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Office of Biostatistics and Pharmacovigilance (OBPV)**

REAL-WORLD EVIDENCE (RWE) REVIEW MEMORANDUM

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Subject: Review of the RANGER study and peer-reviewed literature

Sponsor: Axogen Corporation

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1 OBJECTIVE

To assess the findings from the RANGER study (ANG-CP-005) which examines the utilization, evaluations, and outcomes of the Avance Nerve Graft (from here onward, AVANCE) in repairing peripheral nerve injuries and to evaluate the peer-reviewed literature on AVANCE.

2 BACKGROUND INFORMATION AND REGULATORY HISTORY

Peripheral nerve injuries (PNIs) and unmet medical need. PNIs are a serious condition that can have significant functional and psychological impacts on patients. These injuries can occur through various mechanisms, such as accidental lacerations, surgical complications, birth trauma, or severe accidents involving motor vehicles, industrial equipment, gunshots, or military blasts. When a nerve is injured, it loses continuity, leading to the loss of sensation and/or motor function distal to the injury site. PNIs are relatively common, with an estimated incidence of 16.9 per 100,000 individuals in the United States [John et al.]. Unfortunately, many of these injuries require surgical repair using bridging materials to restore nerve continuity. However, there is a pressing need for more effective and reliable nerve repair options that can provide consistent outcomes across various injury lengths while minimizing patient morbidity. Nerve regeneration in the peripheral nervous system enables functional recovery after injury. Repairing a nerve discontinuity typically involves reconnecting the proximal and distal nerve stumps through direct suture or using bridging materials such as autografts, allografts, or conduits like NeuraGen. However, these materials have significant limitations, including donor site morbidity (autograft), limited availability (autograft), reduced effectiveness for larger discontinuity lengths (>30 mm for conduits and >200 mm for autografts and allografts), lack of internal biochemical cues (conduits), and variability in outcomes due to surgical technique. These limitations highlight the need for more advanced nerve repair solutions that can overcome these challenges and provide better patient outcomes.

Axogen's Avance Nerve Graft. AVANCE is a type of decellularized and sterilized extracellular matrix (ECM) derived from human donor peripheral nerve tissue. The graft's structure is designed to mimic the natural ECM of native nerves, featuring bundles of small diameter endoneurial tubes that provide a scaffold for nerve regeneration. AVANCE works by facilitating axonal growth across discontinuities in the nerve, enabling functional re-innervation of the target tissue and ultimately improving functional deficits. This is achieved through the interaction between the regenerating nerve growth cone and the biologically active laminin surface of the endoneurial tube scaffold. AVANCE is indicated for surgical repair of peripheral nerve discontinuities in adults and children over one month of age. It is available in a range of sizes to accommodate different patient needs, with 16 combinations of diameters (ranging from 1-5 mm) and lengths (ranging from 15-70 mm). Axogen has been distributing AVANCE in international markets since 2009. Currently there are 24 countries where the product is distributed, including the US.

AVANCE Regulatory Background. AVANCE was first introduced to the market in 2007 as a human cell, tissue, or cellular or tissue-based product (HCT/P), which did not require premarket approval. In 2010, the FDA granted Axogen an Enforcement Discretion Letter, allowing the company to continue selling AVANCE under HCT/P regulations while transitioning to full compliance with pharmaceutical regulations. To support this regulatory transition, Axogen conducted a single Phase 3 clinical trial (RECON, 2015-2021) on hand sensory nerves. The RECON study aimed to demonstrate the safety, purity, and potency of AVANCE while maintaining compliance with HCT/P regulations. On September 26, 2018, AVANCE received designation as a Regenerative Medicine Advanced Therapy (RMAT). To facilitate the transition to full pharmaceutical regulation, Axogen filed a BLA with the FDA. As part of this process, the company was granted a waiver under the small business waiver provision for the application fee in November 2023, provided that the marketing application was submitted within one

year. In September 2024, Axogen filed its BLA to comply with the regulatory transition requirement. In addition to the RECON clinical study, Axogen has been collecting real-world data (RWD) on AVANCE through a registry (RANGER) since November 2008. The RANGER registry provides over 15 years of utilization data in support of Avance BLA as a standard of care for repairing all peripheral nerve types where a bridging material is needed.

Reviewer's Note 1 (Age/Neonates): In September 2021, FDA agreed that a waiver for the neonate age group is reasonable, as it would be highly impracticable to enroll subjects from birth to one month of age, and it is unlikely that nerve reconstruction surgery would be performed during this phase.

Reviewer's Note 2 (Younger age groups): In 2021 FDA recognized that the adult and pediatric populations are similar in the pathophysiology of peripheral nerve injury and repair. However, FDA stated that full extrapolation of the adult safety and effectiveness data to the pediatric populations (i.e., infants, children, and adolescents) would not be acceptable.

The FDA considers the RECON study an adequate and well-controlled (AWC) study that met its prespecified primary endpoint, while also recognizing the potential value of RWD from the RANGER registry in evaluating product effectiveness and safety.

This was a rolling BLA submission. Although, priority review was requested, the BLA review classification for this application is a Standard 12 Month based on the current commercial availability of this product, the study results, and the available therapies for this condition.

BLA125816.0 was received on May 14, 2024. September 5, 2024, was when the final submission for the rolling BLA received. On September 26, 2024, the BLA was routed to the RWE reviewer. The action due date is September 5, 2025.

