



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

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DPV, OBPV, CBER, FDA

To: Wen Seeto, PhD
Chair of the Review Committee
Office of Therapeutics

Through: Adamma Mba-Jonas, MD MPH
Branch Chief, PB1
Acting Deputy Director DPV
OBPV, CBER, FDA

Subject: Review of Pharmacovigilance Plan

Sponsor: AxoGen Corporation

Product: Avance® Nerve Graft (Processed Nerve Allograft)

Application Type / Number BLA / STN 125816/0

Proposed Indication For the surgical repair of peripheral nerve
discontinuities to support regeneration across the
defect.

Submission Date: September 5, 2024

Action Due Date: September 5, 2025

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA STN 125816/0 based on the safety profile of Avance® Nerve Graft. Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for Avance® Nerve Graft, should the indication for this product be approved.

2 BACKGROUND

Approximately 500,000 people in the USA experience traumatic peripheral nerve injuries annually,¹ with nerve injuries diagnosed in 2.6% of upper extremity trauma patients and 1.2% of lower extremity trauma patients, respectively.² The debilitating aftermath typically results in pain, disability, and decreased quality of life. Treatment options depend on the extent of the nerve injury and may range from non-invasive methods, including rest, physical therapy, and medication, to surgical techniques for patients in whom the injury is not healing properly.^{2,3}

Avance® Nerve Graft is a decellularized, pre-degenerated and sterilized extracellular matrix processed from donated human nerve. It is a one-time surgical implant that remodels into the recipient's own peripheral nerve tissue via natural nerve regeneration processes. It is currently available in the USA, Canada, and 22 other countries worldwide, and commercially marketed in the USA since 2007 under HCT/P designation.

3 PRODUCT INFORMATION

3.1 Product Description

Avance® Nerve Graft is a decellularized and sterilized extracellular matrix (ECM) derived from human peripheral nerve tissue. The processing method preserves the three-dimensional scaffold of the native peripheral nerve including the bioactive endoneurial tubes, perineurium, epineurium and microvasculature of the ECM. The processing method removes cellular and noncellular debris such as cells, fat, blood, and axonal debris as well as regeneration-inhibiting glycosaminoglycans. Avance® Nerve Graft is processed with Lactated Ringer's Solution which is present in the final product.

3.2 Proposed Indication

The sponsor's proposed indication statement as submitted to the original BLA 125816/0 is:

Avance® Nerve Graft (Processed Nerve Allograft) is a regenerative peripheral nerve scaffold indicated for the treatment of peripheral nerve functional deficits.

OBPV defers to the product office on the final language for the indication statement. Please see the final version of the package insert submitted by the sponsor for the final agreed-upon indication after FDA review.

¹ Cairns C, Kang K. National hospital ambulatory medical care survey: 2019 emergency department summary tables [Internet]. National Center for Health Statistics (U.S.) (2022). <https://stacks.cdc.gov/view/cdc/115748>

² Padovano WM, Dengler J, Patterson MM, Yee A, Snyder-Warwick AK, Wood MD, Moore AM, Mackinnon SE. Incidence of Nerve Injury After Extremity Trauma in the United States. *Hand (N Y)*. 2022 Jul;17(4):615-623.

³ Mayo Clinic. Peripheral nerve injuries – diagnosis and treatment. (2022).

4 PERTINENT REGULATORY HISTORY

Avance® Nerve Graft has been on the market as a 361 HCT/P human tissue product since July 2007. Since November 2010, Avance® Nerve Graft has been distributed in accordance with FDA Enforcement Discretion in the USA and internationally with the regulations of the relevant countries as a human tissue product.

Abbreviated Summary of Key Regulatory Interactions:

- April 19, 2010: Designated a biological product under FDA CBER
- September 26, 2018: FDA grants Regenerative Medicine Advanced Therapy (RMAT) Designation
- March 14, 2023: FDA confirmed RECON as an adequate and well-controlled study and stated that RANGER Registry data may be suitable as confirmatory evidence of effectiveness for an indication corresponding to that assessed in RECON
- November 17, 2023: FDA agreed that the mechanism of peripheral nerve regeneration is generally consistent between sensory neurons and motor neurons
- March 14, 2024: FDA agreed to Initial Pediatric Study Plan (iPSP)
- February 15, 2024: FDA confirmed that the proposed general approach for the BLA on clinical evidence proposed by sponsor was reasonable.
- February 15, 2024: FDA considers real world data from RANGER registry can provide confirmatory evidence of effectiveness and safety for regulatory approval
- September 5, 2024: Submission of completed BLA

