Summary Basis for Regulatory Action

Date:	December 3, 2025
From:	Wen Jun Seeto, PhD Review Committee Chair Office of Cell Therapy and Human Tissues (OCTHT) Office of Therapeutic Products (OTP)
BLA STN:	125816/0
Applicant:	Axogen Corporation
Submission Receipt Date:	September 5, 2024
PDUFA* **Action Due Date:**	December 5, 2025
Proper Name:	acellular nerve allograft -arwx
Proprietary Name:	AVANCE
Indication:	AVANCE (acellular nerve allograft - arwx) is a peripheral nerve scaffold indicated for the treatment of peripheral nerve discontinuity. AVANCE is an acellular nerve scaffold indicated for the treatment of adult and pediatric patients aged one month and older with sensory, mixed and motor nerve discontinuities. Approval for sensory nerve discontinuity >25 mm, mixed and motor nerve discontinuities is under accelerated approval pathway.

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

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

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Acting Director, Office of Clinical Evaluation, Office of Therapeutic Products

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Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
Regulatory	Eden Chane, MS, OTP/ORMRR
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Reports (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Wen (Aaron) Seeto, PhD, OTP/OCTHT Jin Sung Hong, PhD, OTP/OCTHT Courtney Johnson, PhD, OTP/OCTHT Neetu Dahiya, CBER/OCBQ/DMPQ/MRB1 Miriam Ngundi, PhD, CBER/OCBQ/DMPQ/MRB1 Neetu Dahiya, CBER/OCBQ/DMPQ/MRB1 Nicole Li, CBER/OCBQ/DMPQ Wen (Aaron) Seeto, PhD, OTP/OCTHT Jin Sung Hong, PhD, OTP/OCTHT Most Nahid, PhD, CBER/OCBQ/DBSQC/LBVI Hyesuk Kong, CBER/OCBQ/DBSQC/LMIVTS Marie Anderson, PhD, CBER/OCBQ/DBSQC
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DPV) • BIMO	Ying Geng, MD, PhD, CBER/OTP/OCE/DCEGM Srinivas Ayyala, MD, CBER/OBPV/DPV Malcolm Nasirah, PharmD, MS, BCGP, CBER/OCBQ/DIS/BMB
Statistical • Clinical data (OBPV/DB)	Md Tanbin Rahman, Ph.D., CBER/OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Kate Dabirsiaghi, VMD, CBER/OTP/OPT
Clinical Pharmacology	N/A
Labeling • Promotional (OCBQ/APLB) • USPI Review	Benjamin Cyge, PhD, CBER/OCBQ/DCM/APLB Afsah Amin, MD, MPH CBER/OTP/OCE
Other Review(s) not captured above categories, for example: • Clinical data analysis	

Discipline Reviews	Reviewer / Consultant - Office/Division
• Consults	Jessica Hu, PhD & Harry Houghton, MS, CBER/OBPV/DB Osman Yogurtcu, PhD, CBER/OBPV/DABRA Svetlana Shestopal, PhD, CBER/OTP/OPPT Andrey Sarafanov, PhD CBER/OTP/OPPT

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Introduction

Axogen Corporation submitted a Biologics License Application (BLA), STN 125816, for licensure of acellular nerve allograft-arwx, with the proprietary name of AVANCE. AVANCE is an acellular nerve scaffold that is available in 16 size combinations of different lengths and diameters to fit the size and diameter of the nerve(s) to be treated. It consists of a three-dimensional scaffold of the native peripheral nerve including the endoneurial tubes, perineurium, epineurium and microvasculature of the extracellular matrix (ECM). AVANCE is manufactured at the Axogen Corporation facility located at (b) (4) AVANCE is shipped on dry ice and supplied frozen, as a single, intact graft saturated in Lactated Ringer's Solution (LRS) in a sealed and labeled container. At the surgical site, the length and number of AVANCE required is determined by the surgeon based on the nerve deficits identified for repair.

The clinical development program was supported by the RECON trial (ANG-CP-007), a Phase 3, multicenter, randomized, controlled, evaluator- and patient-blinded trial enrolling 220 patients across 23 U.S. sites, conducted from 2015 to 2021. The trial evaluated digital sensory nerve injuries with 5 to 25 mm gaps, comparing AVANCE to NeuraGen Nerve Guide (Nerve Cuff). The primary endpoint objective was successfully met, demonstrating noninferiority of AVANCE to NeuraGen Nerve Guide based on static 2-point discrimination (s2PD). The LS mean for s2PD at Month 12 in the AVANCE intent-to-treat (ITT) population was 9.1 mm (95% CI: 8.12, 10.02), where the upper limit of the 95% CI was < 13 mm. Thus, both success criteria for supporting non-inferiority were met. Together, these results indicate clinically meaningful sensory recovery.

