CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761310Orig1s000

Trade Name:	ELAHERE
Generic or Proper Name:	mirvetuximab soravtansine-gynx
Sponsor:	ImmunoGen, Inc.
Approval Date:	November 14, 2022
Indication:	For the treatment of adult patients with FRα positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

BLA 761310

BLA ACCELERATED APPROVAL

ImmunoGen, Inc.
Attention: Jennifer Eaddy
Executive Director, Regulatory Affairs
830 Winter Street
Waltham, MA 02451

Dear Ms. Eaddy:

Please refer to your biologics license application (BLA) dated March 28, 2022, received March 28, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for IMGN853 (mirvetuximab soravtansine-gynx) 5 mg/mL intravenous injection.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2288 to ImmunoGen, Inc., Waltham, MA, 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 Elahere (mirvetuximab soravtansine-gynx). Elahere is indicated for the treatment of adult patients with folate-α (FRα)-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture mirvetuximab antibody intermediate at (b) (4) and mirvetuximab soravtansine drug substance at (b) (4) The DM4 payload will be manufactured at (b) (4) The Sulfo-SPDB linker will be manufactured at (b) (4) The final formulated product will be manufactured and filled at (b) (4) and labeled and packaged at (b) (4)

[redacted] You may label your product with proprietary name, Elahere, and will market it in a 100 mg/20 mL single-dose vial.

DATING PERIOD

The dating period for Elahere shall be 60 months from the date of manufacture when stored at 5±3 °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 mirvetuximab soravtansine drug substance shall be [redacted] months from the date of manufacture when stored at [redacted] °C. The dating period for your mirvetuximab antibody intermediate shall be [redacted] months from the date of manufacture when stored at [redacted] °C.

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

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Elahere 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 Elahere 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 the provisions of accelerated approval regulations (21 CFR 601.41), effective on the date of this letter, for use as recommended in the enclosed agreed-upon approved labeling. This BLA provides for the use of Elahere for the treatment of adult patients with folate-α (FRα)-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have received one to three prior systemic treatment regimens.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval 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 (Prescribing Information and Medication Guide). 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 carton and container labeling submitted on October 20, 2022, 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 761310**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Elahere 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

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated October 18, 2022. This requirement, along with required completion dates, is listed below.

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[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.

4347-1 Conduct the clinical trial IMGN853-0416 (MIRASOL) titled "A randomized, open-label, Phase 3 study of Mirvetuximab soravtansine vs. Investigator's choice chemotherapy in platinum-resistant, advanced, high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor-alpha expression" and provide the final progression-free survival (PFS), overall response rate (ORR), and overall survival (OS) analyses to obtain data on the clinical efficacy of mirvetuximab soravtansine for patients with platinum-resistant ovarian cancer.

Interim Report Submission:	09/2023
Trial Completion:	06/2024
Final Report Submission:	12/2024

The interim report should contain the final PFS analysis and the interim OS analysis. Include the final OS results in the final report submission.

Submit clinical protocols to your IND 111915 for this product. In addition, under 21 CFR 601.70 you should include a status summary of each requirement in your annual report 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 entered into each study/trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, 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.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable as this indication does not occur in children.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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 assess known serious risks of ocular adverse events, peripheral neuropathy, and other serious adverse events; and to assess a signal of a serious risk of mirvetuximab soravtansine-related toxicity in patients with moderate hepatic impairment.

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 these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risks and assess the signal of a serious risk.

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

4347-2 Conduct a randomized clinical trial of at least 2 dose schedules of mirvetuximab soravtansine to characterize the safety of the recommended dosage of 6 mg/kg AIBW Q3W and alternative dosing schedule(s) (i.e., modified weekly dosing regimen, where lower doses are administered at a weekly frequency, instead of every 3 weeks) for the treatment of adult patients with FRα-positive, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received one to three prior systemic treatment regimens. The trial should evaluate safety parameters including ocular AEs (all grade, Grade ≥2), peripheral neuropathy, (all grade, Grade ≥2), and other adverse events of interest. The trial should evaluate efficacy parameters of the alternate dosing schedules. The trial should also include sufficient clinical pharmacokinetic sampling to analyze the exposure-response relationship for efficacy and safety.