5 MATERIALS REVIEWED

Table 1: Materials Reviewed

Document	Module STN
Clinical Information Amendment	Module 1.11.3 of BLA 125816/SN0030
Clinical Information Amendment	Module 1.11.3 of BLA 125816/SN0033
Clinical Information Amendment	Module 1.11.3 of BLA 125816/SN0048
Multiple Module Information Amendment	Module 1.11.4 of BLA 125816/SN0057
Annotated Prescribing Information	Module 1.14.1.2 of BLA 125816
Risk Management Plan (Non-REMS)	Module 1.16.1 of BLA 125816
Clinical Overview	Module 2.5 of BLA 125816
Summary of Clinical Safety	Module 2.7.4 of BLA 125816
Synopses of Individual Studies	Module 2.7.6 of BLA 125816
Tabular Listing of All Clinical Studies	Module 5.2 of BLA 125816
ANG-CP-007 Clinical Study Report	Module 5.3.5.1 of BLA 125816
ANG-CP-005 Interim Clinical Study Report	Module 5.3.5.2 of BLA 125816
Ad-hoc Narratives of Deaths, Other Serious Adverse Events	Module 5.3.5.2 of BLA 125816

6 DESCRIPTION OF AVANCE NERVE GRAFT® CLINICAL TRIAL SAFETY DATABASE

The clinical study safety data reviewed are from the Clinical Overview submitted to STN 125816/0. Two studies were submitted by the sponsor in support of this BLA: *ANG-CP-007: A Multicenter, Prospective, Randomized, Subject and Evaluator Blinded Comparative Study of Nerve Cuffs and Avance® Nerve Graft Evaluating Recovery Outcomes for the Repair of Nerve Discontinuities (RECON®)* and *ANG-CP-005: A Multicenter Registry Study of Avance® Nerve Graft Utilization, Evaluations and Outcomes in Peripheral Nerve Injury Repair (RANGER®)*.

Two additional studies of note included ANG-CP-004 (CHANGE) and ANG-CP-003. ANG-CP-004 (CHANGE) is a long-term safety and efficacy study that was terminated early while in the pilot phase following discussion with the FDA regarding transitioning the product from a 361 HCT/P product to a biologic product. ANG-CP-003 is a study completed to evaluate the technical feasibility, safety, and functional recovery of male subjects with injury to the cavernous nerve bundle during robotic assisted radical prostatectomy. Results of these studies are not intended for labeling and thus will not be evaluated further in this memo.

OBPV defers to the product office on a final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125816/0 be approved. Please refer to the package insert for the final clinical safety data.

6.1 ANG-CP-007 (RECON)

6.1.1 Description of Clinical Study

Table 2: Summary of ANG-CP-007 (RECON)

Study	Description	Subject Description
ANG-CP-007 (RECON)	<p>Phase 3, multicenter, prospective, randomized, controlled, evaluator and subject blinded study in subjects requiring nerve reconstruction in the hand distal to the superficial palmar arch between June 17, 2015, and July 22, 2021 (completed).</p> <p>Primary Objective: To evaluate the safety and effectiveness of Avance® Nerve Graft as compared to those treated with nerve cuffs (NeuraGen® Nerve Guide) for nerve reconstruction.</p>	<ul style="list-style-type: none"> • 220 patients randomized at 23 sites (112 Avance® Nerve Graft, 108 NeuraGen® Nerve Guide) with primary or secondary nerve injury in adult patients, aged 18-65 • Follow-up for 12 months post-repair • 48 patients discontinued the study before completion of the 12-month follow-up visit • 172 patients completed the final planned study visit (83 Avance® Nerve Graft, 89 NeuraGen® Nerve Guide)

*Adapted from Table 5.2, Tabular Listing of All Clinical Studies, STN 125816/0

Review Comment: Overall, a similar number of patients were randomized to the two treatment groups. Of the 220 randomized patients who started the study, 48 patients discontinued the study before the 12-month visit was completed, including 29 patients (25.9%) in the Avance® Nerve Graft group and 19 patients (17.6%) in the NeuraGen® nerve cuff group. The most common reason for discontinuation was “lost to follow-up” which occurred in 23 patients (20.5%) and 15 patients (13.9%), respectively.