A single-blind, randomized, pilot study (CHANGE study) provided the confirmatory evidence for efficacy.

The RANGER Registry (ANG-CP-005) provided supportive evidence of safety through an observational study of 2,188 patients across 3,613 nerve repairs from 2008 to 2023.

The safety profile of AVANCE was favorable with a small number of serious adverse reactions reported. The most common adverse reactions were procedural pain (3.6%) and implant site hyperesthesia (2.7%).

In the review of AVANCE BLA, regulatory flexibility was applied through, (i) approval based on a single adequate and well-controlled study focused on sensory nerve repairs with 5 to 25 mm gaps (RECON); and confirmatory evidence from a pilot study (CHANGE); (ii) acceptance of real-world, observational data from RANGER Registry as supportive evidence of safety; (iii) s2PD is a clinical endpoint that measures sensory nerve function and does not directly assess motor strength outcomes. However, FDA has determined that s2PD serves as a reasonably likely surrogate endpoint for motor and mixed nerve regeneration because it demonstrates successful axonal regeneration through the AVANCE scaffold - the fundamental therapeutic mechanism that remains consistent across all nerve type injuries regardless of their ultimate functional output. Therefore, FDA has determined to expand the indication for AVANCE to motor and mixed nerve injuries, and sensory nerves with large gaps >25 mm, through an Accelerated Approval pathway with continued approval contingent upon confirmatory clinical trials, (iv) expanding the indication to the pediatric population was supported through extrapolation from adult data based on consistent pathophysiology across age groups, identical mechanism of action (MOA) regardless of age, evidence of superior nerve

regeneration capacity in younger patients, and absence of safety signals in the observational data in 126 pediatric patients in RANGER registry. AVANCE dosing is based on anatomical requirements at the site of nerve injury rather than patient weight or body surface area.

As a post-marketing requirement (PMR), a Phase 3, confirmatory trial (ANG-CP-013) is planned and agreed upon. Axogen commits to conduct a prospective, randomized, assessor-blinded, multicenter study (Protocol ANG-CP-013) to evaluate the clinical benefit of AVANCE (acellular nerve allograft-arwx} compared to sural nerve autograft for functional recovery following mixed and motor peripheral nerve injury. The study targets adults ≥18 years of age with mixed or motor nerve repairs in nerve gaps greater than 25 mm. The participants will be followed for 24 months post-surgical repair. The final study report will be submitted within 6 months of study completion, anticipated by 2031, including primary efficacy endpoints of Medical Research Council Classification (MRCC) motor and sensory recovery scores at Month 24.

Review issues were identified regarding bioburden sampling strategy related to size representation and sample storage. In addition, environmental monitoring performance qualification (EMPQ) and container closure integrity testing (CCIT) were identified during the pre-license inspection (483 observation items). The Applicant submitted substantial information to address these concerns at the end of the original review period. On August 22, 2025, FDA determined that this constituted a major amendment; thus, extending the review timeline by 3 months.

A sterility release testing exception is granted because the data submitted in the application establish adequate controls to support parametric release of AVANCE to assure the safety, purity, and potency of the biological product.

I. Background

Peripheral nerve injuries represent a serious medical condition affecting more than 50,000 cases annually in the U.S. When a peripheral nerve loses continuity, there is immediate loss of sensation and/or motor function distal to the injury, significantly impairing patients' daily activities and quality of life.

Historically, treatment options for nerve gaps requiring bridging materials have included autologous nerve grafts (autografts) and synthetic or biological nerve conduits. Autografts, the historical gold standard, carry significant limitations including donor site morbidity, limited supply, and permanent loss of function at the donor site. The use of nerve conduits is typically limited to the repair of shorter nerve gaps (≤30 mm).

AVANCE is an acellular, processed cadaveric peripheral nerve allograft that functions as a biological scaffold preserving native nerve architecture. The mechanism of action involves preserved endoneurial tubes serving as guidance channels for regenerating axons, while bioactive laminin facilitates axon growth.

