that one subject (b) (6) was not patent at Day 30 because the subject was amputated on Day 4 with myonecrosis, worrisome explant histology with bacteria, and thrombus on histology. The FDA adjudicated the remaining 8 subjects as non-patent due to the lack of definitive imaging assessment or histology evidence for patency. For further details, refer to the clinical review memo by Dr. Prateek Shukla.

Applicant's analysis

The Applicant's analyses were based on the 51 subjects' data submitted in the original BLA submission with a data cut-off date of June 30, 2023. The Applicant's data did not exclude the "patch" subject (b) (6) from the ES group, did not count subject (b) (6) who met the definition of ES but was originally assigned to the torso group, and did not include the 3 additional subjects (b) (6) submitted in the 120-day safety update.

Based on the Applicant's data, the primary patency rate at Day 30 using the while-on-treatment strategy was 84.3% (95% CI: 72.0%, 91.8%). Sensitivity analysis using the composite strategy and a complete case analysis yielded a primary patency rate of 68.6% (95% CI: 55.0%, 79.7%) and 81.4% (95% CI: 67.4%, 90.3%), respectively. The analysis results for Day 30 primary patency rate in the ES group are summarized in Table 4.

Table 4. Primary patency rate at Day 30 in the extremity group in Study CLN-PRO-V005 based on Applicant's data.

	Patency Rate % (n/N)	95% CI
Primary efficacy analysis: Primary patency rate at Day 30 (While-on-treatment) ¹	84.3% (43/51)	72.0%, 91.8%
Sensitivity analysis: Primary patency rate at Day 30 (Composite) ²	68.6% (35/51)	55.0%, 79.7%
Supplementary analysis: Primary patency rate at Day 30 (Complete case) ³	81.4% (35/43)	67.4%, 90.3%

¹IEs were handled using while-on-treatment strategy.

²IEs were handled using composite strategy, where missing 30-day patency due to IE was assigned not patent.

³IEs were excluded as a complete case analysis.

Source: Adapted from BLA125812/0; Module 5.3.5.2, Clinical Study Report, p.87.

Reviewer's comment: The while-on-treatment strategy represents an overestimate of the Day 30 primary patency rate because the adjudicated subjects are counted as patent at the time of the intercurrent event 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. A composite strategy in which deaths and amputations without definitive imaging assessments for patency are considered non-patent should have been used. The complete case analysis is likely biased due to selection bias introduced by excluding non-evaluable subjects who had worse outcomes than subjects who were evaluable for Day 30.

FDA's analysis

The FDA's analysis was based on 54 subjects in the ES group, which excluded the one "patch" subject (b) (6) included the one torso subject (b) (6) in the ES group, and included the 3 new subjects (b) (6) in the 120-day safety update.

Based on FDA's adjudication, the primary patency rate at Day 30 was 66.7% (95% CI: 53.4%, 77.8%). The while-on-treatment strategy and the composite strategy were the same because many of the non-evaluable subjects had no data to support patency. The complete case analysis resulted in a primary patency rate of 78.3% (95% CI: 64.4%, 87.7%), which is likely biased due to selection bias. The analysis results for primary patency at Day 30 in the ES group are summarized in Table 5.

Table 5. Primary patency rate at Day 30 in the extremity group in Study CLN-PRO-V005 based on FDA's data.

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%
Sensitivity 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%

¹IEs were handled using while-on-treatment strategy.

²IEs were handled using composite strategy, where missing 30-day patency due to IE was assigned not patent.

³IEs were excluded as a complete case analysis.

Source: FDA reviewer.

Benchmark from literature

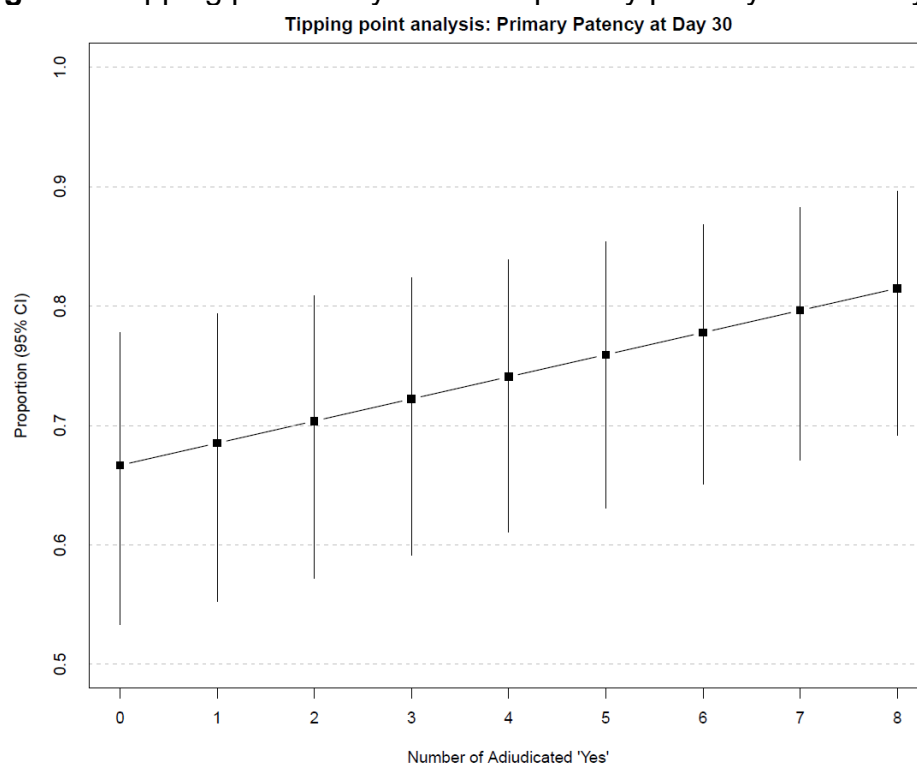
Primary patency for synthetic grafts was extracted from only 1 publication (Stonko et al. 2022), which reported 9 cases out of 51 total patients who needed re-operative interventions. Here, we inferred no need for re-operative interventions meant primary patency, so the estimate from this article was 82.4% (95% CI: 69.7%, 90.4%).