3 MATERIALS REVIEWED

Table 1 Amendments and Documents Reviewed

Amendment	Date IR Sent	Date Amendment Received	Documents Reviewed
BLA125816.3	N/A	September 5, 2024	<ol style="list-style-type: none"> 1. Clinical Overview (2.5) 2. Clinical Summary (2.7) 3. A Multicenter Registry Study of Avance Nerve Graft Utilization, Evaluations and Outcomes in Peripheral Nerve Injury Repair (RANGER study) Interim Clinical Study Report (5.3.5.2) 4. VV-CLIN-000278: Evaluation of Digital Nerve Repairs with Avance Nerve Graft from RANGER and RECON (5.3.5.3) 5. VV-CLIN-000277: Evaluation of Mixed Nerve and Motor Nerve Repairs with Avance Nerve graft and Nerve Autograft from the RANGER Registry (5.3.5.4) 6. VV-CLIN-000113: Systematic Clinical Literature Review - Avance Nerve Graft and Nerve Repair Performance, Including Conduit, Allograft, and Autograft Repairs (5.3.5.4) 7. VV-CLIN-000445 R00: Subgroup Analyses on Data from "Systematic Clinical Literature Review: Avance Nerve Graft and Nerve Repair Performance, Including Conduit, Allograft, and Autograft Repairs" (5.3.5.4) 8. VV-CLIN-000434: Evaluation of Real-World Safety of Avance Nerve Graft in the RANGER Registry (AETION Safety Report) (5.3.5.4) 9. VV-CLIN-000509: Executive Summary Peripheral Nerve Allograft for Pediatric Patients (5.3.5.4)
BLA125816.18	January 21, 2025	January 31, 2025	<ol style="list-style-type: none"> 1. Clinical Information Amendment Jan 21, 2025 2. RANGER 15-25mm and 26-29mm Ad Hoc Analysis 3. RANGER Stratification Data Tabular Summary
BLA125816.21	February 14, 2025	February 20, 2025	Request for RANGER-filtered-to-RECON comparison dataset
BLA125816.30	March 21, 2025	March 31, 2025	Request for treatment response rates by follow up duration Question on gap lengths differences between AVANCE and autograft cohorts in Addendum 1-MATCH
BLA125816.44	May 2, 2025	May 13, 2025	Question on RANGER registry compliance with 21 CFR part 11
BLA125816.60	June 23, 2025	July 9, 2025	Question on validation of effectiveness data presented in the draft USPI, Tables 4, 5, 6, 7, 8, and 10.
BLA125816.65	July 9, 2025	July 16, 2025	Efficacy data set in RANGER registry for patients under 2-year-old
	August 6, 2025	Waiting for response	Question on cohort imbalance and lack of adjusting for potential confounding in MATCH substudy

4 SUMMARY OF STUDY DOCUMENTS AND RWE REVIEW COMMENTS

We assessed the RANGER study (ANG-CP-005) including effectiveness comparison of AVANCE Digital Nerve Repairs from the RANGER study and RECON trial. We also provided comments on peer-reviewed publications pertinent to potential effectiveness of AVANCE.

4.1 RANGER study (ANG-CP-005)

4.1.1 RWE Summary/Rationale:

Peripheral nerve injuries are a common condition with significant functional and psychological impacts on patients, and current treatment options such as surgical repair using bridging materials have limitations. AVANCE is a decellularized and sterilized extracellular matrix derived from human donor peripheral nerve tissue that provides a scaffold for nerve regeneration and has been shown to facilitate axonal growth across discontinuities in the nerve. AVANCE has undergone regulatory transition, including a Phase 3 clinical trial (RECON) and collection of real-world data through a registry (RANGER), and was granted designation as a Regenerative Medicine Advanced Therapy (RMAT) in 2018.

The RANGER study (ANG-CP-005) is an open-label, multi-center observational registry that collects real-world data on the use of AVANCE in surgical nerve repairs. Launched in 2008, this ongoing study aims to monitor and collect data on nerve injuries, repairs, safety, and outcomes across various injury types and locations throughout the body. The RANGER protocol includes two optional addendums designed to create comparative groups and focused subgroups within the registry:

- **Addendum 1 (MATCH)** establishes a comparative arm to collect data on nerve injuries repaired with either nerve autografts or nerve tube conduits at participating RANGER sites.
- **Addendum 2 (SENSATION NOW)** focuses on collecting data on autologous breast reconstruction procedures that involve neurotization. The study includes an internal control group consisting of post-mastectomy autologous breast reconstruction procedures without neurotization.

4.1.2 RWD Source, Evaluation and Management:

The study has collected data on the use of AVANCE in three separate areas:

- **Parent protocol:** Types of nerve injuries repaired, methods used, assessment measures, recovery results, and adverse events associated with AVANCE.
- **Addendum 1:** Outcome measures, results, and adverse events associated with the use of nerve autograft and nerve tube conduits, as well as AVANCE. A study review panel will be formed to review and analyze blinded datasets.
- **Addendum 2:** Neurotization methods during post-mastectomy breast reconstruction, including sensory recovery, quality of life, economics, and patient satisfaction, as well as comparisons with non-neurotization procedures.

In all cases, data are collected, de-identified, and entered into a database for analysis by the sponsor or their representatives.

4.1.3 Key Study/Research Question(s):

- **Parent Protocol:** To evaluate the utilization, safety, and functional recovery outcomes of patients who undergo nerve repair using AVANCE.
- **Addendum 1 (MATCH):**
 - *Primary:* To assess the functional recovery outcomes in patients who undergo nerve repair using either nerve autograft or nerve tube conduit.
 - *Secondary:* To compare the utilization patterns and the functional recovery outcomes among patients who undergo nerve repair with nerve autograft or nerve tube conduit, with AVANCE.
- **Addendum 2 (SENSATION NOW):**
 - *Primary:* To determine the impact of neurotization (nerve repair/reconnection) of autologous tissue flaps on quality of life and patient satisfaction in patients undergoing breast reconstruction.
 - *Secondary:* To compare the outcomes, including sensory recovery, pain reduction, and overall satisfaction, between breast reconstruction surgeries with and without neurotization of autologous tissue flaps.

4.1.4 Methods/Study Design

This is an open-label multicenter observational registry study with centers following their own standard of care for subject treatment, rehab regime, and follow-up assessments. The study had both retrospective and prospective elements as the chart review was performed on medical records on patients who have completed follow-up (retrospective) or would be completing a follow-up.