AVANCE addresses unmet medical need by providing a reliable, off-the-shelf treatment option that eliminates autograft donor site morbidity while maintaining biological advantages of native nerve architecture as well as flexible diameter and length.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. SPA Agreement	August 11, 2011
2. IND submission	April 8, 2013
3. RMAT designation granted	September 25, 2018
4. Pre-BLA meeting	February 13, 2024
5. BLA 125816/0 submission	September 5, 2024
6. BLA filed	November 1, 2024
7. Mid-Cycle communication	March 7 2025
8. Late-Cycle meeting	May 21, 2025
9. Major Amendment	August 22, 2025
10. Action Due Date	December 5, 2025

1. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

This BLA includes an adequate description of the manufacturing process of AVANCE. The CMC review team concludes that the manufacturing material, process, and controls can yield AVANCE with consistent quality attributes meeting all release criteria as a licensed biologic. Thus, the CMC review team recommends approval.

Product Description

AVANCE is available in 16 size combinations (lengths of 15 mm to 70 mm and diameters of 1 to 5 mm) and is intended for surgical implantation. The length and number of AVANCE required is determined by the surgeon based on the nerve deficits identified for repair.

Manufacturing Summary

AVANCE is a decellularized and terminally sterilized extracellular matrix (ECM) derived from peripheral nerve tissue of cadaveric human donor (one donor per lot). In addition to removing cells and debris, the decellularization process removes axonal (b) (4) This process exposes the laminin lining of the endoneurial tubes of AVANCE which was shown to support neurite extension. AVANCE is packaged in a single unit in a clamshell/pouch assembly as container closure system. AVANCE is supplied and stored frozen. It has a shelf-life of 36 months at ≤ -40 °C.

Manufacturing Controls

Manufacturing control strategies include process performance qualification (PPQ) studies, in-process testing (b) (4) and final drug product testing (b) (4) assessment, (b) (4) . The final product tests and release criteria are acceptable and are sufficient to meet regulatory requirements for identity, purity, and potency. Stability studies are appropriate to support product expiration dating.

Process Validation

The Applicant validated the manufacturing process at the Axogen Corporation commercial manufacturing site, (b) (4) , using PPQ batches. The process validation was supported by reliable and consistent manufacture of AVANCE batches which met established release acceptance criteria.

Stability of the final product was established using representative batches manufactured at the clinical manufacturing processing facility, (b) (4) .

Manufacturing Risks, Potential Safety Concerns, and Management

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

A single batch of AVANCE is manufactured using the source material from a single cadaveric donor who met the donor eligibility requirements for transmissible infectious diseases which include screening and testing of risks associated with Human Immune-deficiency Virus 1 (HIV-1); Human Immune-deficiency Virus 2 (HIV-2); Hepatitis B Virus (HBV); Hepatitis C Virus (HCV); and Syphilis (Treponema pallidum). Only screening was performed for Creutzfeldt-Jakob disease (CJD). AVANCE is derived from peripheral nerve tissue and nerve tissue is not considered a viable, leukocyte-rich tissue, making Human T-cell Leukemia-lymphoma Virus (HTLV) testing not required for these donors. However, the sponsor may choose to perform HTLV-1/2 antibody testing to comply with requirements from U.S. state regulatory authorities or international regulatory bodies.

Drug Product Stability and Shelf Life

The real-time stability studies determine the product is stable for 36 months at ≤-40 °C from the date of terminal sterilization.

Comparability

To support product comparability, a comprehensive analytical comparability study between the clinical manufacturing process at (b) (4) , and commercial manufacturing process at Axogen Corporation, (b) (4) has been reviewed and found to be acceptable.

b. Testing Specifications

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

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

Table 2. Final Product Commercial Release Specifications

Attribute	Test	Analytical Method	Acceptance Criteria
Identity	(b) (4)		
Purity	(b) (4)		
	(b) (4)		
Potency	(b) (4)		
Safety	Endotoxin	(b) (4)	
	Sterility	(b) (4)	

c. CBER Lot Release

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

d. Facilities Review / Inspection

Facility information and data provided in BLA STN 125816/0 were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of the processed nerve allograft, AVANCE, are listed in Table 3 below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 3: Manufacturing Facilities