The Applicant also identified only 1 study (Reilly 2019) with 12 non-vein non-synthetic grafts which reported a primary or secondary patency estimate of 78% (95% CI: 49.5%, 97.6%).

Tipping point analysis: primary patency at Day 30

A "tipping point" analysis was conducted to evaluate the impact of adjudicating the 8 subjects who had no definitive imaging assessment or histology evidence and were adjudicated as failures in the FDA's primary analysis. The results of this sensitivity analysis are illustrated in Figure 1.

Figure 1. Tipping point analysis for the primary patency rate at Day 30.



Source: FDA reviewer.

The tipping point analysis shown in Figure 1 illustrated that at least 7 subjects without definitive imaging assessment or histology evidence would need to be patent in order for the primary patency rate to meet the external benchmark of 78% for non-autologous non-synthetic grafts, and all 8 subjects would need to be patent to meet the benchmark of synthetic graft.

Reviewer comment: Comparison to the mean of the benchmark was descriptive in nature and served as supportive evidence. It is unknown whether the trial population and the population included in the meta-analysis were comparable. The primary patency rate of HAV at Day 30 might be lower or comparable to that of synthetic graft. It is difficult to make a conclusion without a randomized controlled trial.

6.1.11.2 Analyses of Secondary Endpoints

Secondary patency at Day 30

Applicant's analysis

Based on the Applicant's adjudication, the secondary patency rate at Day 30 using the while-on-treatment strategy was 90.2% (95% CI: 79.0%, 95.7%). Sensitivity analysis using the composite strategy and a complete case analysis yielded a secondary patency rate of 74.5% (95% CI: 61.1.0%, 84.5%) and 90.5% (95% CI: 77.9%, 96.2%), respectively. The analysis results for secondary patency at Day 30 in the ES group are summarized in Table 6.

Reviewer's comment: As for the primary endpoint, the while-on-treatment strategy represents an overestimate of the Day 30 secondary patency rate because the adjudicated subjects are counted as patent at the time of the intercurrent event 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. A composite strategy in which deaths and amputations without definitive imaging assessments for patency are considered non-patent should have been used. The complete case analysis is likely biased due to selection bias introduced by excluding non-evaluable subjects who had worst outcomes than subjects who were evaluable for Day 30.

Table 6. Secondary patency rate at Day 30 in the extremity group in Study CLN-PRO-V005 based on Applicant's data.

	Patency Rate % (n/N)	95% CI
Key secondary efficacy endpoint: Secondary patency rate at Day 30 (While-on-treatment) ¹	90.2% (46/51)	79.0%, 95.7%
Sensitivity analysis: Secondary patency rate at Day 30 (Composite) ²	74.5% (38/51)	61.1%, 84.5%
Supplementary analysis: Secondary patency rate at Day 30 (Complete case) ³	90.5% (38/42)	77.9%, 96.2%

¹IEs were handled using while-on-treatment strategy.

²IEs were handled using composite strategy, where missing 30-day patency due to IE was assigned not patent.

³IEs were excluded as a complete case analysis.

Source: Adapted from BLA125812/0; Module 5.3.5.2, Clinical Study Report, p.89.

FDA's analysis

In the FDA's dataset, all the subjects that the FDA adjudicated as patent for Day 30 primary patency were counted as patent for Day 30 secondary patency, in addition to the 3 subjects (b) (6) who were included as patent for secondary patency.

Based on the FDA's adjudication, the secondary patency rate at Day 30 using the while-on-treatment strategy was 72.2% (95% CI: 59.1%, 82.4%). The while-on-treatment strategy and the composite strategy were the same because many of the non-evaluable subjects had no data to support patency. The complete case analysis resulted in a secondary patency rate of 84.8% (95% CI: 71.8%, 92.4%), which is likely biased due to selection bias. The analysis results for secondary patency at Day 30 in the ES group are summarized in Table 7.

Table 7. Secondary patency rate at Day 30 in the extremity group in Study CLN-PRO-V005 based on FDA's data.

	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%
Sensitivity 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%

¹IEs were handled using while-on-treatment strategy.

²IEs were handled using composite strategy, where missing 30-day patency due to IE was assigned not patent.

³IEs were excluded as a complete case analysis.

Source: FDA Reviewer.