6.1.2 Study Demographics

Table 3: RECON Summary of Baseline Demographic Characteristics

Parameter	Avance® Nerve Group (N=112)	Neuragen® Nerve Guide Group (N =108)	Overall (N = 220)
Age (years)			
< 40 years, n (%)	71 (63.4)	61 (56.5)	132 (60.0)
> 40 years, n (%)	41 (36.6)	47 (43.5)	88 (40.0)
Mean (Std)	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]
Sex, n(%)			
Female	34 (30.4)	31 (28.7)	65 (29.5)
Male	78 (69.9)	77 (71.3)	155 (70.5)
Race, n(%)			
American Indian/Alaska Native	0	0	0
Asian	2 (1.8)	0	2 (0.9)
Black or African American	17 (15.2)	16 (14.8)	33 (15.0)
Hispanic or Latino	1 (0.9)	2 (1.9)	3 (1.4)
Native Hawaiian/Pacific Islander	1 (0.9)	1 (0.9)	2 (0.9)
White	89 (79.5)	85 (78.7)	174 (79.1)
Other	2 (1.8)	4 (3.7)	6 (2.7)

* Adapted from Table 3, Summary of Clinical Safety, STN 125816/0

***Reviewer Comment:** Overall, the baseline demographic variables between the two treatment groups are similar.*

6.1.3 Adverse Events Related to Avance® Nerve Graft

1) Summary of Treatment-Emergent Adverse Events (TEAEs):

The most common (incidence > 2%) TEAEs reported were procedural pain (4/112 patients, 3.6%) and implant site hypersensitivity (3/112 patients, 2.7%).

***Reviewer Comment:** These AEs are expected given the nature of the study product or procedure.*

2) Summary of Serious Adverse Events (SAEs):

There were no common (incidence > 2%) SAEs reported.

***Reviewer Comment:** Only wound dehiscence, experienced by patient (b) (6), was assessed by the investigator and this reviewer as possibly related to the study product or procedure. The other SAEs were assessed by the investigator and this reviewer as not related to the study product or procedure and can be explained by underlying illness, treatment of the underlying illness, comorbidities, or non-adherence to post-operative care.*

3) Deaths: One patient experienced a TEAE with a fatal outcome, *determined to be due to the injection of a lethal quantity of illicit drugs*.

Reviewer Comment: Patient (b) (6) 's death was assessed by the investigator and this reviewer as not related to the study product or procedure.

4) AESI: The sponsor did not identify any AESIs of concern as part of the safety evaluation in this study. However, this reviewer assessed “allergic reactions/other adverse immune responses” as an AESI and no cases were identified.

6.2 ANG-CP-005 (RANGER)

6.2.1 Description of Clinical Study

Study	Description	Subject Description
ANG-CP-005 (RANGER)	<p>Open-label, multicenter, observational, prospective, and retrospective registry cohort study of Avance® Nerve Graft for any peripheral sensory, motor, or mixed nerve injury repair between July 13, 2007, and October 4, 2022 (ongoing).</p> <ul style="list-style-type: none"> Parent protocol collected data on nerve repairs throughout the body, with exception of events occurring in association with breast reconstruction Addendum 2, the breast reconstruction subgroup (Sensation NOW), establishes a focused arm to collect data on autologous breast reconstructive procedures where neurotization was completed. <p>The primary objective of this study is to collect data to evaluate utilization, functional recovery, and health outcomes limited to adverse events the sponsor considered potentially related to the nerve repair, among subjects who have had nerve repair using Avance® Nerve Graft, under usual care conditions across injury locations and nerve types.</p>	<ul style="list-style-type: none"> 2122 patients with nerve transection repair conducted across 48 study centers as of DLP of original BLA submission, 4 October 2022 (study sites: 45 USA; 1 Austria, 1 Canada, 1 UK) 2188 patients captured as of May 2025 (total safety population) Follow-up for up to 3 years post-surgical implant Clinical histories representative of the spectrum of peripheral nerve injuries occurring throughout the body including digital/hand, upper extremity, lower extremity, head/neck, and breast.

*Adapted from Table 5.2, Tabular Listing of All Clinical Studies, STN 125816/0

Reviewer Comment: Of note, the study enrolled subjects in an Addendum 1 (MATCH) cohort who did not receive Avance® Nerve Graft, as a comparator arm. This subgroup will not be evaluated further in this memo. All recipients of Avance® were evaluated as the safety population.