Name/Address	FEI number	DUNS number	Inspection/ Waiver	Justification /Results
Axogen Corporation (b) (4) *DS material storage, DS manufacture, DP manufacture, in-process control testing, DP release testing, DP stability testing, DP labeling and packaging, DP storage and DP distribution*	(b) (4)	(b) (4)	PLI	OCBQ/DMPQ (b) (4) VAI
(b) (4) *DP release and stability testing (identity and purity)*	(b) (4)	(b) (4)	PLI	OCBQ/DMPQ (b) (4) VAI
(b) (4) *DP release and stability testing (potency)*	(b) (4)	(b) (4)	704(a)(4) records request	OCBQ/DMPQ (b) (4) rNAI OII/OBMI (b) (4) NAI
(b) (4) DP (b) (4) and DP parametric release	(b) (4)	(b) (4)	Waiver	ORA/OMDRHO (b) (4) NAI

(b) (4) *DP release testing (endotoxin), DP stability testing (endotoxin and sterility)*	(b) (4)	(b) (4)	Waiver	ORA/OHADI (b) (4) VAI OII/OBI (b) (4) VAI

Acronym key: DMPQ – Division of Manufacturing and Product Quality; DP – drug product; DS – drug substance; OCBQ – Office of Compliance and Biologics Quality; ORA – Office of Regulatory Affairs; OMDRHO – Office of Medical Device and Radiological Health Operations; OHADI – Office of Human & Animal Drug Inspectorate; OII – Office of Inspections and Investigations; OBI – Office of Biologics Inspectorate; OBMI – Office of Bioresearch Monitoring Inspectorate; NAI – No Action Indicated; PLI – Pre-license Inspection; VAI – Voluntary Action Indicated

OCBQ/DMPQ conducted a PLI of the Axogen Corporation facility (b) (4) . A Form FDA 483 was issued at the end of the inspection, and the corrective actions were reviewed. All inspectional issues were resolved, and the inspection was classified as VAI.

OCBQ/DMPQ conducted a PLI of (b) (4) from (b) (4) A Form FDA 483 was issued at the end of the inspection, and the corrective actions were reviewed and evaluated. All inspectional issues were resolved, and the inspection was classified as VAI.

OCBQ/DMPQ conducted a Remote Regulatory Assessment (RRA) – 704(a)(4) Assessment of (b) (4) . There were no inspectional issues, and this inspectional assessment was classified as rNAI. ORA/DBMI2 performed a surveillance inspection from (b) (4) . The inspection was conducted under Compliance Program CP 7348.808 Good Laboratory Practice (GLP) (Nonclinical Laboratories) and covered the bioanalytical portion of three completed preclinical GLP studies. There were no significant objectionable findings, and the inspection was classified as NAI.

ORA/OMDRHO performed the most recent FDA surveillance inspection of (b) (4) . All inspectional issues were resolved, and the inspection was classified as NAI.

ORA/OHADI performed a surveillance inspection of (b) (4) All inspectional issues were resolved, and the inspection was classified as VAI. The most recent FDA surveillance inspection of the (b) (4) was conducted in (b) (4) , and the inspection is

classified VAI.

e. Container/Closure System

AVANCE is packaged into a sterile barrier system consisting of primary, secondary, and tertiary packaging components.

The primary package consists of a clamshell, Tyvek-Poly Pouch, and Foil/Poly Pouch. The clamshell (4.0" wide x 4.0" long x 0.4" tall) which is a thermoformed single-piece tray with a lid made from a (b) (4)

The clamshell is sealed within a Tyvek-Poly Pouch, (b) (4) The Tyvek-Poly Pouch is then contained within a sealed Foil/ Poly Pouch, (b) (4) . The Tyvek-Poly Pouch is a heat-sealable, peel pouch made from Tyvek (b) (4) and (b) (4) The Foil/Poly Pouch is a (b) (4) Both the Tyvek-Poly Pouch and Foil/Poly Pouch are puncture resistant, provide a microbial barrier, and are compatible with (b) (4) .

The secondary packaging consists of a sterilization carton (b) (4) used to store the packaged nerve grafts before and after (b) (4) .

The tertiary packaging is a commercial carton (b) (4) sealed with Carton Seal Tape (b) (4) and placed in a zip-top bag (b) (4) for freezer storage protection.

The Foil/Poly Pouch was selected and qualified as a sterile barrier for the terminally sterilized AVANCE. The container closure integrity testing on the Foil/Poly Pouch was performed at (b) (4) using a (b) (4) test method in accordance with (b) (4) ; all acceptance criteria were met.

f. Environmental Assessment

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

2. Nonclinical Pharmacology/Toxicology

In vivo studies were conducted in rat and rabbit models of nerve injury to assess nerve regeneration and functional recovery. The animal studies evaluated rat and

rabbit nerve allografts that were manufactured using various iterations of the Avance method. Despite minor differences between the nonclinical and clinical processing methods, the nerve allografts used in the animal studies were adequately representative of the clinical product.