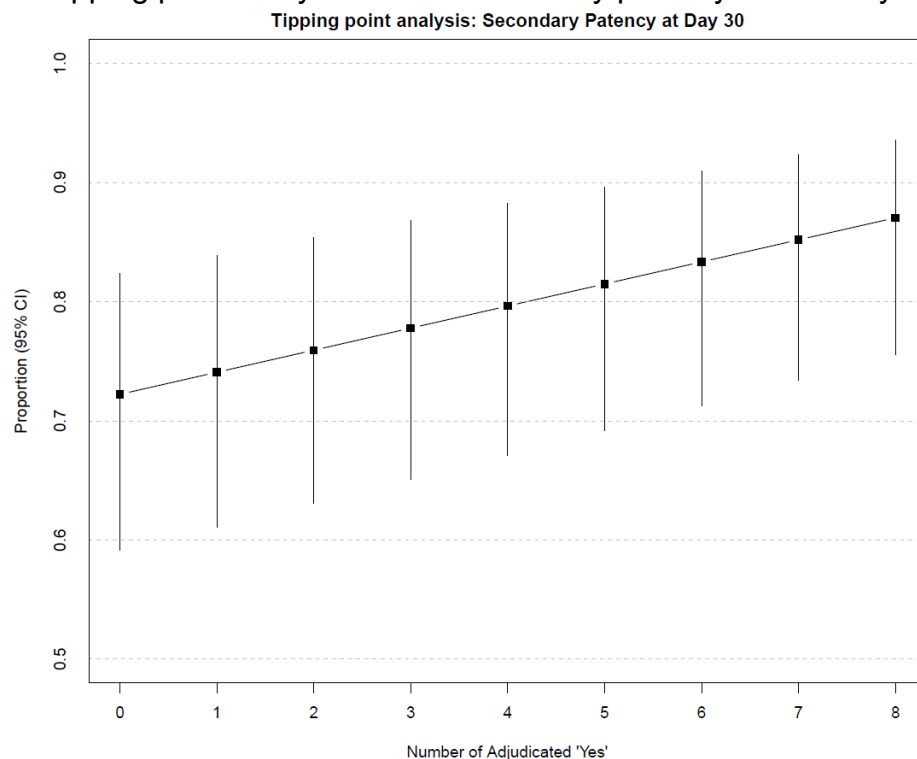
Benchmark from literature

The benchmark for secondary patency rate was derived from 7 studies on synthetic grafts. The meta-analysis resulted in a mean estimate of 78.9% (95% CI: 68.0%, 88.4%).

Tipping point analysis: secondary patency at Day 30

A "tipping point" analysis was performed to assess the robustness of the secondary patency rate. This sensitivity analysis is illustrated in Figure 2. At least 4 subjects would need to be patent for the secondary patency rate to be 78%, and 5 subjects would need to be patent to achieve a patency rate of 80%.

Figure 2. Tipping point analysis for the secondary patency rate at Day 30.



Source: FDA Reviewer.

HAV Infection rate at Day 30

Applicant's analysis

Based on the Applicant's dataset, only 1 subject (b) (6) had HAV infection by Day 30. The HAV infection rate at Day 30 was 2.0% (95% CI: 0.4%, 10.3%). This analysis underestimated the risk of HAV infection as it counted subjects who were not evaluable for Day 30 and/or had no culture taken for infection evaluation as having no infection for Day 30. Nine out of the 12 subjects did not make it to Day 10 and two subjects had HAVs removed on Day 1, but all were counted as not infected for Day 30.

Reviewer's comment: The 12 subjects in the Applicant's dataset not evaluable for infection included: subject (b) (6) (amputation on Day 4), (b) (6) (death on Day 4), (b) (6) (LTFU on Day 5), (b) (6) (amputation on Day 19), (b) (6) (amputation on Day 6), (b) (6) (explant/amputation on Day 17), (b) (6) (LTFU on Day 20), (b) (6) (death on Day 9), (b) (6) (explant due to thrombosis on Day 1), (b) (6) (amputation on Day 9), (b) (6) (death on Day 8), (b) (6) (explant due to thrombosis on Day 1).

The Applicant did not evaluate HAV infection for many of the subjects who were amputated or died. This analysis used the while-on-treatment strategy of handling the IEs for estimation of infection rate, which was not pre-specified in the SAP. It is unknown whether HAV was infected for many of the subjects who were amputated or died or were lost to follow-up. Including subjects with missing

data on HAV infection as having no infection for Day potentially underestimated the risk of infection, biasing in favor of HAV.

FDA's analysis

Based on the FDA's adjudicated dataset, the HAV infection rate at Day 30 was 3.7% (95% CI: 1.0%, 12.5%) in 2 subjects (b) (6). The FDA also identified one subject (b) (6) who had HAV infection past Day 30, but it was unknown when infection took place. The HAV infection rate over the entire study duration was 5.6% (95% CI: 1.9%, 15.1%). For further details, refer to the clinical review memo by Dr. Prateek Shukla.

Benchmark from literature

To establish an external benchmark comparator, the Applicant performed a SLR for synthetic graft infection in a similar manner as described previously for patency rates. Of the 5 papers included in the Applicant's meta-analysis, 3 papers concerned a civilian population while 2 papers concerned a military population.

Much lower infection rates were reported in civilian trauma than in military trauma: 0% in 0 out of 51 subjects, 6.4% in 3 out of 47 subjects, and 6.3% in 1 out of 16 subjects in the three civilian population papers, compared to 28.6% in 4 out of 14 subjects and 40.0% in 2 out of 5 subjects in the two military population papers. The 8.4% infection rate that the Applicant initially reported as benchmark was much higher due to the inclusion of the 2 military trauma papers and thus biased in favor of HAV.