6.2.2 Adverse Events Related to Avance® Nerve Graft

Parent Protocol (N=1780 patients)

1) Summary of Treatment-Emergent Adverse Events (TEAEs):

The sponsor provided information with respect to overall TEAEs among all subjects from the parent protocol within the total safety population (1780/2188). The most common (incidence>2%) TEAEs reported were neuroma at the repair site (51 patients, 2.9%), and infection at the reconstruction site (40 patients, 2.2%).

Reviewer Comment: Neuroma formation can occur due to nerve injury from surgical trauma, blunt force trauma, nerve transection or chronic inflammation⁴, while infection is a risk inherent to any surgical procedure. Thus, both AEs are likely or possibly related to the study product or procedure.

2) Summary of Serious Adverse Events (SAEs): The sponsor provided information with respect to SAEs among subjects from the total safety population captured prior to the DLP of the original submission (2122/2188); SAE information specific to the parent protocol was not provided with the initial submission. The most common (incidence>0.5%) SAEs reported were neuroma (35 patients, 1.6%), infection at the reconstruction site (19 patients, 0.9%), and tissue necrosis (12 patients, 0.6%).

Reviewer Comment: Neuroma formation can occur due to nerve injury from surgical trauma, blunt force trauma, nerve transection or chronic inflammation⁴, while infection is a risk inherent to any surgical procedure. Tissue necrosis may be precipitated by the underlying nerve injury, complications relating to the surgical repair of the underlying injury or comorbidities.⁵ Thus, all of the most common SAEs are likely or possibly related to the study product or procedure.

3) Deaths: No patients experienced an SAE with a fatal outcome.

3) AESI: The sponsor did not identify any AESIs of concern as part of the safety evaluation in this study. However, this reviewer assessed “allergic reactions/other adverse immune responses” among the parent protocol (1780/2188) as an AESI and no cases were identified.

Addendum 2 (N=408 patients)

1) Summary of Treatment-Emergent Adverse Events (TEAEs)/ Summary of Serious Adverse Events (SAEs):

The sponsor provided information with respect to overall TEAEs among all subjects from the Addendum 2 cohort within the total safety population (408/2188). The most common (incidence > 2%) TEAEs reported were tissue necrosis (30/408, 7.4%), incision complications at donor site (23/408, 5.6%), incision complications at the reconstruction site (breast) (22/408, 5.4%), infection at the reconstruction site (22/408, 5.4%), other (13/408, 3.2%) and flap complications (11/408, 2.7%).

Reviewer Comment: Per the sponsor, the adverse event rate of the breast reconstruction subgroup (Addendum 2) was higher than that of the parent population for two reasons: first, per protocol,

⁴ Zabaglo M, Dreyer MA. Neuroma. [Updated 2024 Feb 17]. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK549838/>

⁵ Nelson JA, Voineskos SH, Qi J, Kim HM, Hamill JB, Wilkins EG, Pusic AL. Elective Revisions after Breast Reconstruction: Results from the Mastectomy Reconstruction Outcomes Consortium. *Plast Reconstr Surg*. 2019 Dec;144(6):1280-1290.

addendum 2 included adverse events related to the reconstructed breast and the free flap donor site which broadened the scope of events collected, and second, the inherent nature of post-mastectomy autologous breast reconstruction procedures typically require multiple procedures to achieve a satisfactory reconstruction. Tissue necrosis may be precipitated by the underlying nerve injury, complications relating to the surgical repair of the underlying injury or comorbidities.⁵. Incision complications and flap complications are risks inherent to surgical procedures of the breast.

2) Summary of Serious Adverse Events (SAEs): SAEs for Addendum 2 were analyzed as part of the total safety population (discussed above); SAE analysis specific to the addendum 2 cohort was not provided by the sponsor with the initial submission.

3) Deaths: Four patients (b) (6) experienced the SAE of death; narratives suggested that deaths were secondary to progression of metastatic breast cancer.

Reviewer Comment: As the deaths of all 4 patients were due to progression of underlying disease, these AEs were assessed by the investigator and this reviewer as unrelated to the study product or procedure.

4) AESI: The sponsor did not identify any AESIs of concern as part of the safety evaluation in this study. However, this reviewer assessed “allergic reactions/other adverse immune responses” among all subjects from Addendum 2 within the total safety population (408/2188) as an AESI. 2/408 subjects experienced such an AE. Patient (b) (6) was diagnosed with a “maculopapular rash around the lower incision” while patient (b) (6) was diagnosed with “contact dermatitis from dermabound, at all operative sites from revision.” Both events were non-serious and successfully managed with topical corticosteroids resulting in complete symptom resolution.