Avance-processed rat nerve allografts at lengths of 5, 14, 15, and 28 mm were surgically implanted into a sciatic nerve defect in rats and assessed at various time points up to 22 weeks. All graft sizes were well-tolerated and showed increased numbers of nerve fibers regenerating across the nerve defect over time. The type of nerve (motor, sensory, or mixed fiber) used as a source for Avance-processed allografts did not appear to have a significant impact on the short-term outcome of nerve regeneration. Results from an electrical stimulation assay and neuromuscular junction staining demonstrated that functional motor axons reinnervated the muscle and showed improved motor nerve regeneration in the Avance-processed allograft groups compared to a collagen conduit. There was no evidence of immunogenicity and no concerning histological findings in these studies.

Studies in a rabbit model of peroneal nerve injury were conducted to evaluate Avance-processed rabbit nerve allografts with larger gap lengths than could be feasibly evaluated in the rat model. Avance-processed nerve allograft lengths of 30 and 70 mm were assessed at 4, 17, and 26 weeks. Both allograft lengths showed axonal growth and evidence of ongoing nerve regeneration at each time point. Functional assessments of Avance-processed allografts at 17 and 26 weeks showed improved functional recovery as compared to a collagen conduit.

No carcinogenicity or tumorigenicity studies were conducted. Mutagenic potential was assessed with an Ames test using Avance-processed nerve graft extracts using an earlier version of the clinical AVANCE manufacturing process. No evidence of bacterial mutagenicity was observed.

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

3. Clinical/Statistical

a. Clinical Program

The primary evidence of safety and effectiveness of AVANCE in treatment of sensory nerve discontinuities ≤25 mm was provided by RECON Study (ANG-CP-007), a Phase 3, multicenter, randomized, controlled, evaluator- and patient-blinded trial enrolling 220 patients across 23 U.S. sites, comparing AVANCE to NeuraGen Nerve Guide for digital sensory nerve injuries with 5-25 mm gaps. The trial successfully met its primary endpoint objective, demonstrating noninferiority of AVANCE to NeuraGen Nerve Guide based on static 2-point discrimination (s2PD). The least square (LS) mean difference for s2PD at Month 12 in the per-protocol (PP) population was 0.2 mm (95% CI, -1.09, 1.57), where the lower

limit of 95% CI was > -2 mm. The LS mean for s2PD at Month 12 in the AVANCE intent-to-treat (ITT) population was 9.1 mm (95% CI: 8.12, 10.02), where the upper limit of the 95% CI was < 13 mm. Thus, both success criteria for supporting non-inferiority were met. Together, these results indicate clinically meaningful sensory recovery.

The confirmatory evidence of efficacy in sensory nerve discontinuities was from the CHANGE Study, a multicenter, randomized, single-blind, two-phase, comparative clinical trial designed to evaluate the difference in functional recovery outcomes between AVANCE and hollow nerve conduits for nerve repair in the hand and the primary endpoint was recovery of static 2-point discrimination. Twenty-three patients were randomized (14 to AVANCE and 9 to hollow nerve conduit). In the AVANCE group, the mean s2PD value was 4.83 (95% CI: 3.29, 6.37) at Month 12 based on 6 digits assessed. The upper limit of the 95% CI was less than 13 mm, suggesting clinically meaningful sensory recovery. This study provided confirmatory evidence supporting clinically meaningful effectiveness of AVANCE for treatment of sensory nerve discontinuities.

Based on the data from one adequate and well-controlled (AWC) Phase 3 study (RECON) and confirmatory evidence from a randomized, single-blind, pilot study (CHANGE), AVANCE received traditional approval for sensory nerve discontinuity ≤25mm in adult and pediatric patients ≥1 month of age. For mixed and motor nerve discontinuities, AVANCE received accelerated approval based on the surrogate endpoint of, improvement in s2PD at Month 12 in sensory nerve, which is reasonably likely to predict clinical benefit given similarities in pathophysiology and anticipated therapeutic effects between sensory and motor/mixed nerve repairs. The accelerated approval pathway was utilized because, while the biological mechanism of nerve regeneration is fundamentally similar across nerve types, the clinical evidence was primarily derived from sensory nerve repairs, requiring confirmatory studies to verify clinical benefit in motor and mixed nerve applications as well as sensory nerve discontinuity >25mm. There was no major safety signals identified, and the risk-benefit profile was favorable for a regulatory approval. Key review considerations included (i) extrapolation from AWC clinical trial in adults to pediatric populations based on similar pathophysiology and MOA, and (ii) the use of accelerated approval regulatory pathway for motor/mixed nerve discontinuities and sensory nerve discontinuities >25 mm based on the surrogate endpoint of s2PD in sensory nerve discontinuities ≤25 mm, given similar mechanisms of nerve repair across all nerve types.