Because Study CLN-PRO-V005 enrolled only civilian trauma subjects, an appropriate external benchmark should be based on the 3 civilian trauma papers. Based on the 3 papers in civilian trauma, the infection rate benchmark could have been 2.5% (95% CI: 0%, 11%). The HAV infection rate of 3.7% exceeded this benchmark. In addition, one paper (Stonko et al., 2022) that enrolled 51 civilian trauma subjects with an injury severity score (mean: 21.1, median, 17.5) very similar to subjects in CLN-PRO-V005 (mean: 20.8, median, 17.0), did not report any infections.

Based on these findings, the data do not support the Applicant's claim that the HAV is infection resistant and can be used in grossly contaminated trauma wounds.

Limb salvage rate at Day 30

Applicant's analysis

Based on the Applicant's data, the limb salvage rate at Day 30 was 90.2% (95% CI: 79.0%, 95.7%).

FDA's analysis

Based on the FDA's adjudicated data, the limb salvage rate at Day 30 was 75.9% (95% CI: 63.1%, 85.4%) in 41 out of 54 subjects. Five subjects were amputated and 4 died. The amputation rate at Day 30 was 9.3% (95% CI: 4.0%, 19.9%). For further details, refer to the clinical review memo by Dr. Prateek Shukla.

Reviewer's comment: The limb salvage rate was estimated to be much lower in FDA's analysis compared to the Applicant's. This large discrepancy was due to the Applicant's use of the while-on-treatment strategy in handling intercurrent events, which considered subjects who died, had HAV explanted, HAV occlusion, or were lost to follow up as limb salvaged. In contrast, the FDA assumed the conservative values of limb not salvaged for these subjects. In particular, subjects who died and were no longer at risk for amputation should not be counted as limb salvage.

Benchmark from literature

To establish an external benchmark comparator, the Applicant performed a SLR for synthetic graft amputation rate in a similar manner as described previously for patency rates. Amputations for synthetic graft subjects were extracted from 86 grafts reported in 6 papers. The meta-analysis pooled amputation rate was 24.3% (95% CI: 8.7%, 43.7%). Only one study (Reilly 2019) was identified with non-vein non-synthetic grafts (n = 12), which reported an amputation rate of 16.7% (95% CI: 4.7%, 44.8%). The amputation rate throughout the study was similar to the rate reported in the non-vein non-synthetic graft population.

6.1.11.3 Subpopulation Analyses

The FDA conducted post-hoc exploratory subgroup analyses to assess the patency rate based on FDA's adjudicated patency data.

By age

Subgroup analysis by age was not performed due to insufficient pediatric or older adult subjects enrolled in the study.

By sex

The primary patency rate at Day 30 in males was 65.0% (n = 40; 95% CI: 49.5%, 77.9%) and in females was 71.4% (n = 14; 95% CI: 45.4%, 88.3%). The primary patency rate at Day 30 was similar between males and females.

By race

The primary patency rate at Day 30 in black or African American subjects was 76.9% (n = 26; 95% CI: 58.0%, 89.0%) and in white subjects it was 65.2% (n = 23; 95% CI: 44.9%, 81.2%). Only 1 subject out of 5 was patent in the 'Other' (non-black, non-white) race group, so the patency rate was 20.0% (95% CI: 3.6%, 62.5%). The primary patency rate at Day 30 was similar between black

and white subjects. The patency rate was much lower in subjects of other races, but this subgroup was limited by the small sample size.

Primary patency at Day 30 by HAV lengths

There is currently no accepted graft length in literature that would suggest a threshold for subgroup analysis. Based on the clinical reviewer's recommendation, FDA conducted subgroup analyses by HAV length, < 15 cm versus ≥ 15 cm. One subject (b) (6) did not have HAV length recorded. The following results were reported assuming this subject received an HAV < 15cm in the subgroup analysis.

Twenty-seven (69.2%) subjects were patent at Day 30 for those with HAV < 15 cm, compared to 9 (60.0%) with HAV ≥ 15 cm. The subgroup analyses were then repeated assuming subject (b) (6) received an HAV ≥ 15 cm in the subgroup analysis, with similar results. Subjects with longer HAV lengths had somewhat lower primary patency rate at Day 30. However, no conclusions about the relationship between HAV lengths and patency can be reached due to limited sample size in the subgroups and the post hoc nature of the analysis.

Primary patency at Day 30 by trauma type

A subgroup analysis by blunt versus penetrating trauma was performed. The primary patency rate at Day 30 among subjects with blunt trauma was 65.2% (95% CI: 44.9%, 81.2%) in 15 out of 23 subjects. The primary patency rate at Day 30 among subjects with penetrating trauma was 67.7% (95% CI: 50.1%, 81.4%) in 21 out of 31 subjects. The patency rates were similar between the two trauma types.

6.1.11.4 Dropouts and/or Discontinuations

In total, 13 subjects in the ES experienced IEs or discontinued from the study before Day 30. These subjects were adjudicated by both the Applicant and the FDA. Of these 13 subjects, 4 died, 5 were amputated, 2 had HAV explanted on Day 1 due to immediate thrombosis, and 2 were lost to follow-up. For further details, refer to the clinical review memo by Dr. Prateek Shukla.

Section 6.1.9 describes the planned strategy for handling intercurrent events and missing data due to loss to follow up.