The RANGER study is sponsored by Axogen which involves financial support to the participating sites to cover the costs associated with data collection, patient follow-up, and other study-related activities.

a. Study Period/Setting:

Parent Protocol	Addendum 1	Addendum 2
November 6, 2008 to July 1, 2022	2004 to July 1, 2022	October 10, 2017 to May 1, 2023

b. Participants/Eligibility Criteria:

	Parent Protocol	Addendum 1	Addendum 2
Participants	Male and female subjects who have been surgically repaired with AVANCE.	Male and female subjects that have been surgically repaired using a nerve autograft or nerve tube conduit after 2004 for the repair of a nerve injury of the upper extremity.	Female subjects with a previous mastectomy who have undergone autologous breast reconstruction
Inclusion Criteria	Subjects must: <ul style="list-style-type: none"> • Have undergone surgical nerve repair using AVANCE • Returned for at least one post-operative follow-up visit 	Subjects must: <ul style="list-style-type: none"> • Have nerve transection injuries to the upper extremity; • Have undergone tension free end to end nerve coaptation on both the proximal and distal portion of the nerve gap with nerve autograft or nerve entubulation with nerve tube conduit at a participating RANGER registry site after 2004; 	Subjects must: <ul style="list-style-type: none"> • Female \geq 18 years old • Undergo post mastectomy autologous breast reconstruction with one type of autologous flap; • Complete Sensory Assessment Testing with Semmes Weinstein Monofilaments (SWMF) and the following Breast-Q Questionnaires 60 - 120 days post reconstruction;

		<ul style="list-style-type: none"> Have completed sufficient follow-up assessments at a regeneration rate of 2mm/day to determine the outcomes of the repair or is willing to comply with site specific post-operative care procedures and assessments to determine the outcome of the repair. 	<ul style="list-style-type: none"> Able to provide informed consent and are willing to comply with post-operative care procedures and assessments.
Exclusion Criteria	Subjects who, in the opinion of the investigator, have not or likely will not complete at least some portion of the investigator's recommended follow-up.	<ul style="list-style-type: none"> Direct nerve repairs; Nerve gaps > 70 mm; Subjects who, in the opinion of the investigator, were non-compliant to the investigator's post-operative treatment or rehabilitation instructions; Any subject who at the discretion of the Investigator is not suitable for inclusion in the study. 	<ul style="list-style-type: none"> Surgical history of secondary revision surgery for partial or total flap loss; Bilateral reconstruction with non-uniform treatment; Currently prescribed medication known to impact nerve regeneration or to cause peripheral neuropathy; Currently undergoing IV chemotherapy or radiation; Any subject who at the discretion of the Investigator is not suitable for inclusion in the study or is unlikely to comply with follow-up schedule.

c. Exposure of interest/ascertainment:

Parent Protocol	Addendum 1	Addendum 2
AVANCE	<ul style="list-style-type: none"> - AVANCE - Nerve Autograft - Nerve Tube Conduit 	Neurotization (can be via direct neuroorrhaphy, the use of AVANCE, nerve autograft, or nerve conduit)

d. Outcome of interest/ascertainment:

- Effectiveness outcomes:** The study used various assessment tools, including sensory and motor scores, sensation tests, strength testing, and range of motion assessments. The study analyzed the effectiveness of nerve reconstruction treatments in two groups:
 - OP (Outcomes Population).** Repairs of subjects with at least 120 days follow-up, are categorized into:
 - Quantitative data (e.g., sensory scores, strength testing): positive (Q+) or no response (Q-)
 - Qualitative data (e.g., patient reports of improved sensation): positive (S+) or negative response (S-)
 - OP MR (Outcomes Population with Meaningful Recovery).** OP subjects with follow-up specific for the regenerative distance of the repair and quantitative data to determine the outcome of the nerve repair where repairs were categorized as:
 - Achieving Meaningful Recovery (Medical Research Council Classification (MRCC) score of S3/M3 or higher)
 - Not achieving Meaningful Recovery (MRCC score of S0-S2/M0-M2)
 - Response to treatment, MRCC Score of S1/M1 or higher
- Please note that an assessment of safety outcomes is not part of this RWE effectiveness review.

- e. **Variables:** In addition to the primary variables of interest, several others were also considered in the analysis to provide a more comprehensive understanding of the relationship between AVANCE and nerve repair outcomes. These additional variables included the body region where the injury occurred, with a distinction made between joint and non-joint regions. The subject's age was also considered, as well as the mechanism of injury, which was categorized as complex, laceration, or neuroma. Furthermore, the time to repair after injury was considered, along with the type of nerve affected, whether it was sensory, motor, or mixed. Other factors that were examined included the length of the gap in the nerve, the subject's smoking history, and any pertinent medical history that may have impacted the outcome. Additionally, improvements in pain levels were also assessed, as well as the use of alternative coaptation techniques.
- f. **Data Sources/Settings/Collection:** This is a multi-center postmarket registry (RANGER) study to collect utilization, safety, and outcomes data from medical record chart review on nerve injuries repaired with AVANCE (for Parent protocol and Addendum 2), and nerve autograft and nerve tube conduit (for Addendum 1). RANGER was designed by Axogen and is not linked to another registry or another data system.

47 study centers provided data for the study report. The study centers are located in the United States (44), Austria (1), Canada (1), and the United Kingdom (1). 7 of these were RECON clinical trial study sites.

