BLA 761485

CORRECTED BLA ACCELERATED APPROVAL

Denali Therapeutics Inc.
Attention: Erica Cox, PhD
Executive Director, Regulatory Affairs
161 Oyster Point Boulevard
South San Francisco, CA 94080

Dear Dr. Cox:

Please refer to your biologics license application (BLA) dated and received May 5, 2025, and your amendments, submitted under section 351(a) of the Public Health Service Act for Avlayah (tividenofusp alfa-eknm) for injection.

We acknowledge receipt of your major amendment dated September 30, 2025, which extended the goal date by three months.

We also refer to our approval letter dated March 24, 2026, which contained the following error: the storage temperature should be (b) (4) °C for the dating period of the drug substance following manufacture.

This corrected action letter incorporates the correction of the error. The effective action date will remain March 24, 2026, the date of the original letter.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2385 to Denali Therapeutics Inc., South San Francisco, CA, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Avlayah (tividenofusp alfa-eknm). Avlayah is indicated for the treatment of neurologic manifestations of Hunter syndrome (Mucopolysaccharidosis type II, MPS II) when initiated in presymptomatic or symptomatic pediatric patients weighing at least 5 kg prior to advanced neurologic impairment.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture tividenofusp alfa-eknm drug substance at [redacted] (b) (4) The final formulated product will be manufactured and filled at [redacted] (b) (4) and labeled and packaged at [redacted] (b) (4) You may label your product with the proprietary name Avlayah and will market it in 150 mg/vial for injection.

DATING PERIOD

The dating period for Avlayah shall be 24 months from the date of manufacture when stored at 2°C to 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be [redacted] (b) (4) months from the date of manufacture when stored at [redacted] (b) (4) °C.

Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Avlayah to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Avlayah, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 601.41, effective on the date of this letter, for use as recommended in the enclosed agreed-upon approved labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information). Information on submitting SPL files using eLIST may be found in the draft guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* (October 2009).[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (February 2020, Revision 7)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761485**." Approval of this submission by FDA is not required before the labeling is used.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 761485. All correspondences related to this voucher should refer to this tracking number.

This PRV entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologics license application submitted under section 351(a) of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the PRV must notify FDA of its intent to submit an application with a PRV at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

[2] When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

notification should be prominently marked, “Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”

- This PRV may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the PRV may be transferred, but each person to whom the PRV is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this PRV, you should refer to this letter as an official record of the voucher. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the PRV was transferred.

- FDA may revoke the PRV if the rare pediatric disease product for which the PRV was awarded is not marketed in the U.S. within 1 year following the date of approval.

- The sponsor of an approved rare pediatric disease product application who is awarded a PRV must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:

    - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),

    - the estimated demand in the U.S. for the product, and

    - the actual amount of product distributed in the U.S.

You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.[3]

ADVISORY COMMITTEE

Your application for Avlayah was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 601.41, you are required to conduct a further adequate and well-controlled clinical trial intended to verify and describe clinical benefit. You are required to conduct this clinical trial with due diligence.

[3] https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs

If your required postmarketing clinical trial fails to verify clinical benefit or is not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated March 6, 2026. This requirement is listed below.

4953-1 Conduct a double-blind, randomized, active (standard-of-care)-controlled trial to verify and describe the clinical benefit of tividenofusp alfa-eknm in patients with mucopolysaccharidosis type II (MPS II).

The timetable you submitted on March 6, 2026, states that you will conduct this trial according to the following schedule:

Trial Completion:	11/2027
Final Report Submission:	11/2028

Submit clinical protocols to your IND 139904 for this product. FDA considers the term final to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this BLA 180 days after the date of approval of this BLA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open study or clinical trial required under 506(c). The initial report will be a standalone submission and the subsequent report will be combined with your application's annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted.[4]

Your 180-day reports must include the information listed in 21 CFR 601.70(b). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[5]

180-day reports must be clearly designated "**BLA 761485 180-Day AA PMR Progress Report**."

[4] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.

[5] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this BLA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of developing neutralizing antibodies that inhibit cellular uptake of tividenofusp alfa-eknm in patients treated with tividenofusp alfa-eknm.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following study:

4953-2 Develop and validate assay(s) for detection of neutralizing antibodies that inhibit cellular uptake of tividenofusp alfa-eknm.

The timetable you submitted on March 6, 2026, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/2026

Submit clinical protocol(s) to your IND 139904 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o), REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o), REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4953-3 Conduct historical control studies (embryo fetal development - and pre and postnatal development) to characterize the $TfR^{mu/hu}$ KI mouse model. Identify whether the F1 generation of $TfR^{mu/hu}$ KI mice have human TfR expression during the embryofetal period to best evaluate maternal and fetal development and reproductive toxicities of tividenofusp alfa-eknm.

The timetable you submitted on March 6, 2026, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2026
Draft Report Submission:	05/2026
Study Completion:	09/2026
Final Report Submission:	06/2027

4953-4 Conduct embryofetal and pre- and postnatal development studies in a relevant nonclinical species with tividenofusp alfa-eknm treatment.

The timetable you submitted on March 6, 2026, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 09/2027
Study Completion: 06/2028
Final Report Submission: 02/2029

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4953-5 Develop, validate, and implement an enzyme kinetics assay with quantitative acceptance criteria for K_M and k_{cat} parameters to supplement the current enzyme activity method for tividenofusp alfa drug substance and drug product release and stability specifications.

The timetable you submitted on November 24, 2025, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/2026

4953-6 Develop, validate, and implement a Mannose-6-Phosphate Receptor (M6PR)-mediated cellular uptake assay for tividenofusp alfa drug substance and drug product release and stability specifications to ensure consistent potency related to lysosomal delivery of tividenofusp alfa.

The timetable you submitted on November 24, 2025, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2027

4953-7 Develop, validate, and implement a transferrin receptor (TfR)-mediated cellular uptake assay for drug substance and drug product release and stability specifications to ensure consistent potency related to blood-brain barrier (BBB) crossing of tividenofusp alfa. Alternatively, establish an adequate correlation between a TfR-mediated cellular uptake assay and the current TfR binding assay.

The timetable you submitted on November 24, 2025, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2027

4953-8 Provide additional method validation data for the following test methods, SE-HPLC, NR CE-SDS, R CE-SDS, icIEF, Enzyme activity, TfR binding, and M6PR binding, with appropriate stressed or impurity-spiked samples to support adequate stability indicating capabilities of these methods performed at both sites, (b) (4) (b) (4)

The timetable you submitted on December 8, 2025, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2026

4953-9 To provide suitable endotoxin detection method and method validation to ensure potential endotoxin contaminations can be detected, and submit the final report with results from the study.

The timetable you submitted on December 1, 2025, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2026

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 139904 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[6]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

[6] https://www.fda.gov/media/128163/download

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Avinash Kalsi, Regulatory Project Manager, at (301) 348-1432 or Avinash.Kalsi@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Janet W Maynard, MD, MHS
Director
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JANET W MAYNARD
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