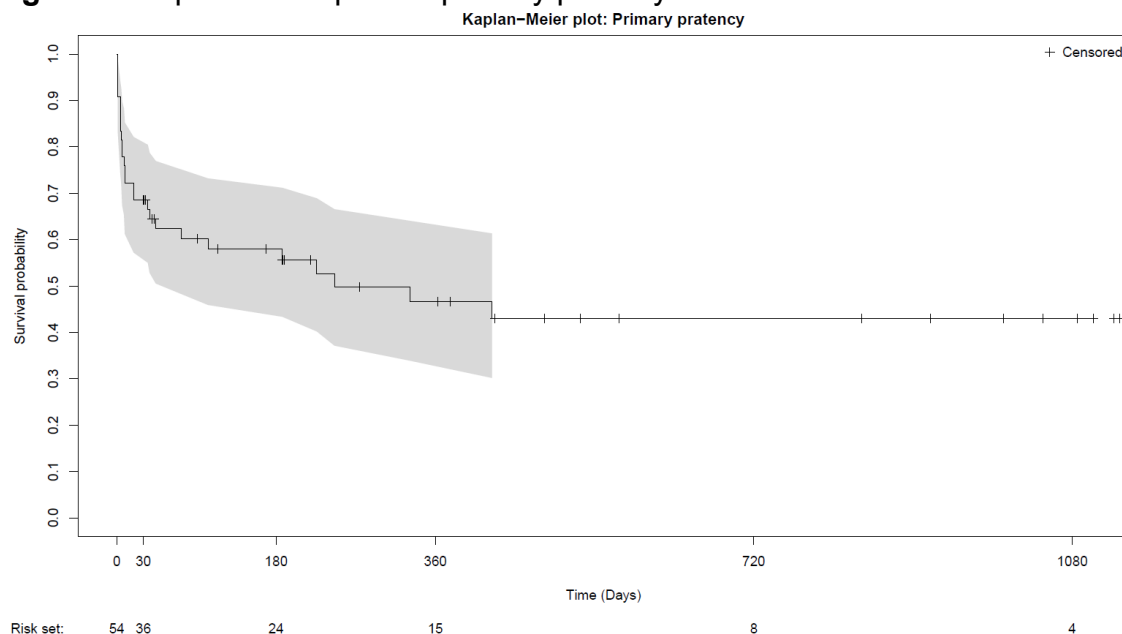
6.1.11.5 Exploratory and Post Hoc Analyses

The FDA conducted post-hoc exploratory analyses per FDA clinical review team's request.

Long term primary patency rate

The 30-day landmark primary patency estimate based on a Kaplan-Meier (KM) survival curve was 68.5% (95% CI: 57.2%, 82.1%) and the 6-month landmark estimate was 58.0% (95% CI: 45.9%, 73.2%). The KM plot for the primary patency rate is illustrated in Figure 3.

Figure 3. Kaplan-Meier plot for primary patency.

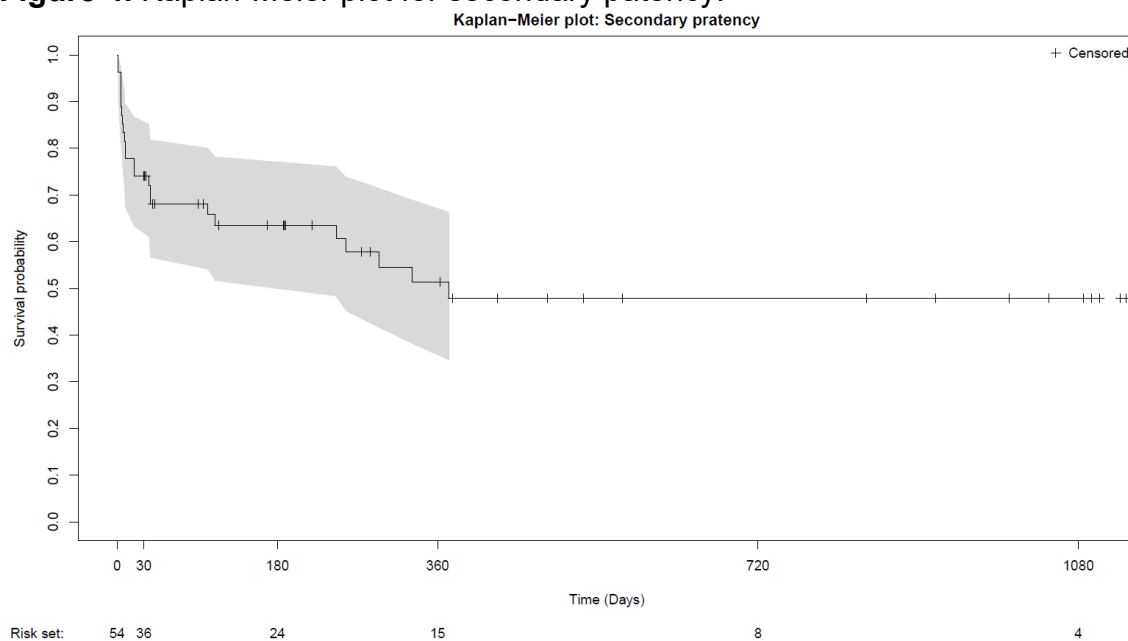


Source: FDA Reviewer.

Long term secondary patency rate

The 30-day landmark secondary patency estimate based on a KM survival curve 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 4.

