U.S. FOOD & DRUG ADMINISTRATION

BLA 103909/S-5197

SUPPLEMENT APPROVAL

Genentech, Inc.
Attention: Wren Thomas, PhD
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Thomas:

Please refer to your supplemental biologics license application (sBLA), dated and received January 31, 2024, and your amendments, submitted under section 351(a) of the Public Health Service Act for TNKase (tenecteplase) for injection, for intravenous use.

We acknowledge receipt of your major amendment dated September 30, 2024, which extended the goal date by three months.

This Prior Approval supplemental biologics license application provides for the treatment of acute ischemic stroke (AIS) in adults.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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] that is identical to the enclosed labeling (text for the Prescribing Information) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

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

[2] 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.

The SPL will be accessible via publicly available labeling repositories.

Also, within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on December 23, 2024, 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*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 103909/S-5197**." Approval of this submission by FDA is not required before the labeling is used.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for children less than 2 years of age because the necessary studies are impossible or highly impracticable. This is because very few children can be definitively diagnosed with acute ischemic stroke in the timeframe needed to administer this drug.

We are deferring submission of your pediatric studies for children 2 to 18 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.28 and

section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

4716-1 Conduct a randomized, controlled trial to evaluate the efficacy and safety of TNKase (tenecteplase), compared to an appropriate control, for the treatment of acute ischemic stroke in patients at least 12 years through less than 18 years of age.

Draft Protocol Submission:	09/2025
Final Protocol Submission:	06/2026
Study Completion:	06/2036
Final Report Submission:	06/2037

4716-2 Conduct a clinical study, or studies, in patients at least 2 years through less than 12 years of age with acute ischemic stroke. A study, or substudy in a single study, should determine the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of TNKase (tenecteplase) to determine the appropriate dose or doses in patients less than 12 years of age. A study, or substudies within a single study, should determine if an appropriate dose of TNKase (tenecteplase) is safe and effective for the treatment of acute ischemic stroke in patients at least 2 years through less than 12 years of age. The safety and efficacy study, or studies, may be initiated after completion of the study in patients at least 12 years through less than 18 years of age intended to fulfill PMR 4716-1.

Draft Protocol Submission:	12/2037
Final Protocol Submission:	09/2038
Study Completion:	09/2042
Final Report Submission:	10/2043

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.[3]

Submit the protocols to your IND 139995, with a cross-reference letter to this BLA. Reports of these required pediatric postmarketing studies must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

We remind you of your postmarketing commitments:

4716-3 To provide the new bacterial retention study and [redacted] (b) (4) is validated during the new bacterial retention study.

The timetable you submitted on 2/19/2025, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/25

4716-4 To conduct [redacted] (b) (4) with tenecteplase 25 mg container closure system to support [redacted] (b) (4) process validation.

The timetable you submitted on 2/19/2025, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/25

4716-5 To provide additional container closure integrity testing (CCIT) data from [redacted] (b) (4)

The timetable you submitted on 2/19/2025, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/25

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. 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.*[4]

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 601.12(f)(4)]. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Lyal Tressler, Regulatory Project Manager, by email at lyal.tressler@fda.hhs.gov, or by telephone at (240) 402-0434.

Sincerely,

{See appended electronic signature page}

Paul R. Lee, MD, PhD, MA
Director (Acting)
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information

[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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/

PAUL R LEE
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