Study Description

Phase 3 Study (RECON)

RECON trial (ANG-CP-007), a Phase 3, multicenter, randomized, controlled, evaluator- and patient-blinded trial enrolling 220 patients across 23 U.S. sites, comparing AVANCE to NeuraGen Nerve Guide for digital sensory nerve injuries with 5-25 mm gaps. Demographic information for 220 patients in the Phase 3 trial (ANG-CP-007) is shown in Table 4.

Table 4. Baseline Demographics, Trial ANG-CP-007 (Intent-to-Treat Population)

Demographic	AVANCE N=112	NeuraGen Nerve Guide N=108	All N=220
Age (years)	-	-	-
Mean (SD)	37.2(13.56)	39.8(14.05)	38.5(13.83)
Median (min, max)	36.0 [18,68]	39.5 [18,69]	37.0 [18,69]
Age group at randomization, n (%)	-	-	-
<40 years	71(63.4)	61(56.5)	132 (60)
>40 years	41(36.6)	47(43.5)	88 (40)
Sex, n (%)	-	-	-
Female	34 (30.4)	31 (28.7)	65 (29.5)
Male	78 (69.5)	77 (71.3)	155 (70.5)
Race, n (%)	-	-	-
White	89(79.5)	85(78.7)	174(79.1)
Asian	2(1.8)	0	2(0.9)
Black or African American	17(15.2)	16(14.8)	33(15)
Hispanic or Latino	1(0.9)	2(1.9)	3(1.4)
Native Hawaiian or Pacific Islander	1(0.9)	1(0.9)	2(0.9)
Other	2(1.8)	4(3.7)	6(2.7)
Ethnicity, n (%)	-	-	-
Hispanic or Latino	10(8.9)	16(14.8)	26(11.8)
Not Hispanic or Latino	102(91.1)	90(83.3)	192(87.3)

Source: Adapted from BLA 125816/03 (Module 2.7.3 summary-clin-efficacy.pdf, Table 4, page 20 of 10
Abbreviations: max, maximum; min, minimum; N, number of patients; n, number of patients; SD, standard deviation

Efficacy Endpoints

Primary endpoint was s2PD at Month 12. s2PD is a sensory assessment that measures nerve innervation density (the number of nerve endings present in the area tested) by determining the patient's ability to discern the functional difference between one and two points between 2 mm (best value) and 15 mm.

Clinical Efficacy Findings:

In Study ANG-CP-007 (RECON), a total of 220 patients were randomized 1:1 to nerve injury repair with AVANCE (N=112) or NeuraGen Nerve Guide (N=108).

In the per protocol (PP) population (N=183), the LS mean (95% CI) s2PD at Month 12 was 9.1 mm (95% CI: 8.12, 10.04) in the AVANCE group compared to 9.3 mm (95% CI: 8.40, 10.24) in the NeuraGen Nerve Guide group, with LS mean difference of 0.2 mm (95% CI -1.09, 1.57). In the intent to treat (ITT) population (N=220), the LS mean (95% CI) s2PD at Month 12 was 9.1 mm (95% CI: 8.12, 10.02) in the AVANCE group compared to 9.4 mm (8.50, 10.30) in the NeuraGen Nerve Guide group, with LS mean difference of 0.3 mm (95% CI, -0.98, 1.64). These results satisfied both study success criteria for establishing non-inferiority: the lower limit of the 95% CI for the LS mean difference in the PP population was > -2 mm and the upper limit of the 95% CI for s2PD for AVANCE group in the ITT population was <13 mm.