The study involved collecting data on the safety and recovery outcomes of nerve repair using AVANCE through a series of follow-up visits. The number and type of assessments during these visits varied depending on the extent of the injury and were determined by the physician. The study aimed to collect data from four specific follow-up events per subject:

- Early post-operative care: Visit 1
- Mid post-operative care: Visit 2
- Late post-operative care: Visit 3
- Final post-operative care: Visit 4

If a subject was lost to follow-up, fewer visits were collected. Additional visits were scheduled if necessary to collect missed data or assess safety. In cases where revision surgery was required, details about the surgery and any adverse experiences were recorded. If AVANCE was used in the revision surgery, four additional follow-up visits may be collected. Once all available data had been collected, an End of Study form was completed for each subject.

Source documents are original records of a clinical investigation's data, observations, and activities that inform CRF data such as the hospital records, screening logs, therapy notes, and automated instrument readings. To ensure accurate data collection, information from source documents is transcribed onto standardized case report forms (CRFs) and entered directly into the electronic data capture (EDC) system or transmitted to Axogen. Changes made to CRFs, study progress notes, or other source documents are initialed and dated by authorized site staff.

An independent Contract Research Organization (CRO) oversees data management, storing all study data in a secure, validated database according to a global Data Management Plan. Clinical sites maintain original records, with copies transmitted to the data manager for scanning and electronic storage. Axogen or their designee conducts routine monitoring visits to ensure safe and ethical study conduct, including data

monitoring of critical variables. Also, Axogen's Quality Management Unit conducts audits at study sites to verify compliance with the protocol, including document presence, informed consent processes, and case report form accuracy. Also, regulatory authorities conduct audits, and investigators cooperate fully with these audits, notifying Axogen immediately if contacted.

The investigator maintains the study center file in accordance with Good Clinical Practice (GCP) guidelines and FDA regulations. Essential research documents, including informed consent forms, are retained for at least two years after marketing application approval or as required by regulatory requirements or sponsor agreement. Axogen notifies the principal investigator when these documents can be disposed of.

Reviewer's Comments:

A RWD source should be reliable and relevant to help support a regulatory decision.

Reliability. *The term reliability includes accuracy, completeness, and traceability. Since 2008, RANGER registry sites have been collecting real-world data (RWD) in accordance with a prespecified protocol. However, as RANGER Protocol ANG-CP-005 Version 5 states that "This study does not mandate or require specific procedures or assessments. The study sites should follow their own standard of care for subject treatment, rehabilitation regime and follow-up measures." This can lead to a multitude of issues, including variability in treatment protocols, inconsistent rehabilitation regimes, divergent follow-up measures, and increased risk of bias and confounding, ultimately compromising the validity of the study findings.*

Although loss to follow-up is expected for post-operative clinical care and RANGER site staff made additional attempts to follow-up with enrolled subjects that were within their follow-up period, 68% of enrolled patients and 70% repairs in the registry do not have an outcome record. If the patients with missing data are more likely to have poor outcomes, the results may not be generalizable to the broader population and the analysis may overestimate the effectiveness of the treatment. Missing data can lead to biased estimates of treatment effects, as the observed outcomes may not reflect the true effect of the treatment. The lack of control data in RANGER (except for 25 autograft motor neuron repairs) also limits the ability to evaluate the effectiveness of AVANCE.

Per Sponsor's response on May 13, 2025 to an information request from the RWE reviewer dated May 2, 2025, the RANGER registry complies with 21 CFR part 11 for ensuring maintenance of access controls and audit trails to demonstrate the provenance of the registry data and to support traceability of the data. For additional information, please refer to the Bioresearch Monitoring Final Discipline Review Memo.

Relevance. *The term relevance includes the availability of data for key study variables (exposures, outcomes, covariates) and sufficient numbers of representative patients for the study. The RANGER study (ANG-CP-005) is an open-label, multi-center observational registry that collects real-world data on the use of AVANCE in surgical nerve repairs. The RANGER registry has a geographically diverse range of sites, with the majority located within the United States. In the RANGER registry, there were only around 1,000 repairs for the effectiveness evaluation (Table 2) out of more than 100,000 repairs performed using AVANCE since 2008 globally (per Sponsor's Clinical Overview). OP MR (Outcomes Population with Meaningful Recovery, i.e., Analysis population) population is even smaller*

than the OP population, hence less data for evaluation. Although data on outcomes, exposures, and covariates are generally complete for the analysis population, outcome information is missing for approximately two-thirds of the subjects in the registry. If the unrecorded outcomes are less favorable than those observed in the analysis population, the reported AVANCE outcomes results may overestimate the true outcomes, potentially leading to an inaccurate representation of the actual effects.

g. Study Size:

Table 2 RANGER Registry Study Sizes for various study populations

Population	Parent Protocol	Addendum 1	Addendum 2
Safety/Utilization	1,780 subjects, 2,967 repairs	Autograft: 113 subjects, 128 repairs	408 subjects, 646 repairs
Outcomes Population (OP)	624 subjects, 975 repairs	Autograft: 45 subjects, 47 repairs	68 subjects, 109 repairs
Analysis Population (AP)	482 subjects, 750 repairs	Autograft: 24 subjects, 25 repairs	Not applicable

- h. Data Analyses:** To evaluate the outcomes of nerve repair, a combination of quantitative and qualitative assessments was employed. Quantitatively, patients underwent a range of tests to measure sensory and motor function, including MRCC scores, protective sensation assessments, two-point discrimination tests (both static and moving), Semmes-Weinstein Monofilament testing, strength testing, and range of motion evaluations. Qualitatively, medical records were reviewed to gather subjective information about patients' experiences with nerve repair, such as improvements in sensation or satisfaction with restored mobility.

The data collected from these assessments were then summarized using descriptive statistical methods, and 95% confidence intervals. No inferential statistics or hypothesis testing were provided.

