CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761416Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761416
PDUFA Goal Date	November 29, 2024
Nexus TTT #	2024-8916, 2024-8917
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP
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Deputy Division Director	Laura Zendel, Pharm.D.
Review Completion Date	November 21, 2024
Subject	Evaluation of Need for a REMS
Established Name	zanidatamab-hrii
Trade Name	Ziihera
Name of Applicant	Jazz Pharmaceuticals Ireland Limited
Therapeutic Class	bispecific HER2-directed antibody
Formulation(s)	300 mg vial
Dosing Regimen	zanidatamab-hrii 20 mg/kg intravenous infusion once every 2 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Ziihera (zanidatamab-hrii) is necessary to ensure the benefits outweigh its risks. Jazz Pharmaceuticals Ireland Limited submitted a Biologic Licensing Application (BLA) 761416 for zanidatamab-hrii with the proposed indication for the treatment of adults with previously treated, unresectable locally advanced or metastatic HER2-positive biliary tract cancer (BTC), as detected by an FDA-approved test. The FDA approved indication is for the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) BTC, as detected by an FDA-approved test. The serious risks associated with zanidatamab-hrii include embryo-fetal toxicity, left ventricular dysfunction, infusion-related reactions, and diarrhea. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and Division of Oncology 3 (D03) agree that a REMS is not necessary to ensure the benefits of zanidatamab-hrii outweigh its risks. The efficacy of zanidatamab-hrii was supported by the HERIZON-BTC-01 study cohort 1, in which the zanidatamab-hrii group had an objective response rate (ORR) of 52%. DO3 recommends accelerated approval based on the currently available data. The serious risk associated with zanidatamab-hrii of embryo-fetal toxicity will be communicated in a boxed warning and in the warnings and precautions section of the label. The other serious risks including left ventricular dysfunction, infusion-related reactions, and diarrhea will be communicated in the warnings and precautions section of the label. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with zanidatamab-hrii.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Ziihera (zanidatamab-hrii) is necessary to ensure the benefits outweigh its risks. Jazz Pharmaceuticals Ireland Limited submitted a Biologic Licensing Application (BLA) 761416 for zanidatamab-hrii with the proposed indication for the treatment of adults with previously treated, unresectable locally advanced or metastatic HER2-positive biliary tract cancer (BTC), as detected by an FDA-approved test.[1] This application was approved by the Division of Oncology 3 (D03) on November 20, 2024. The applicant did not submit a proposed REMS or risk management plan.

2. Background

2.1. Product Information

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

Ziihera (zanidatamab-hrii), a NME, is proposed for the treatment of adults with previously treated, unresectable locally advanced or metastatic HER2-positive BTC, as detected by an FDA-approved test. Zanidatamab-hrii is a bispecific HER2-directed antibody that binds to two extracellular sites on HER2. It induces complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP). Zanidatamab-hrii is supplied as a 300 mg lyophilized powder in a single-dose vial. The approved dosing regimen is zanidatamab-hrii 20 mg/kg intravenous infusion once every 2 weeks until disease progression or unacceptable toxicity.[b] Zanidatamab-hrii was approved by the FDA on November 20, 2024. Zanidatamab-hrii was designated as an orphan product, received fast track designation, and breakthrough therapy. The indication was approved under accelerated approval based on overall response rate and duration of response.

2.2. Regulatory History

The following is a summary of the regulatory history for zanidatamab-hrii BLA 761416 relevant to this review:

- 12/12/2019: Fast track designation granted
- 12/18/2019: Orphan drug designation granted
- 11/27/2020: Breakthrough therapy designation granted
- 03/29/2024: BLA 761416 submission for the treatment of adults with previously treated, unresectable locally advanced or metastatic HER2-positive BTC, as detected by an FDA-approved test received
- 07/22/2024: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for zanidatamab-hrii
- 11/20/2024: FDA approved zanidatamab-hrii, BLA 761416, for the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) BTC, as detected by an FDA-approved test.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Biliary tract cancers are predominately adenocarcinomas which include intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder carcinoma.[2,3,4] Risk factors for