Table 5 : Efficacy Results for RECON Study

Analysis set	LS Means Estimate (95%)[3] AVANCE	LS Means Estimate (95%)[3] NeuraGen Nerve Guide	LS Means Difference[3] (95%)
ITT[1] population	9.1 (8.12, 10.02)	9.4 (8.50, 10.30)	0.3 (-0.98, 1.64)
PP[2] population	9.1 (8.12, 10.04)	9.3 (8.40, 10.24)	0.2 (-1.09, 1.57)

CI=Confidence Interval; LS=Least Squares; ITT=Intent-to-treat; PP=Per Protocol
[1] All randomized patients. Patients were analyzed according to assigned treatment
[2] Randomized patients who completed minimum of 6 months follow-up and had no major protocol violation
[3] Estimated using repeated measures Analysis of Covariance (ANCOVA) model with fixed effects for repair type, visit, and gap length and a random effect for patient. Screening, Month 1, 3, 6, 9, and 12 visits were included.

CHANGE Study:

Study ANG-CP-007 enrolled male and female patients who sustained injury to at least one nerve distal to the superficial palmar arch, resulting in a nerve gap of 5-20 mm after resection. Twenty-three patients were randomized to treatment (14 to AVANCE and 9 to hollow nerve conduit). In the AVANCE group, the mean s2PD value was 4.83 (95% CI: 3.29, 6.37) at Month 12 based on 6 digits assessed. The upper limit of the 95% CI was less than 13 mm, suggesting clinically meaningful sensory recovery. This study provides confirmatory evidence supporting clinically meaningful effectiveness for the AVANCE.

Only three adverse events were reported during the study. Two events were reported in the conduit group (one non-serious and one serious). One serious adverse event (infection) was reported in the AVANCE group, which was considered to be unrelated to AVANCE. All adverse events resolved, demonstrating a comparable safety profile between the two treatment groups.

Efficacy Conclusions:

The primary evidence of efficacy of AVANCE is based on the data from an adequate and well-controlled Phase 3 multicenter, non-inferiority study, ANG-CP-007, demonstrating non-inferiority of AVANCE compared to NeuraGen Nerve Guide on the primary endpoint of s2PD at Month 12. Based on the available data from Study ANG-CP-007, the statistical evidence supports the efficacy of AVANCE for repair of sensory nerve discontinuities 25 mm or less in adult patients. The confirmatory evidence of effectiveness was provided by a pilot clinical study (CHANGE).

Efficacy of AVANCE in repair of motor and mixed nerve discontinuities and sensory nerve discontinuities >25 mm was based on improvement in s2PD at Month 12 in sensory nerve discontinuities $\leq$25 mm, reasonably likely to predict clinical benefit given similarities in pathophysiology and anticipated therapeutic effects between sensory and motor/mixed nerve repairs.

Real-World Study (RANGER Registry)

RANGER (ANG-CP-005) is an open-label, multicenter observational registry initiated in 2008 that collected real-world data on the use of AVANCE in surgical nerve repairs across various injury types and body locations. The study enrolled 2,188 patients across 3,613 repairs from 47 centers (44 in the US, plus Austria, Canada, and UK).

PMR/PMC Requirement:

The definitive clinical benefit for sensory nerve discontinuity (>25mm) and mixed and motor nerve discontinuity has not yet been established due to limited data and issues with study design and data analysis. Therefore, a confirmatory trial is required under 21 CFR 601.41 to verify and describe the anticipated clinical benefit of AVANCE that was the basis for accelerated approval. Continued approval for this indication is contingent upon the results of this trial.

Clinical Safety Findings:

The total safety database of AVANCE included 220 patients from RECON and 2,188 patients from the RANGER registry, demonstrating favorable safety. In the RECON trial, the most common adverse reactions were procedural pain (3.6%) and implant site hyperesthesia (2.7%). No deaths were attributed to the product, and no cases of infectious disease transmission or immune rejection were observed. There are two

populations included in the RANGER study: the parent protocol safety population with 1780 patients and the Addendum 2 safety population with 408 patients. According to available information, a total of 146 adverse events were reported in 125 patients in the parent protocol population while a total of 149 adverse events were reported in 101 patients in the Addendum 2 safety population. The most common adverse events were neuroma (2.7%) and infection (1.7%) at the reconstruction site in the parent protocol population, and infection (13.4%) and tissue necrosis (19.5%) for the Addendum 2 safety population.