Reviewer's Comments on RANGER Study Design and Conduct:

The RANGER study is an open-label, multi-center, single-arm, uncontrolled, unblinded, and subject to retrospective sampling bias. The lack of evaluator blinding may lead to various biases (e.g., confirmation bias) and no specific measures were taken to address this issue. Also, potential differences by study sites regarding standard of care for subject treatment, rehabilitation regime and follow-up measures were not addressed. By protocol, the data collection and follow-up measures (with minimum follow-up threshold) were standardized, and a well-established quantitative scoring system (MRCC score) was used to quantify outcomes. Relevant and appropriate subject demographics and baseline characteristics including medical history, injury history, age, gender, race, occupation, smoking history, and hand dominance were collected for effectiveness analysis.

The study protocol was reviewed and approved by an Independent Ethics Committee or Institutional Review Board at each participating site, which ensured that the study was conducted ethically and with informed consent from all subjects, in accordance with relevant regulations and guidelines. Unfortunately, the RANGER Registry study protocol versions 3, 4, and 5 were not shared with FDA during the IND stage (IND 015419).

4.1.5 Key Results

Overall treatment effectiveness rates in RANGER. 89.5% (95% CI: 86.9, 91.6) of the subjects in the outcome's population had at least one repair with a positive qualitative or

quantitative response. Of those subjects who have an MRCC score to evaluate meaningful recovery, 96.7% (95% CI: 94.4-98.0) had positively responded to at least one repair with AVANCE, and 90.7% (95% CI: 87.7-93.1) had at least one repair with meaningful recovery (MRCC score ≥ 3). Also, 83.3% (95% CI: 80.5-86.0) of all evaluable repairs (i.e., OP MR population) had a meaningful recovery.

RANGER Subgroup Analysis. The Sponsor analyzed the association between different factors and the rate of meaningful recovery after nerve repair with AVANCE (Table 3). Please note that the results are from univariate descriptive analyses without adjusting for any potential confounders. The results showed that most factors, such smoking history, and type of injury, were not significantly associated with the recovery rate. There were slightly better outcomes observed in upper extremity repairs compared to lower extremity repairs. However, patients with shorter gap lengths tended to have better recovery outcomes, while those with diabetes had poorer recovery rates compared to those with other medical conditions.

Recovery in Joint vs. Non-Joint Regions. The distinction between joint and non-joint areas is important because it relates to the level of mobility and stress at the reconstruction site. Joints are areas of high mobility, which can subject nerve repairs to greater mechanical stress, movement, and potential disruption. In contrast, non-joint areas tend to be more stable and experience less mechanical stress. The Sponsor analyzed RANGER nerve repair outcomes in areas near joints (e.g. hand, wrist, knee) versus non-joint areas (e.g. forearm, upper arm) as shown in Table 4.

Reviewer's Comments:

The subgroup analysis results in Table 4 showed that Response to Treatment and Meaningful Recovery rates were similar between joint and non-joint areas. The two subgroups have similar point estimates and largely overlapping confidence intervals.

Additional Analyses and Results. The Sponsor performed two additional analyses. First, to justify the use of RANGER by way of demonstrating similarity between RANGER and RECON outcomes, they compared RECON clinical trial outcomes with those of the individuals who have data in the RANGER registry and who would have been eligible to participate in the RECON clinical trial. Second, to better evaluate motor function recovery in motor and mixed nerve repairs, they compared results of autologous nerve repair outcomes obtained from sites that provide data to RANGER study against those of the AVANCE nerve repairs. In the following pages, we present those and our assessments separately.

Table 3: Summary of Meaningful Recovery by Factors (OP MR Repairs - Parent Protocol, excluding Sensation-NOW).

Factor	OP Repairs (N)	OP MR Repairs (N)	Meaningful Recovery (N)	Meaningful Recovery Rate (%) (95% CI)
OP MR by repair	975	750	625	83.3% (80.5-86.0)
Body region (nerve injury area)				
Lower extremity repairs	38	21	14	66.7% (43.0-85.4)
Upper extremity repairs	917	709	597	84.2% (81.3-86.8)
Nerve type				
Mixed	170	119	99	83.2% (75.2-89.4)
Motor	23	18	15	83.3% (58.6-96.4)
Sensory	782	613	511	83.4% (80.2-86.2)
Gap length (mm)				
<15	214	185	167	90.3% (85.1-94.1)
15 to 29	386	306	256	83.7% (79.0-87.6)
30 to 49	226	162	135	83.3% (76.7-88.7)
50 to 70	104	67	47	70.1% (57.7-80.7)
Time to repair				
Acute	740	586	487	83.1% (79.8-86.1)
Chronic	161	106	92	86.8% (78.8-92.6)
Delayed	67	52	42	80.8% (67.5-90.4)
Unknown	7	6	4	66.7% (22.3-95.7)
Age				
29 days to < 2 years	0	0	0	NA
29 days to < 1 year	0	0	0	NA
2 to 11 years	5	4	4	100.0% (39.8-100.0)
12 to 17 years	39	38	36	94.7% (82.3-99.4)
18 to 29 years	263	205	177	86.3% (80.9-90.7)
18 to < 22 years	74	49	45	91.8% (80.4-97.7)
30 to 49 years	369	276	222	80.4% (75.3-84.9)
50 to 64 years	188	143	125	87.4% (80.8-92.4)
65+ years	111	84	61	72.6% (61.8-81.8)
Mechanism of injury				
Complex	325	240	192	80.0% (74.4-84.9)
Neuromas	145	403	346	85.9% (82.1-89.1)
Lacerations	505	107	87	81.3% (72.6-88.2)
Smoking history				
Non-smoker	637	510	431	84.5% (81.1-87.5)
Previous smoker	74	48	37	77.1% (62.7-88.0)
Smokeless tobacco	5	5	5	100.0% (47.8-100.0)
Smoker	224	167	135	80.8% (74.0-86.5)
Unknown	35	20	17	85.0% (62.1-96.8)
Pertinent medical history				
Diabetes	75	56	34	60.7% (46.8-73.5)
Hypertension	177	130	111	85.4% (78.1-91.0)
Peripheral neuropathy	5	4	3	75.0% (19.4-99.4)

CI = Confidence interval, OP MR = Outcomes Population Meaningful Recovery NA = Not applicable, OP = Outcomes Population, 95% CI calculated using the Clopper-Pearson method.