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

cholangiocarcinoma include primary sclerosing cholangitis, hepatolithiasis, choledochal cysts, and liver fluke infections.[4] Risk factors for gallbladder cancer include cholelithiasis, calcification of the gallbladder wall, anomalous pancreaticobiliary duct junction, gallbladder polyps (>1 cm), chronic typhoid infection, primary sclerosing cholangitis, and inflammatory bowel disease. The estimated annual incidence of cholangiocarcinoma in the United States is 0.35 to 2 cases per 100,000.[2] In addition, the estimated annual incidence of gallbladder carcinoma in the United States is 1.5 cases per 100,000. The median age at diagnosis of gallbladder cancer in the US is 67 years with female predominance. Human epidermal growth factor receptor 2 (*HER2*) is estimated to be overexpressed or amplified in 15% to 24% of gallbladder cancer, 8% to 13% of extrahepatic cholangiocarcinoma, and 3% to 4.5% of intrahepatic cholangiocarcinoma.[2,5,c] The median overall survival in patients with BTC who had disease progression after systemic therapy is approximately 6 months.[2,6,d]

3.2. Description of Current Treatment Options

There are no therapies approved by the FDA for HER2-amplified or HER2-expressing BTC.[2] Current guidelines from the National Comprehensive Cancer Network (NCCN) for Biliary Tract Cancers list durvalumab + gemcitabine + cisplatin and pembrolizumab + gemcitabine + cisplatin in the "Preferred Regimens" section for systemic therapy for primary treatment for unresectable and metastatic disease.[4] The regimen FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) is listed in the "Preferred Regimens" section for systemic therapy for subsequent-line therapy for BTC if disease progression. In the "Useful in Certain Circumstances" section for subsequent-line therapy for BTC if disease progression for HER2-positive tumors, the NCCN guidelines recommend fam-trastuzumab deruxtecan-nxki (immunohistochemistry (IHC) 3+), trastuzumab + pertuzumab, and tucatinib + trastuzumab.

Enhertu (fam-trastuzumab deruxtecan-nxki), a HER2-directed antibody and topoisomerase inhibitor conjugate, was approved by the FDA for indications including adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.[7] This indication was approved under accelerated approval based on objective response rate and duration of response. Labeling includes a boxed warning for interstitial lung disease and embryo-fetal toxicity. The other serious risks associated with fam-trastuzumab deruxtecan-nxki in the warnings and precautions section of the label include neutropenia and left ventricular dysfunction. Fam-trastuzumab deruxtecan-nxki was approved in 2019. It did not require a REMS for approval.

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[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Please refer to D03 multi-disciplinary review and evaluation for zanidatamab-hrii for a detailed clinical review on treatment armamentarium relevant to the proposed indication.

4. Benefit Assessment

The pivotal trial HERIZON-BTC-01 (NCT 04466891) supporting this application for efficacy and safety consisted of a Phase 2 open-label, multicenter, single arm trial which evaluated zanidatamab-hrii in patients with locally advanced unresectable or metastatic BTC and disease progression after prior therapy with at least one prior gemcitabine-based chemotherapy regimen for advanced disease.[1,2] HERIZON-BTC-01 cohort 1 assessed patients with HER2 amplification by in situ hybridization (ISH) and HER2 overexpression by IHC (2 or 3+). In the HERIZON-BTC-01 study cohort 1, there was 62 patients with HER2-positive (IHC 3+ by central assessment) BTC. Patients received zanidatamab-hrii 20 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) as determined by an independent central review (ICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The zanidatamab-hrii treatment group had an ORR of 52% (95% CI 39% to 65%). A secondary endpoint included duration of response (DOR). The median DOR was 14.9 months in the zanidatamab-hrii group (95% CI 7.4 to not estimable). The clinical reviewer concluded that study HERIZON-BTC-01 demonstrated a clinically meaningful and durable ORR in patients with previously treated, locally advanced or metastatic BTC with HER2 ISH-amplified IHC3+ tumors.[e] (b) (4)