Figure 4. Kaplan-Meier plot for secondary patency.



Source: FDA Reviewer.

The KM analysis of primary and secondary patency are limited by the availability of long-term patency data after 1 year. The KM estimates for patency rates at Day 30 are aligned with estimates reported in Sections 6.1.11.1 and 6.1.11.2.

Reviewer's comment: The data on long-term efficacy and safety were very limited by the large number of dropouts. Subject follow-up ranged from 1-1134 days (median = 188.5 days) with 41 subjects (75.9%) followed through day 30 and 30 subjects (55.6%) followed for at least six months. The KM analyses also assumed non-informative censoring which might not be reasonable. The long-term efficacy and safety of HAV is unknown.

6.1.12 Safety Analyses

Descriptive statistics were used to summarize safety data for Study CLN-PRO-V005. AEs were reported from the time of informed consent through the data cutoff date of June 30, 2023.

6.1.12.3 Deaths

Six subjects in the extremity group died. Four deaths occurred in the first 30 days of the study. Two additional subjects died on days 42 and 128, respectively. None of the deaths was deemed related to HAV.

6.1.12.4 Nonfatal Serious Adverse Events

In the ES group, 28 subjects experienced 78 SAEs. The most frequent adverse events ($\geq 3\%$ of subjects) reported in the ES were wound infection, thrombosis, pyrexia (fever), pain, anastomotic stenosis, HAV rupture and infection. Sixteen subjects (29.6%) had wound infection, 15 (27.8%) had thrombosis, 5 (9.3%) anastomotic stenosis, 4 (7.4%) had HAV rupture, and 3 (5.6%) had HAV infection. Out of the 5 cases of anastomotic stenosis, two cases (3%) were assessed as serious adverse events.

6.1.12.5 Adverse Events of Special Interest (AESI)

In the ES group, 15 out of 54 subjects (27.8%) experienced a thrombotic event involving the HAV, and 5 out of 54 extremity subjects (9.3%) developed anastomotic stenosis of the HAV. Other complications of the HAV include anastomotic bleeding or rupture ($n = 4$, 7.3%), pseudoaneurysm ($n = 2$, 3.7%), and aneurysm ($n = 1$, 1.9%).

Reviewer's comment: We defer to the clinical review team to assess the impact of the 7.4% rupture risk on the overall benefit-risk profile of HAV.

6.2 Study #2: CLN-PRO-V017

Study CLN-PRO-V017 was a retrospective, observational study to evaluate the safety and efficacy of the HAV for arterial repair or reconstruction in Ukrainian subjects with life or limb-threatening vascular trauma. This study serves as supportive evidence of safety and efficacy of HAV.

6.2.1 Objectives (Primary, Secondary, etc)

Primary efficacy objective:

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

Secondary efficacy objectives include:

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

6.2.2 Design Overview

CLN-PRO-V017 was a retrospective, observational, cohort, multicenter study in 19 Ukrainian subjects, aged ≥ 18 to ≤ 85 years old, to evaluate the safety and efficacy of the HAV for arterial replacement or reconstruction in subjects with life- or limb-threatening vascular trauma.

6.2.3 Population

The study population included Ukrainian subjects, aged ≥ 18 to ≤ 85 years old, with HAV implanted to repair or reconstruct an arterial vessel following life- or limb-threatening traumatic injury of the extremity between June 2022 and 15 May 2023 (inclusive). The subjects received the HAV under the Humacyte Humanitarian Aid Program in Ukraine.

Reviewer comment: Based on the CLN-PRO-V017 clinical study report, surgeons who received HAVs for humanitarian aid were provided a document entitled "Humacyte Human Acellular Vessel (HAV) for Arterial Replacement or Reconstruction in Patients with Limb-threatening Vascular Trauma (Recommendations for UKRAINE)", that recommended the use of the same inclusion and exclusion criteria as CLN-PRO-V005. However, the inclusion/exclusion criteria in the CLN-PRO-V017 protocol simply stated that the study population included subjects 18 to 85 years old with a need for arterial repair following extremity trauma, with no mention of severity of injuries, feasibility of autologous vein graft, size of conduit, or life expectancy. It is unknown if the recommendations were followed in practice.

6.2.6 Sites and Centers

The study was conducted at 3 sites located in Ukraine.

6.2.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint:

- Primary HAV patency for at least 30 days after implant

Key secondary efficacy endpoints:

- Secondary patency for at least 30 days after implant
- HAV infection free rate for 30 days
- Limb salvage rate for 30 days

Other secondary endpoints:

- HAV 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

CLN-PRO-V017 was a retrospective, observational study in which subjects received the HAV. There was no formal hypothesis testing, no pre-specified significance level or Type 1 error control, and no multiplicity adjustment. Efficacy evaluation was based on descriptive statistics.

The analysis populations included the AHS and ES. The AHS includes all subjects who underwent arterial repair with an HAV in an extremity and has been consented for the study. The ES includes all subjects in the AHS who underwent non-iatrogenic arterial vascular repair with an HAV in an extremity.

No formal sample size calculations were performed. The sample size was determined by the number of subjects 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 CLN-PRO-V005. Missing data and intercurrent event handling strategies were also the same as study CLN-PRO-V005.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

In total, 19 subjects received the HAV in Ukraine under the Humanitarian program. Two subjects were lost to follow-up and could not be contacted for informed consent.