Table 4: Subgroup Analysis by Joint vs. Non-Joint Regions - OP Positive Response and OP MR Treatment Response.

Region	OP Repairs (N)	OP Positive Response	Positive Response Rate (%) (95% CI)	OP MR Repairs (N)	OP MR Treatment Response (N)	OP MR Treatment Response Rate (%) (95% CI)
Joint/joint-adjacent	841	736	87.5% (85.1-89.7)	650	614	94.5% (92.4-96.1)
Non-joint	118	106	89.8% (82.9-94.6)	89	86	96.6% (90.5-99.3)
Unknown	16	13	81.3% (54.4-96.0)	11	9	81.8% (48.2-97.7)

CI = Confidence interval, OP MR = Outcomes Population Meaningful Recovery OP = Outcomes Population, 95% CI calculated using the Clopper-Pearson method.

Reviewer's Comments:

The RANGER study has several limitations that impact the interpretation of its findings. The retrospective, non-controlled, and non-randomized design introduces potential biases and limits comparative inferences with alternative treatments. Additionally, the RANGER registry has a limited sample size for certain subgroups, which is detailed below.

The analyses' reliance on descriptive summary statistics precludes comparative analyses with other treatments, such as nerve conduits and autografts and the lack of a control group limits the assessment of the AVANCE's effectiveness. Furthermore, the exclusion of subjects unlikely to complete follow-up and variability in treatment sites' standard of care may have introduced selection bias, affecting the generalizability of results. The limited duration of subject follow-up restricts the evaluation of long-term outcomes and meaningful recovery.

In addition, the following factors decrease generalizability of the results of RANGER registry analyses in supporting the indication expansion of AVANCE from that studied in the RECON clinical trial (i.e., ages 18-65 years, digital sensory nerve repair, nerve gaps between 5-25 mm):

- In the RANGER registry, there were only around 1,000 repairs for the effectiveness evaluation out of more than 100,000 repairs performed using AVANCE since 2008 globally. OP MR (Outcomes Population with Meaningful Recovery) population is even smaller than the OP population, hence less data for evaluation.*
- The digital sensory nerve repairs accounted for the vast majority of repairs; only about 26% were performed elsewhere.*
- Analysis population exclusion criterion was left to clinical site investigators' judgement on subject follow up and sites follow their standard of care for treatment and post-operative care for the specific nerve reconstruction and injury.*
- In the registry there were only about 20 motor-only nerve repairs.*
- Only 44 reported nerve repair cases in 2-18 years of age, just 5 in the younger subgroup 2-12 years of age.*
- Nerve repair MRCC response rates were found to be statistically decreasing with increasing repair gap lengths, which is presented separately in the clinical review memorandum.*

In summary, while the RANGER study provides some insights into the effectiveness of AVANCE, its numerous limitations and biases, including issues related to study design, sample size, follow-up duration, and generalizability, significantly restrict the reliability and applicability of its findings.

4.2 Evaluation of Digital Nerve Repairs with Avance Nerve Graft from RANGER and RECON.

In addition to broad RANGER Registry analysis, the Sponsor also analyzed RANGER subjects meeting RECON trial enrollment criteria and with outcome results to demonstrate the potential robustness of their registry (Table 6).

Table 5 Baseline Characteristics, RANGER Registry Study and RECON Trial (Analysis Population)

Demographic Characteristic	RANGER N=72	RECON Trial N=90
Age (yrs), mean (SD)	38.5 (13.3)	37.9 (14.3)
Gender, n (%)	-	-
Male	60 (83.3)	62 (68.9)
Female	12 (16.7)	28 (31.1)
Race/ethnicity, n (%)	-	-
Not Hispanic or Latino	90 (100)	-
White	-	72 (80.0)
Black or African American	-	13 (14.4)
Asian	-	2 (2.2)
Other	-	3 (3.3)
Smoking status, n (%)	-	-
Current smoker	23 (31.9)	23 (25.6)
Former smoker	7 (9.7)	18 (20.0)
Never smoker	44 (61.1)	47 (52.2)
Injury characteristics	-	-
Gap length (mm)	16.3 (5.2)	13.6 (5.1)
Time to repair (d)	8.5 (17.7)	27.7 (39.0)
Mechanism of injury, n (%)	-	-
Abrasion	3 (4.2)	1 (1.1)
Crush	7 (9.7)	2 (2.2)
Contusion/blunt saw	29 (40.3)	21 (23.3)
Laceration/sharp	27 (37.5)	59 (65.6)
Motor vehicle accident	0 (0.0)	0 (0.0)
Puncture	6 (8.3)	2 (2.2)
Other	0 (8.3)	5 (5.6)

Table 6: Repair response rates for digital sensory repair in filtered RANGER and RECON.

Proportion of Patients	RANGER, n = 62	RECON, n = 90
Response to Treatment, (95% CI)	95% (86.5 - 99.0)	100% (96.0 - 100)
Meaningful Recovery (\geq S3), (95% CI)	89% (78.1 - 95.3)	90% (81.9 - 95.3)

Reviewer's Comments on RANGER vs. RECON:

This post-hoc analysis aims to compare outcomes between a clinical trial and a registry study. However, it is essential to note that these two studies have distinct protocols, which may introduce differences in their results. To mitigate this issue, the Sponsor attempted to identify a subset of registry participants who would have met the inclusion criteria for the clinical trial, thereby creating a more comparable group for analysis. However, regarding baseline characteristics (Table 5), the subset of patients from the RANGER study had several baseline characteristics that are different than those in the RECON study, including gender, smoking status, and mechanism of injury.