The timetable you submitted on October 18, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	04/2023
Final Protocol Submission:	07/2023
Trial Completion:	08/2026
Final Report Submission:	02/2027

Submit the datasets with the final report submission.

4347-3 Conduct an open-label, non-randomized, dose escalation trial, with expansion in a sufficient number of patients, to determine an appropriate starting dose of mirvetuximab soravtansine in patients with moderate hepatic impairment, according to National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria, in the target patient population. Collect safety and pharmacokinetic information for

mirvetuximab soravtansine, unconjugated DM4, and s-methyl DM4 from the trial and utilize this information to determine the appropriate starting dose of mirvetuximab soravtansine for this population.

The timetable you submitted on October 18, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	04/2023
Final Protocol Submission:	07/2023
Trial Completion:	08/2026
Final Report Submission:	02/2027

Submit the datasets with the final report submission.

4347-4 Conduct a clinical trial, or amend existing clinical trials, of mirvetuximab soravtansine to incorporate prospectively specified, scheduled ophthalmologic assessments in all patients (symptomatic or asymptomatic) to further characterize the incidence and severity of mirvetuximab soravtansine-related ocular adverse events and evaluate the additional risk mitigation strategies for ocular adverse events.

The timetable you submitted on October 18, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	02/2023
Final Protocol Submission:	05/2023
Study Completion:	08/2025
Final Report Submission:	02/2026

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 clinical protocol(s) to your IND 111915 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

[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.

undertaken to investigate a safety issue. Section 506B 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 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:

4347-5 Conduct an integrated analysis containing data from clinical trials and other data sources such as post-marketing reports, real-world evidence and other sources to further characterize the safety and efficacy of mirvetuximab soravtansine in patients from racial and ethnic minority groups. The analyses should support comparative safety and efficacy outcome analyses between the aforementioned populations and White patients.

The timetable you submitted on October 18, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission (Analysis Plan):	02/2023
Final Protocol Submission (Analysis Plan):	05/2023
Interim Report Submission:	12/2024
Study Completion:	05/2028
Final Report Submission:	11/2028

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.

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

We remind you of your postmarketing commitments:

4347-6 To provide results for the stability indicating product quality attributes of the IMGN853 DP shipped during the summer and winter months from the (b) (4) manufacturing site to the end-users. Submit the final study report

containing data for the product quality attributes and shipping container temperatures (internal, external) from the drug product shipping studies performed per the performance qualification protocols to BLA 761310 to qualify the commercial shipping process of mirvetuximab soravtansine DP.

The timetable you submitted on September 6, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2023

4347-7 To validate a gravimetric method to test the mirvetuximab soravtansine drug product (DP) gross content/vial. Submit the final study report containing the description of the method and the results to support that the gravimetric method is suitable to test the DP gross content/vial.

The timetable you submitted on September 23, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2023

4347-8 To repeat the endotoxin method verification for in-process samples of drug substance (DS) intermediate with one additional batch of product verifying the lysate sensitivity in quadruplicates as per USP <85> and update Section S.2.4 of the DS intermediate.

The timetable you submitted on October 11, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2023

4347-9 To conduct a study to identify where (b) (4) occurs in the DS manufacturing process and to implement an additional (b) (4) specification (b) (4)

The timetable you submitted on September 16, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2023

4347-10 To develop a method capable of reliably detecting endotoxin levels for release testing of DS and DP, to perform method qualification with three batches of product and to implement the new endotoxin detection method.

The timetable you submitted on September 16, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2023

4347-11 To provide the shipping validation report of the drug substance intermediate [redacted] (b) (4)

The timetable you submitted on September 16, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

4347-12 To submit [redacted] (b) (4) sterilization validation report demonstrating sterility assurance [redacted] (b) (4)

The timetable you submitted on October 4, 2022, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2023

Submit clinical protocols to your IND 111915 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 MATERIAL

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*.[4]

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:

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

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

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 Alice Lee, Senior Regulatory Project Manager, at (301) 796-8881 or at Alice.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Office Director
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- 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/

RICHARD PAZDUR
11/14/2022 01:41:38 PM