5. Risk Assessment & Safe-Use Conditions

The safety of zanidatamab-hrii was evaluated in a Phase 2 clinical trial HERIZON-BTC-01.[1,2,f] In the safety population, 80 patients received zanidatamab-hrii in HERIZON-BTC-01 cohort 1. However, the safety population for the serious risks described in labeling reflects exposure to zanidatamab-hrii 20 mg/kg intravenously as a single agent in 233 patients from studies HERIZON-BTC-01 and ZWI-ZW25-101 (NCT 02892123)[g], 109 patients with BTC and 124 patients with other cancers. Discontinuation due to an

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[g] ZWI-ZW25-101 was a supportive Phase 1 study in patients with locally advanced (unresectable) and/or metastatic HER2-expressing cancers.

adverse reaction occurred in 2.5% of the zanidatamab-hrii group. Common adverse reactions reported with zanidatamab-hrii included diarrhea, infusion-related reaction, abdominal pain, and fatigue.

Two deaths due to an adverse event within 30 days of the last dose of zanidatamab-hrii were reported in HERIZON-BTC-01 cohort 1.[8] The causes of death due to an adverse event included cholangiocarcinoma and hepatic failure.

The serious risks[h] associated with zanidatamab-hrii which include embryo-fetal toxicity, left ventricular dysfunction, infusion-related reactions, and diarrhea are summarized in the sections below.

5.1. Embryo-Fetal Toxicity

Zanidatamab-hrii can cause fetal harm based on the mechanism of action of the drug. No clinical data is available with zanidatamab-hrii in pregnancy in humans. However, oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death has been reported with HER2-directed antibodies during pregnancy in literature reports. The risk of embryo-fetal toxicity is included in a boxed warning, the warnings and precautions section of the label, and patient information. The label states to advise pregnant women and females of reproductive potential that exposure to zanidatamab-hrii during pregnancy or within 4 months prior to conception can result in fetal harm. The label recommends in females of reproductive potential to verify pregnancy status before starting zanidatamab-hrii and that effective contraception be used during treatment and for 4 months after the last dose.

5.2. Left Ventricular Dysfunction

Zanidatamab-hrii can cause decreases in left ventricular ejection fraction (LVEF). An adverse reaction of LVEF decline by greater than 10% and decrease to less than 50% occurred in 4.3% of patients receiving zanidatamab-hrii. The label states the safety of zanidatamab-hrii has not been established in patients with a baseline ejection fraction below 50%. The label recommends to assess LVEF prior to initiation of zanidatamab-hrii and at regular intervals during treatment and to withhold the dose or permanently discontinue zanidatamab-hrii based on severity of adverse reactions. This risk will be communicated in the warnings and precautions section of the label.

5.3. Infusion-Related Reactions

Zanidatamab-hrii can cause infusion-related reactions. An adverse reaction of infusion-related reactions occurred in 31% of patients receiving zanidatamab-hrii, with Grade 2 infusion-related reactions reported in 25% of patients and Grade 3 infusion-related reactions reported in 0.4% of patients. Infusion-related

[h] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

reactions occurred on the first day of dosing in 28% of patients; 97% of infusion-related reactions resolved within one day. The label recommends prior to each dose of zanidatamab-hrii, administer premedications to prevent potential infusion-related reactions. Recommended premedications (acetaminophen, an antihistamine (such as diphenhydramine) and a corticosteroid (such as hydrocortisone) are addressed in section 2 of the label.

The label states to monitor patients for signs and symptoms of infusion-related reactions during zanidatamab-hrii administration and as clinically indicated after completion of infusion. It also states to have medications and emergency equipment to treat infusion-related reactions available for immediate use. The label recommends if an infusion-related reactions occurs, slow, or stop the infusion and administer appropriate medical management and to monitor patients until complete resolution of signs and symptoms before resuming. It recommends to permanently discontinue zanidatamab-hrii in patients with recurrent severe or life-threatening infusion-related reactions. Recommendations for dosage modifications of infusion-related reactions are addressed in section 2 of the label. This risk will be communicated in the warnings and precautions and dosage and administration sections of the label.