Even if we did not have concerns regarding the differences in the baseline characteristics of the two cohorts, the results presented in Table 5 would only be true for the limited indication studied in the RECON clinical trial and we are unable to make an extrapolation from the RANGER registry as to the meaningful recovery rates in other indications, including mixed and motor nerve repairs, pediatric and geriatric age groups, and longer gap lengths.

4.3 Evaluation of Mixed and Motor Nerve Repair Outcomes with Avance Nerve Graft and Nerve Autograft from the RANGER Registry (Addendum 1 - MATCH).

This study was developed to summarize and analyze 1) motor recovery in mixed nerves and motor nerves and 2) adverse events in mixed nerves and motor nerves for AVANCE and nerve autograft. data here consist of Avance Nerve graft and nerve autograft repairs less than or equal to 70 mm with an available quantitative outcome measure (e.g., MRCC score) that completed a minimum evaluable post-operative visit based on the regenerative distance of the injury (distance prespecified in the SAP) that were not an amputation or avulsion injury.

Table 7 Population Baseline Characteristics, MATCH Study

Parameter	AVANCE N=25	Autograft N=25
Average age (yrs)	29.2 (s.e.m. 2.7)	39.5 (s.e.m. 3.4)
Gender (male)	21	22
Gender (female)	4	3
Average gap length (mm)	34.1 (s.e.m. 3.4)	42.7 (s.e.m 3.2)
Perioperative interval (days)		
Mean (SD)	16.1 (37.4)	55.5 (65.6)
Median	1	23
Mechanism of injury	-	-
Crush/compression	3	2
Sharp laceration	12	8
Iatrogenic	1	3
Gunshot/blast	3	6
Blunt laceration	0	1
Saw laceration	4	4
Other	2	1

Abbreviations: N, population size; s.e.m., standard error of the mean

Table 8: MRCC Scores in Addendum 1 - MATCH of the RANGER registry study

	AVANCE	Autograft
Analysis population (AP)	25 repairs	25 repairs
Meaningful motor recovery	80% (95% CI: 59.3-93.2)	64% (95% CI: 42.5-82.0)
Analysis population (AP)	25 repairs	25 repairs
Motor response to treatment	88.0% (95% CI: 68.8-97.5)	84.0% (95% CI: 63.9-95.5)
Outcomes population (OP)	84 repairs	47 repairs
Motor response to treatment	89.3% (95% CI: 80.6-95.0)	87.2% (95% CI: 74.3-95.2)

Reviewer's Comments on MATCH Substudy:

Table 8 presents the response to treatment rates and meaningful recovery rates for motor function after nerve reconstruction using Avance and autograft (standard-of-care treatment) in both the AP and OP groups. The comparative outcomes between Avance and autograft shows higher response to treatment and meaningful recovery rates for Avance subjects, with specific rates ranging from 80.0% (meaningful motor function recovery, MRCC scores ≥ 3) to 89.3% (motor response to treatment, MRCC scores ≥ 1). However, there are methodological and baseline data concerns. Similar to our comments about the RANGER study, this substudy has limitations. Most significantly, the AVANCE cohort in the analysis population had demographic differences compared to the autograft cohort (Table 7). For example, they were significantly younger than the autograft cohort, had a shorter perioperative interval, shorter gap lengths, and less severe injuries. These

differences in baseline characteristics can introduce confounding bias and create an unbalanced comparison, potentially leading to overestimation of treatment effects of AVANCE. Nevertheless, we should note that perioperative interval was not considered a clinically distinguishing factor. Additionally, the sample sizes for outcome measures are small (only 25 AVANCE and Autograft repairs in the analysis population), which may impact the accuracy of the results.

4.4 RANGER Study (ANG-CP-005) Assessment

The RANGER study is an open-label, multicenter, observational registry collecting real-world data (RWD) on AVANCE use in surgical nerve repairs. While the RANGER study provides confirmatory evidence from RWD in favor of effectiveness for the treatment of peripheral nerve discontinuities in patients 2 years of age and older, we have methodological and data concerns regarding its use to support indications not studied in RECON. These include the following:

1. Investigator-judged eligibility may have introduced bias and limited generalizability.
2. Site-specific variations in treatment and follow-up could introduce bias if patient inclusion or retention differs by local standards of care.
3. The study did not enable direct comparisons between AVANCE and alternatives like nerve conduit and autograft, except for the MATCH portion of the RANGER study. However, this portion had limitations: only 25 cases per group, baseline imbalances between AVANCE and Autograft arms, and no adjustment for potential confounders.
4. Although more than 100,000 nerve repairs have been performed globally with AVANCE, the RANGER registry includes only 3,613 repairs. Of these, 1,021 had a follow up of >120 days to evaluate the product's effectiveness. The available data becomes limited when evaluating outcomes of meaningful recovery, which requires longer follow-up periods. In the subgroups, most notably, the registry has very limited data to assess effectiveness (1) in the 2-18 years of age group, with only 44 reported nerve repair cases, and even fewer (just five) in the younger subgroup of 2-12 years old, and (2) there are only 20 motor-only nerve repairs. Moreover, increasing nerve repair gap lengths were demonstrated to be correlated with decreasing meaningful recovery rates by the CBER reviewers.

4.5 Peer-Reviewed publications for potential demonstration of effectiveness

The Sponsor provided a systematic literature review of peripheral nerve repairs to potentially provide evidence analogous to the evidence presented in the RANGER clinical study report. A total of 666 articles were retrieved using the pre-defined literature search strategies. Based on the pre-defined inclusion criteria, 60 articles were retrieved for full-text review. Screening of the bibliographies of these articles identified 43 additional articles for full-text review. Of all articles reviewed at full-text, 75 were excluded. A total of 28 studies comprising 1078 repairs were included in this systematic review. The level of evidence was moderate (Oxford Level 2 - Oxford Level 4) for allograft and conduit repair, and for autograft repair (Oxford Level 3 - Oxford Level 4), with Level 1 being the strongest and Level 5 the weakest.

