

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761320Orig1s000

OTHER ACTION LETTERS



BLA 761320

COMPLETE RESPONSE

Outlook Therapeutics, Inc.
Attention: Jennifer Kissner, PhD
Executive Vice President
111 South Wood Avenue
Unit #100
Iselin, NJ 08830

Dear Dr. Kissner:

Please refer to your biologics license application (BLA) dated and received August 29, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for bevacizumab-vikg injection.

We acknowledge receipt of your amendment dated October 31, 2025, which constituted a complete response to our August 27, 2025, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in § 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. NORSE TWO met its primary endpoint for effectiveness. In NORSE EIGHT, Lytenava (bevacizumab-vikg) injection did not meet the primary efficacy endpoint of mean change from baseline in ETDRS BCVA score at the Week 8 visit in comparison to ranibizumab using a non-inferiority margin of -3.5 letters.

The submitted additional mechanistic and natural history data information does not alter the review conclusion that while one adequate and well controlled study demonstrating efficacy has been provided, adequate confirmatory evidence has not been provided.

Therefore, there is not sufficient evidence to demonstrate that Lytenava (bevacizumab-vikg) 1.25 mg is effective as being claimed in the proposed indication for its use when dosed monthly to treat wet-AMD. It is recommended that confirmatory evidence of efficacy be submitted to support the application.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources¹ and Pregnancy and Lactation Labeling Final Rule² websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to our correspondence dated, December 29, 2025, which addresses the proposed proprietary name, LYTENAVA. This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all the application deficiencies that have been identified in this letter.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

- (1) Describe in detail any significant changes or findings in the safety profile.
- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

² <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

- (3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
- (6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
- (7) Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please contact Michael Puglisi, Senior Regulatory Project Manager, at michael.puglisi@fda.hhs.gov or at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Alex Gorovets, MD
Director
Office of Specialty Medicine
Office of New Drugs
Center for Drug Evaluation and Research

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/

ALEXANDER GOROVETS
12/30/2025 01:26:55 PM



BLA 761320

COMPLETE RESPONSE

Outlook Therapeutics, Inc.
Attention: Jennifer Kissner, PhD
Senior Vice President, Clinical and Regulatory Affairs
111 South Wood Avenue
Unit #100
Iselin, NJ 08830

Dear Dr. Kissner:

Please refer to your biologics license application (BLA) dated and received August 29, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for bevacizumab-vikg injection.

We acknowledge receipt of your amendment dated February 27, 2025, which constituted a complete response to our August 29, 2023, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in § 314.126, that the product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its proposed labeling. NORSE 2 met its primary endpoint for effectiveness. In NORSE EIGHT, Lytenava (bevacizumab-vikg) injection did not meet the primary efficacy endpoint of mean change from baseline in ETDRS BCVA score at the Week 8 visit in comparison to ranibizumab using a non-inferiority margin of -3.5 letters. Therefore, there is not sufficient evidence to demonstrate that Lytenava (bevacizumab-vikg) 1.25 mg is noninferior to ranibizumab 0.5 mg dosed monthly to treat wet-AMD. It is recommended that confirmatory evidence of efficacy be submitted to support the application.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources¹ and Pregnancy and Lactation Labeling Final

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

Rule² websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to our correspondence dated, April 21, 2025, which addresses the proposed proprietary name, LYTENAVA. This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to all the application deficiencies that have been identified in this letter.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

- (1) Describe in detail any significant changes or findings in the safety profile.
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² <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

- (4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
- (6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
- (7) Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

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The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please contact Michael Puglisi, Senior Regulatory Project Manager, at michael.puglisi@fda.hhs.gov or at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Alex Gorovets, MD
Deputy Director
Office of Specialty Medicine
Office of New Drugs
Center for Drug Evaluation and Research

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/

ALEXANDER GOROVETS
08/27/2025 01:00:37 PM



BLA 761320

COMPLETE RESPONSE

Outlook Therapeutics, Inc.
Attention: Terry J. Dagnon, MS
Chief Operations Officer
485 Route 1 South
Building F, Suite 320
Iselin, NJ 08830

Dear Mr. Dagnon:

Please refer to your biologics license application (BLA) dated and received August 29, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Lytenava (bevacizumab-vikg) injection. We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

1. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability. Specifically,

(b) (4)



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24. The potential of the drug product to affect the health of the corneal endothelial cells is unknown. It is recommended that you conduct a controlled trial to evaluate the corneal endothelial health of eyes treated with bevacizumab-vikg by monitoring the number/density of corneal endothelial cells using specular microscopy at baseline and over a period of at least one year in at least 100 patients receiving bevacizumab-vikg.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources¹ and Pregnancy and Lactation Labeling Final Rule² websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.³

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

Please refer to correspondence dated November 21, 2022, which addresses the proposed proprietary name, Lytenava. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

OTHER

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

² <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

³ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

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You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please contact Michael Puglisi, Regulatory Project Manager, at michael.puglisi@fda.hhs.gov or at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Charles Ganley, MD
Director
Office of Specialty Medicine
Office of New Drugs
Center for Drug Evaluation and Research

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/

CHARLES J GANLEY
08/29/2023 03:31:22 PM