Among the remaining 17 subjects, one subject had iatrogenic injury to the limb, and 16 subjects had non-iatrogenic arterial injury to the limb. The 16 subjects were included in the ES group, the primary analysis population for efficacy endpoints.

6.2.10.1.1 Demographics

The 16 subjects in the ES were all male, white, with ethnicity not Hispanic or Latino, and had a mean age of 34.2 (SD 9.0) and median age of 30.5, ranging

from 22 to 54 years old. The subject with iatrogenic injury (b) (6) was a 55 years old, non-Hispanic, white male.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Comorbid conditions and medical history issues were infrequent in this population. Subject (b) (6) sustained a right common femoral artery iatrogenic injury (penetrating trauma).

The baseline medical characteristics for the 16 subjects in the ES are summarized in Table 10. The majority of subjects sustained injury to the femoral artery (68.8%) in the lower extremity (87.5%). The nature of injuries was mostly penetrating trauma (87.8%) and the cause of injuries were mostly due to blast shrapnel (75%). The majority of subjects were categorized severe (31.3%) on the AIS, followed by serious (18.8%) and critical (12.5%). Four subjects had missing AIS. The median Injury Severity Score (ISS) was 16, with a minimum score of 1 and a maximum score of 73.

The 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 10. Baseline disease and medical characteristics in study CLN-PRO-V017.

Parameter	ES (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%)
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 (87.5%)
Open fracture injury	13 (81.3%)

Abbreviations: SD = Standard Deviations; Min = Minimum; Max = Maximum

Source: FDA reviewer.

Reviewer's comment: The subjects enrolled in CLN-PRO-V017 likely did not represent the typical serious military trauma. In terms of AIS, V017 subjects were categorized severe (31.3%), serious (18.8%), critical (12.5%), and minor (12.5%) and missing (25.0%). The ES group in CLN-PRO-V005 had overall more serious injuries, with 26 (47.3%) subjects of severe AIS, 14 (25.5%) of critical, 15 (27.3%) of serious. Among the subjects with non-missing ISS scores in CLN-PRO-V017 the mean and median ISS were 21 and 16 (with range: 1, 73), respectively. The ES group in the CLN-PRO-V005 had similar ISS scores, with mean and median ISS of 20.8 and 17 (range: 9, 50), respectively.

6.2.10.1.3 Subject Disposition

In total, 17 subjects provided informed consent to allow retrospective data collection for Study CLN-PRO-V017, with a data cutoff date of July 31, 2023. Of the 17 subjects, HAV was implanted in 16 subjects to repair non-iatrogenic vascular injuries to an extremity, and in one patient to repair an iatrogenic

vascular injury. The length of follow-up was limited, where 3 subjects did not have follow-up past 30 days and 7 subjects did not have follow-up past 6 months. No subjects died or were amputated.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The primary patency rate at Day 30 was 93.8% (95% CI: 71.7%, 98.9%) in 15 of the 16 subjects in the ES group. Duplex imaging was performed in 15 subjects at Day 30, and confirmed patency of the conduit in all cases where ultrasound was performed. One subject, who lost patency prior to Day 30 and had the HAV removed, did not complete Duplex imaging.

Reviewer comment: Because the study population consisted of all white and male subjects, subgroup analysis for race and sex was not performed. The one non-patent subject (b) (6) was 54 years old.

6.2.11.2 Analyses of Secondary Endpoints

The secondary patency rate at Day 30 was also 93.8%. No subjects were reported to have died or amputated at Day 30. All subjects were evaluated as having successful limb salvage at Day 30.

One subject (b) (6) who lost patency prior to Day 30, was observed in one section of the HAV to have the presence of bacteria along the abluminal surface, suggestive of extension of infection from the surrounding tissues. The HAV infection rate in the ES group was 6.3% (95% CI: 1.1%, 28.3%).

Reviewer's comment: The efficacy results in CLN-PRO-V017 were more positive than the efficacy results in CLN-PRO-V005. This could be due to differing populations and/or selection bias impacting the patency and infection rates favorably toward HAV. In addition, Dr. Robert Lee noted that "the data were skewed to shrapnel injuries and not the more typical devastating sever limb or polytraumatic injuries that could provide robust data of HAV in terms of infection resistance."

6.2.12 Safety Analyses

6.2.12.3 Deaths

No deaths were reported in this study.

6.2.12.4 Nonfatal Serious Adverse Events (SAE)

One subject (b) (6) who was non-patent at Day 30, was reported to have 3 instances of SAE. On Day 8, bleeding from the surgical site led to the discovery of a "2 mm" rupture in the HAV that was repaired with sutures. On Day 12, the subject was operated on again for bleeding from the sutured HAV site. This was

repaired with a new end to end anastomosis after resecting 1 cm of the HAV. The surgeon noted at the time of operation that there were signs of wound infection. On Day 13, due to persistent bleeding from the postoperative site, the HAV was excised and removed.

Another subject (b) (6) was reported to have HAV occlusion on Day 235. Reintervention failed and the HAV was abandoned on Day 293.

6.2.12.5 Adverse Events of Special Interest (AESI)

Two AESIs were reported during the data review period. As described in Section 6.2.12.4, one subject had HAV rupture with HAV infection. The other AESI was a vascular graft thrombosis in Subject (b) (6) after Month 6.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

HAV is an acellular tissue-engineered vessel composed of human extracellular matrix (ECM) proteins typically found in human blood vessels. Results from CLN-PRO-V005 and CLN-PRO-V017 were submitted in this BLA to support the indication of HAV's 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.