Overall, meaningful recovery rates for repairs that used AVANCE, nerve conduit, autograft, and allograft were comparable with AVANCE repairs having the highest MR rate of all four (Table 9).

The Sponsor also performed a subgroup analysis on the literature data. In general, response to treatment and MR rates from the RANGER study followed a similar pattern of outcome rates observed in the literature review analysis for autograft, conduit, and allograft repairs.

- MR rates decreased as the patient age increased by approximately 29% for allograft, 33% for autograft, and 38% for conduits.
- MR rates also decreased approximately 35% for allograft and 43% for autograft as the gap length increased.
- For upper extremity repairs in comparison to lower extremity repairs, there is a decrease of approximately 37% in MR rate for allograft repairs and approximately 58% for autograft repairs.

Reviewer's Comments on MATCH Substudy:

A comparison of the AVANCE cohort in the MATCH substudy ([Table 7](#)) revealed previously that participants were significantly younger and had shorter gap lengths than those in the autograft cohort. This is notable because, as the literature review analysis above suggests, autograft repair outcomes are particularly sensitive to increases in age and gap length. Consequently, the relatively favorable demographics of the AVANCE cohort may have contributed to overestimated treatment effects in the MATCH substudy, raising concerns about the generalizability of these findings.

Table 9: Reviewer's summary of Sponsor's Literature Review Analysis of meaningful recovery rates in nerve conduit, autograft, and allograft repairs compared with RANGER clinical study report (CSR). MRCC ≥ 3 scores are considered as meaningful recovery. All ages, repair gap lengths and body regions are included.

	Number of Repairs	Number of Repairs with Meaningful Recovery	Meaningful Recovery rate 95% CI
Nerve Conduit	201	142	70.6% (63.8-76.8)
Autograft	142	109	76.8% (69.0-83.4)
Allograft	255	206	80.8% (75.4-85.4)
AVANCE RANGER CSR	750	625	83.3% (80.5-86.0)

In the literature identified in the Sponsor's analysis, data for individuals with pertinent medical history were not available.

Reviewer's Comments:

This literature review analysis is distinct from a meta-analysis, as it does not involve weighted assessments of individual study quality or bias risk. The published studies have different follow up durations and are not harmonized to those presented in RANGER clinical study report. Furthermore, no calculations were made to determine effect sizes for individual studies or combinations of studies, nor was a pooled summary effect size calculated. It is also important to note that the FDA lacks access to subject-level data from the individual studies, which would be necessary to validate the findings presented in this section.

5 REVIEWER'S CONCLUSIONS

RWD are data relating to patient health status and/or delivery of health care routinely collected from a variety of sources. RWE is clinical evidence regarding the usage and potential benefits/risks of a medical product derived from analysis of RWD. RWD-RWE can support regulatory decisions if the RWD are reliable and relevant, and the study design provides adequate scientific evidence to address the regulatory question. This includes consideration of the quality of the study design, use of appropriate prespecified statistical methods and analyses, and adherence to FDA regulatory requirements. Whether an RWD source may be appropriate to develop RWE that serves as confirmatory evidence depends on these factors and must be evaluated on a case-by-case basis.

The RANGER registry's reliability is compromised due to several issues related to accuracy, completeness, and traceability. Approximately 68% of enrolled patients and 70% of repairs lack outcome records, potentially resulting in biased estimates of treatment effects and overestimation of the effectiveness of AVANCE. The lack of control data, except for a small subset of autograft motor neuron repairs, also limits the ability to evaluate the effectiveness of AVANCE. While the registry complies with 21 CFR part 11 for ensuring access controls and audit trails, the significant amount of missing data and potential biases introduce concerns about the accuracy and generalizability of the study findings, ultimately impacting the reliability of the data and its applicability to support indication expansion of AVANCE.

The RANGER registry has limitations related to relevance, including the availability of data for key study variables and sufficient numbers of representative patients. Although the registry collects real-world data on the use of AVANCE in surgical nerve repairs with a geographically diverse range of sites, there are concerns about missing outcome information for approximately two-thirds of the subjects, which could lead to biased estimates of treatment effects. The analysis population is relatively small, with only around 1,000 repairs for effectiveness evaluation out of over 100,000 repairs performed globally since 2008. Furthermore, the registry has limited representation of certain subgroups, such as pediatric and geriatric age groups, mixed and motor nerve repairs, and longer gap lengths. These limitations impact the generalizability of the results and restrict the ability to evaluate the effectiveness of AVANCE in various patient populations.

The RANGER study has several limitations related to its design and conduct, which impact the interpretation of its findings. As an open-label, multi-center, single-arm, uncontrolled, and unblinded study, it is subject to various biases, including confirmation bias, selection bias, and presence of confounding variables. The lack of evaluator blinding and control group limits comparative inferences with alternative treatments, such as nerve conduits and autografts. Additionally, the study's retrospective design, limited sample size for certain subgroups, and variability in treatment sites' standard of care may have introduced biases affecting the generalizability of results. The exclusion of subjects unlikely to complete follow-up and limited duration of subject follow-up also restrict the evaluation of long-term outcomes and meaningful recovery. Also, the study protocol's flexibility, allowing sites to follow their own standard of care for subject treatment, rehabilitation regime, and follow-up measures, may have led to inconsistencies in data collection and introduced additional biases. These limitations significantly restrict the reliability and applicability of the RANGER study's findings.

To conclude, the RANGER study does not meet the criteria for an adequate and well-controlled clinical investigation as defined under 21 CFR 314.126, and therefore its data, along with the Sponsor's systematic literature review, cannot serve as primary evidence of effectiveness for regulatory purposes.

6 REFERENCES

John, Albin, et al. "Assessment of Motor Function in Peripheral Nerve Injury and Recovery." *Orthopedic reviews* 14.3 (2022).