# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

# 761416Orig1s000

| | |
|---|---|
| ***Trade Name:*** | Ziihera injection |
| ***Generic or Proper Name:*** | zanidatamab-hrii |
| ***Sponsor:*** | Jazz Pharmaceuticals Ireland, Limited |
| ***Approval Date:*** | November 20, 2024 |
| ***Indication:*** | For the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC3+) biliary tract cancer as detected by an FDA approved test. |

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# 761416Orig1s000

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761416Orig1s000

# APPROVAL LETTER

U.S. FOOD & DRUG ADMINISTRATION

BLA 761416

**BLA ACCELERATED APPROVAL**

Jazz Pharmaceuticals Ireland, Limited
Attention: Nina Moore, M.S.
Associate Director, Regulatory Affairs
c/o Jazz Pharmaceuticals, Inc.
3170 Porter Drive
Palo Alto, CA 94304

Dear Nina Moore:

Please refer to your March 29, 2024, biologics license application (BLA), submitted under section 351(a) of the Public Health Service Act for Ziihera (zanidatamab-hrii) injection.

## LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2167 to Jazz Pharmaceuticals Ireland Limited, Dublin, Ireland, 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 Ziihera (zanidatamab-hrii). Ziihera is indicated for the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC3+) biliary tract cancer as detected by an FDA approved test.

## MANUFACTURING LOCATIONS

Under the license, you are approved to manufacture zanidatamab-hrii at (b) (4) The final formulated product will be labeled and packaged at (b) (4) You may label your product with the proprietary name, Ziihera, and will market it in a 300 mg of lyophilized powder in a single-dose vial.

## DATING PERIOD

The dating period for Ziihera shall be 24 months from the date of manufacture when stored at 2-8°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 (b) (4) months from the date of manufacture when stored at (b) (4) °C.

We have approved the stability protocol 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 Ziihera 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 Ziihera, 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. This BLA provides for the use of Ziihera for the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC3+) biliary tract cancer as detected by an FDA approved test.

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 and Patient Package Insert. 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.

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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.

## CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to carton and container labeling submitted on November 7, 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 (February 2020, Revision 7)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761416**." Approval of this submission by FDA is not required before the labeling is used.

## ADVISORY COMMITTEE

Your application for Ziihera was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

## ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 601.41, you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If required postmarketing clinical trials fail to verify clinical benefit or are 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 November 19, 2024. This requirement is listed below.

4732-1 Complete the ongoing randomized clinical trial, Study JZP598-302, entitled, "An Open-Label Randomized Trial of the Efficacy and Safety of Zanidatamab with Standard-of-Care Therapy Against Standard-of-Care Therapy Alone for Advanced HER2-Positive Biliary Tract Cancer", intended to verify and describe the clinical benefit of zanidatamab for patients with HER2-positive (IHC3+), unresectable or metastatic biliary tract cancer. The trial should compare zanidatamab in combination with the standard of care in patients with HER2-positive (IHC3+), unresectable or metastatic biliary tract cancer.

The timetable you submitted on November 19, 2024, states that you will conduct this trial according to the following schedule:

| | |
|---|---|
| Trial Completion: | 03/2029 |
| Final Report Submission: | 09/2029 |

Submit clinical protocols to your IND 142519 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[3].

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.[4]

180-day reports must be clearly designated "**BLA 761416 180-Day AA PMR Progress Report**."

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)**."

[3] 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.
[4] 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.

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

4732-2 Conduct an integrated analysis of clinical trial data to allow for further characterization of the clinical effects of zanidatamab, including pharmacokinetics (PK), efficacy and safety in the underrepresented racial and ethnic minority populations. These clinical data, which may come from other ongoing trials with zanidatamab, should report an evaluation of comparative efficacy and safety between the aforementioned population and the population primarily represented in your trial.

The timetable you submitted on November 19, 2024, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Trial Completion: | 03/2029 |
| Final Report Submission: | 09/2029 |

4732-3 Conduct an assessment of binding and neutralizing anti-zanidatamab antibody responses to evaluate the incidence of anti-drug antibodies (ADAs). Reanalyze the biliary tract cancer (BTC) samples from Study ZWI-ZW25-101 and all samples from Study ZWI-ZW25-203 using a validated assay capable of sensitively detecting ADA responses in the presence of zanidatamab levels that are expected to be present in the serum at the time of patient sampling. Reevaluate the immunogenicity of zanidatamab and the effect of ADAs on efficacy, pharmacokinetics (PKs), and safety of zanidatamab. Include the level of zanidatamab in each patient's test sample at each sampling point in the final report.

The timetable you submitted on November 19, 2024, states that you will conduct this study according to the following schedule:

| | |
|---|---|
| Draft Protocol Submission: | 06/2025 |
| Final Protocol Submission: | 09/2025 |
| Study Completion: | 03/2026 |
| Final Report Submission: | 09/2026 |

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

We remind you of your postmarketing commitments:

4732-4 To implement a two-tiered reference standard (RS) system consisting of primary and working RS (PRS and WRS), prior to the depletion of the current RS, through the submission of a prior approval supplement (PAS) per 21 CFR 601.12. Protocols including qualification of future PRS and WRS and requalification of PRS and WRS, should be included in the PAS.

The timetable you submitted on October 25, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 01/2025

4732-5 To update the drug substance and drug product release and stability specifications for zanidatamab to include a validated C1q binding ELISA method with justified quantitative acceptance criteria, as a surrogate method to control the complement dependent cytotoxicity (CDC) activity. The updated specifications, method validation data, and other supporting information will be submitted to the BLA as a PAS per 21 CFR 601.12.

The timetable you submitted on October 25, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2026

4732-6 To develop, validate, and implement a test method for control of (b) (4) with justified quantitative acceptance criteria in the drug substance release specification for zanidatamab. The updated specification, method validation report, and any other supporting information will be submitted to the BLA as a PAS per 21 CFR 601.12.

The timetable you submitted on October 25, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2026

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 142519 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*.[5]

## 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:

[5] 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 Rebecca Cohen, Regulatory Health Project Manager, at (240) 402-4998.

Sincerely,

{See appended electronic signature page}

Paul Kluetz, M.D.
Supervisory Associate Director for Solid Tumor Oncology (Acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

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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.**

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/s/

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PAUL G KLUETZ
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