5.4. Diarrhea

An adverse reaction of diarrhea occurred in 48% of patients receiving zanidatamab-hrii, with Grade 2 diarrhea reported in 17% of patients and Grade 3 diarrhea reported in 6% of patients. The label recommends if diarrhea occurs to administer antidiarrheal treatment as clinically indicated. It recommends to perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. It also recommends to withhold or permanently discontinue zanidatamab-hrii based on severity. This risk will be communicated in the warnings and precautions section of the label.

6. Expected Postmarket Use

Zanidatamab-hrii will primarily be used in both inpatient and outpatient (such as infusion centers) settings. The likely prescribers will be oncologists who are trained in managing toxicities related to cancer treatment.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for zanidatamab-hrii beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of zanidatamab-hrii on the basis of the efficacy and safety information currently available. At the time of documentation of this review, zanidatamab-hrii was approved on November 20, 2024. The indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. Zanidatamab-hrii is a bispecific HER2-directed antibody and is a treatment option in adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) BTC, as detected by an FDA-approved test. The efficacy of zanidatamab-hrii was supported by the HERIZON-BTC-01 study cohort 1, in which the zanidatamab-hrii group had an ORR of 52%. The serious risk associated with zanidatamab-hrii of embryo-fetal toxicity will be communicated in a boxed warning and in the warnings and precautions section of the label. The other serious risks including left ventricular dysfunction, infusion-related reactions, and diarrhea will be communicated in the warnings and precautions section of the label. The clinical reviewer stated the safety profile for zanidatamab-hrii is consistent with the class of HER2 targeted therapies.

Biliary tract cancers are predominately adenocarcinomas which include intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, and gallbladder carcinoma. The estimated annual incidence of cholangiocarcinoma in the United States is 0.35 to 2 cases per 100,000. The estimated annual incidence of gallbladder carcinoma in the United States is 1.5 cases per 100,000. In addition, *HER2* is estimated to be overexpressed or amplified in 15% to 24% of gallbladder cancer, 8% to 13% of extrahepatic cholangiocarcinoma, and 3% to 4.5% of intrahepatic cholangiocarcinoma. The median overall survival in patients with BTC who had disease progression after systemic therapy is approximately 6 months. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with zanidatamab-hrii. Based on the efficacy and risks associated with zanidatamab-hrii for the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) BTC, as detected by an FDA-approved test, the DRM and DO3 agree that a REMS is not necessary to ensure that the benefits outweigh the risks as the risk can be adequately communicated in labeling.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for zanidatamab-hrii to ensure the benefits outweigh the risks.

10. Appendices

10.1. References

[1] Proposed prescribing information for zanidatamab-hrii as currently edited by FDA, last accessed November 6, 2024.

[2] Zanidatamab BLA 761416 multi-disciplinary review and evaluation, last accessed November 6, 2024.

[3] Valle JW, Kelley RK, Nervi B, Oh DY, Zhu AX. Biliary tract cancer. *Lancet*. 2021;397(10272):428-444.

[4] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Biliary Tract Cancers (version 4.2024 – August 29, 2024). https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf (accessed 2024 October 31).

[5] Lee CK, Chon HJ, Cheon J, et al. Trastuzumab plus FOLFOX for HER2-positive biliary tract cancer refractory to gemcitabine and cisplatin: a multi-institutional phase 2 trial of the Korean Cancer Study Group (KCSG HB19-14). *Lancet Gastroenterol Hepatol*. 2023;8(1):56-65.

[6] Lamarca A, Palmer DH, Wasan HS, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. *Lancet Oncol*. 2021;22(5):690-701.

[7] Enhertu (fam-trastuzumab deruxtecan-nxki) package insert. Basking Ridge, NJ: Daiichi Sankyo, Inc.; 2024 April.

[8] Kumar V, Casak S, Mushti S, Song C. Division of Oncology 3 (DO3). Zanidatamab. Mid-Cycle Meeting, clinical and statistics reviewer slides. July 2, 2024.

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