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

BIMO inspection assignments were issued for the Applicant and three clinical study sites that participated in the conduct of Phase 3 Study ANG-CP-007 (RECON). The inspections did not reveal substantive issues that impact the data submitted in this BLA.

c. Pediatrics

The FDA Pediatric Review Committee (PeRC) reviewed the acellular nerve allograft application for surgical repair of peripheral nerve discontinuities and agreed with the Applicant's proposed pediatric development plan. The plan includes a partial waiver for neonates from birth to less than 1 month of age due to low incidence rates and impracticality of conducting studies in this population, as most surgical interventions occur after 1 month of age. For the pediatric population older than one month, effectiveness is supported by extrapolation of efficacy from adult data and safety is supported by real world data.

d. Other Special Populations

None.

4. Safety and Pharmacovigilance

The Applicant submitted a pharmacovigilance plan for AVANCE. The important potential risks associated with AVANCE include infection, allergic reactions or other adverse immune responses, and risks associated with peripheral nerve procedures. OBPV/DPV recommends routine pharmacovigilance, which includes adverse event reporting in accordance with 21 CFR 600.80.

The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a safety-related post-marketing requirement (PMR), and there is no agreed upon safety-related post-marketing commitment (PMC) at this time.

5. Labeling

The proposed proprietary name, AVANCE, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on December 6, 2024, and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on December 16, 2024.
The APLB review addressed the proposed prescribing information and the proposed package and container labels, submitted on September 5, 2024.

The Office of Review Management and Regulatory Review (ORMRR) and the Office of Cell Therapy and Human Tissues (OCTHT) reviewed the package and container labels on November 19, 2025, and determined they meet regulatory/statutory requirements.

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

6. Advisory Committee Meeting

The submitted information, including clinical study design and trial results, did not raise unresolved scientific or regulatory questions that would benefit from advisory committee discussion. Therefore, this BLA was not referred to the Cellular, Tissue, and Gene Therapies Advisory Committee.

7. Other Relevant Regulatory Issues

This application received Regenerative Medicine Advanced Therapy Designation.

8. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Based on the primary evidence of effectiveness demonstrated in the adequate and well-controlled, Phase 3 study (RECON) and supported by the pilot study (CHANGE), the review team recommends traditional approval for sensory nerve discontinuity ≤25mm in adult and pediatric patients ≥1 month of age and accelerated approval for motor/mixed nerve discontinuities of all gap lengths as well as sensory nerve discontinuity >25mm.

b. Benefit/Risk Assessment

The overall benefit/risk profile is favorable for AVANCE (acellular nerve allograft-arwx) for the treatment of peripheral nerve discontinuities in patients 1 month of age and older with sensory nerve gaps of ≤25 mm. AVANCE demonstrated substantial evidence of effectiveness for serving as scaffold for nerve regeneration based on the primary evidence from the adequate and well-controlled Phase 3 Study RECON, which successfully met its noninferiority endpoint with a LS mean difference in static 2-point

discrimination of 0.2 mm (95% CI: -1.09, 1.57) compared to NeuraGen Nerve Guide, plus the confirmatory evidence of efficacy from the pilot study (CHANGE).

The safety of AVANCE is characterized based on a comprehensive safety database of 220 patients in the Phase 3 study and 2,188 patients from the RANGER registry. Favorable safety profile includes procedural pain (3.6%) and implant site hyperesthesia (2.7%) as the most common adverse reactions from RECON study. The safety profile of 126 pediatric atients aged 1 month to 17 years in the RANGER registry supports safety across the approved pediatric age groups. No deaths were attributed to AVANCE, and no cases of infectious disease transmission or immune rejection were observed. The risks can be mitigated through routine medical management, appropriate prescribing information labeling, standard surgical technique and routine pharmacovigilance.

c. Recommendation for Postmarketing Activities

The Applicant agreed to the following Clinical PMR:

Study ANG-CP-013 is designed as a prospective, randomized, assessor-blinded, controlled cohort, multicenter comparative study to evaluate the clinical benefit of AVANCE compared to sural nerve autograft for functional recovery following peripheral nerve reconstruction. The proposed study targets adults ≥18 years of age with mixed or motor nerve injuries requiring repair of gaps greater than 25 mm. Participants will be followed for 24 months post-surgical repair to assess recovery outcomes. The dual primary endpoints focus on functional recovery at Month 24, measuring both motor recovery using the Medical Research Council Classification (MRCC) motor recovery score for all nerve repairs, and sensory recovery using the MRCC sensory recovery score specifically for mixed nerve repairs.

The following milestones for Study ANG-CP-013 were submitted on December 3, 2025 and agreed upon:

Final Protocol Submission: February 5, 2026
Study/Trial Completion: December 5, 2030
Final Report Submission: June 5, 2031