The primary source of evidence to support this BLA is from study CLN-PRO-V005. Study CLN-PRO-V005 was a Phase 2/3, prospective, multicenter, non-randomized, open-label, single-arm study in a total of 72 subjects aged 18 to 85 years old, with life or limb threatening traumatic injury to an arterial vessel in the limb or torso, who need replacement or reconstruction. Of the 72 subjects, 54 subjects with non-iatrogenic, extremity arterial injuries who received HAV as a conduit were included in the primary efficacy evaluation. The primary endpoint was primary vessel patency at Day 30. The key secondary endpoints included secondary vessel patency at Day 30, HAV infection at Day 30, and limb-salvage at Day 30. Among the 54 subjects, 13 subjects were not evaluable at Day 30 due to death (n=4), amputation (n=5), intraoperative thrombosis (n=2) or loss to follow up (n=2). Twelve of the thirteen subjects were not evaluable for patency at Day 30, while one subject was determined to be non-patent before 30 days; all thirteen subjects were not evaluable for infection and limb-salvage at 30 days. The Food and Drug Administration (FDA) performed an internal adjudication for these subjects.

Based on the FDA adjudication, the primary patency rate at Day 30 was 66.7% (95% CI: 53.4%, 77.8%), which was lower than the mean primary patency rate for synthetic grafts of 82.4% (based on literature search). The secondary patency rate at Day 30 was 72.2% (95% CI: 59.1%, 82.4%), which was lower than that for synthetic grafts of 78.9% (based on literature search). The limb salvage rate at Day 30 was 75.9% (95% CI: 63.1%, 85.4%). The HAV infection rate at Day 30

was 3.7% (95% CI: 1.0%, 12.5%), which was higher than the mean infection rate of 2.5% for synthetic grafts in civilian trauma (based on literature search). The risk of HAV infection was likely underestimated due to the 13 subjects not evaluable for infection at Day 30 but counted as HAV infection-free.

There were six deaths (11.1%) in this extremity group, of which four deaths occurred in the first 30 days, one on Day 42, and one on Day 128. None of the deaths were deemed related to the HAV. Of the 54 subjects, 15 (28%) experienced HAV thrombosis, 5 (9%) developed anastomotic stenosis of the HAV, 4 (7%) had HAV rupture or anastomotic failure, and 3 (6%) had HAV infection. Other adverse events included fever in 9 (17%) subjects and procedural pain in 8 (15%) subjects.

Study CLN-PRO-V017 was a retrospective, observational, open-label, single-arm study in 17 subjects aged ≥ 18 to ≤ 85 years old, with arterial injury of the extremity, who received the HAV under the Humacyte Humanitarian Aid Program in Ukraine between June 2022 and 15 May 2023. One subject had iatrogenic injury to the limb and 16 subjects had non-iatrogenic arterial injury to the limb. Results from the 16 subjects with a data cut-off date of July 31, 2023 serve as supportive evidence of efficacy and safety.

The primary and secondary patency rates at Day 30 were both 93.8% (95% CI: 71.7%, 98.9%). The HAV infection rate in this group was 6.3% (95% CI: 1.1%, 28.3%). None of the subjects were amputated, and no deaths were reported. One subject was reported to have 3 instances of SAE, due to persistent bleeding caused by a rupture in the HAV which was consequently excised and removed. Another subject was reported to have HAV occlusion and the HAV was abandoned.

10.2 Conclusions and Recommendations

Neither study met the usual criteria for an adequate and well-controlled trial. In Study CLN-PRO-V005, the analyses were not prespecified before the outcomes were known, and the analyses were all descriptive without formal hypothesis testing planned. Multiple major changes were introduced while the open-label study was ongoing. The study also had conduct issues with poor data quality and questionable trial integrity. For example, several cases were identified in which an implanted HAV subsequently became occluded, but the limb survived without revascularization, which raises the question of whether HAV implantation was necessary in the first place for these subjects. Other subjects treated with the HAV were later identified to have vein available for autologous graft, in which case HAV use would not be mandatory or preferred.

Study CLN-PRO-V017 was a retrospective observational study, which is prone to selection bias and offers only limited supportive evidence due to the different study population and settings. The efficacy results in CLN-PRO-V017 appeared to be better than those in CLN-PRO-V005. However, this could be attributed to

selection bias, because CLN-PRO-V017 data were skewed to shrapnel injuries and not the more typical devastating severe limb or polytraumatic military injuries that could provide robust data of HAV in terms of infection resistance. Study CLN-PRO-V017 also consisted of less severe injuries compared to CLN-PRO-V005, based on the injury severity score. Comparing the results between the two studies is difficult.

There was no clinical evidence submitted that demonstrates that HAV's infection resistance. Consequently, there was no evidence to support HAV's use in heavily contaminated wounds. However, the analysis results did show that HAV may be efficacious, with an unknown long-term safety and efficacy profile, for some adults needing urgent arterial repair following extremity vascular trauma who have alternative treatment options available (e.g., autologous vein or synthetic graft). In these subjects, there is uncertainty on how HAV compares to other treatment options. It is not apparent from the study data whether there are situations where the benefit of HAV outweighs the risk. Therefore, I defer to the clinical reviewer on the approval recommendation based on the overall benefit risk assessment and aspects of unmet need.