Reviewer Comment: This reviewer assessed these 2 events of “allergic reactions/other adverse immune responses” as possibly related to the product given temporality and location; however, lack of available clinical information for these non-serious events precludes complete assessment.

7 SUMMARY OF POSTMARKETING EXPERIENCE

Post-marketing data currently available is based on the marketing experience of Avance® Nerve Graft domestically and internationally as a Human Cells, Tissues and Cellular and Tissue-based Product (HCT/P) since 2007.

There were no deaths or serious adverse reactions involving a communicable disease reported with the use of Avance® Nerve Graft during the post-marketing experience.

7.1 FDA Analysis

7.1.1 VAERS Reports

The TARS QQ_LL report was run on July 25, 2025. The only input was “Axogen.” From 2007-2025 there was only one case reported.

Reviewer Comment: TARS ID Case # 4334 involved a product problem that was not relevant to pharmacovigilance. Spontaneous surveillance systems such as VAERS are subject to many limitations, including underreporting, stimulated reporting, variable report quality and accuracy, inadequate data regarding dosing, and lack of direct and unbiased comparison groups. Reports in VAERS may not be medically confirmed and are not verified by FDA. Also, there is no certainty that the reported event was actually due to the product

8 SPONSOR'S PHARMACOVIGILANCE PLAN

Table 4: Sponsor's Pharmacovigilance Plan

Type of Concern	Safety Concern	Description	Planned Risk Mitigation
Potential	Infection	<ul style="list-style-type: none"> Inherent nature of surgical procedures Possibility of transmission of infectious materials from donated human tissue/final product 	<ul style="list-style-type: none"> Routine Pharmacovigilance Labeling - Section 6 of the USPI
Potential	Allergic Reactions or Other Adverse Immune Responses	<ul style="list-style-type: none"> Inherent nature of any surgical procedures including a permanent implant 	<ul style="list-style-type: none"> Routine Pharmacovigilance Labeling - Section 6 of the USPI
Potential	Risks Associated With Peripheral Nerve Procedures	<ul style="list-style-type: none"> Infection at surgical site Mild incisional redness Tenderness of surgical area Mild edema of surgical area Minimal pain at surgical area Numbness Decreased or increased sensation (e.g. hypoesthesia, hyperesthesia) Neuroma formation Failure of the nerve to regenerate 	<ul style="list-style-type: none"> Routine Pharmacovigilance Labeling - Section 6 of the USPI
Missing Information	Use in Special Populations	<ul style="list-style-type: none"> Exposure in Pregnancy and Lactation Use in Neonates and Infants (<1 month of age) 	<ul style="list-style-type: none"> Routine Pharmacovigilance Labeling - Section 8 of the USPI

*Adapted from 1.16.1 Risk Management (Non-REMS), STN 125816/0

The sponsor plans to conduct routine pharmacovigilance in accordance with 21 CFR 600.80.

9 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

9.1 Important Identified Risks

None.

9.2 Important Potential Risks

Important potential risks include infection, allergic reactions or other adverse immune responses, and risks associated with peripheral nerve procedures including infection at the reconstruction site, neuroma formation and tissue necrosis.

Across both the RECON and RANGER studies, the incidence of infection at the reconstruction site was 2.7% (62/2300 patients), allergic reaction was 0.5% (2/408 patients), neuroma formation was 2.3% (52/2300 patients) and tissue necrosis was 1.6% (36/2300 patients). OBPV/DPV encouraged the sponsor to reclassify these AEs as important identified risks, but the sponsor ultimately declined to do so.

9.3 Missing Information

Missing information includes exposure in pregnancy and lactation as well use in neonates and infants (≤ 1 month of age).

Reviewer Comment: The sponsor clarified that there were no patients with a documented pregnancy included in the RECON study while the RANGER study contained one pregnant patient at 33 weeks gestation at the time of enrollment with no reported adverse events.

10 DPV ASSESSMENT

DPV defers assessment of the adequacy of the proposed PVP in light of the decision by the review team to provide a Complete Response (CR) to this submission; please see CR letter for additional details.

11 DPV RECOMMENDATIONS

DPV recommends routine pharmacovigilance in accordance with 21 CFR 600.80. DPV defers additional pharmacovigilance recommendations given that this submission is resulting in a Complete Response.