Jazz Pharmaceuticals Announces U.S. FDA Approval of Ziihera® (zanidatamab-hrii) for the Treatment of Adults with Previously Treated, Unresectable or Metastatic HER2-positive (IHC 3+) Biliary Tract Cancer (BTC)

November 20, 2024

Ziihera is the first and only dual HER2-targeted bispecific antibody approved for HER2+ BTC in the U.S.

Ziihera received accelerated approval based on results including a 52% objective response rate and median duration of response of 14.9 months as determined by independent central review (ICR) from the HERIZON-BTC-01 clinical trial

Company to host investor webcast on Dec. 11, 2024

For U.S. media and investors only

DUBLIN, Nov. 20, 2024 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced the U.S. Food and Drug Administration (FDA) accelerated approval of Ziihera® (zanidatamab-hrii) 50mg/mL for injection for intravenous use for the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), as detected by an FDA-approved test.[1] *Ziihera* was approved under accelerated approval based on a 52% objective response rate (ORR) and a median duration of response (DOR) of 14.9 months as determined by independent central review (ICR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.[1] The Phase 3 HERIZON-BTC-302 confirmatory trial is ongoing to evaluate zanidatamab in combination with standard-of-care therapy versus standard-of-care therapy alone in the first-line setting for patients with HER2-positive BTC.



"BTC is a devastating disease with a poor prognosis and five-year survival rates under five percent in the metastatic setting. Patients with unresectable or metastatic HER2-positive BTC have had a high unmet need with limited treatment options and few approved therapies," said Rob Iannone, M.D., M.S.C.E., executive vice president, global head of research and development, and chief medical officer of Jazz Pharmaceuticals. "The approval of *Ziihera,* which previously received Breakthrough Therapy Designation from the FDA for this indication, is an important advance and offers the first and only dual HER2-targeted bispecific antibody and chemotherapy-free treatment for patients living with BTC. We look forward to advancing research of zanidatamab in BTC and other HER2-expressing solid tumors, with the goal of improving outcomes for more people diagnosed with these difficult-to-treat HER2-positive cancers."

The FDA approval of *Ziihera* is based on compelling data from the HERIZON-BTC-01 trial, which included the evaluation of zanidatamab as a single agent in previously treated HER2-positive (as determined by Roche Diagnostic's PATHWAY® anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody companion diagnostic) BTC and is the largest Phase 2b clinical trial to date specifically for this patient population. The trial achieved its primary endpoint of confirmed objective response rate (cORR) by independent central review (ICR) and results were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2023, published in *The Lancet Oncology,* and included in the 2023 Best of ASCO® program. Longer follow-up data showing improvement upon previously reported DOR were reported at the ASCO Annual Meeting 2024.[1]

"As a clinical investigator and medical oncologist focused on advancing the care of patients with biliary tract and liver cancers, I have experienced firsthand the significant unmet need for effective therapies for patients with these diseases," said Dr. James Harding, associate attending, Gastrointestinal Oncology and Early Drug Development Services, at Memorial Sloan Kettering Cancer Center. "Zanidatamab has demonstrated antitumor activity and is now a new option for patients with HER2-positive biliary tract cancer. I look forward to continued and successful drug development for patients with biliary tract cancer."

"Metastatic biliary tract cancer, BTC, places a significant burden on patients, affecting their quality of life and their emotional and mental well-being, as well as that of their families," said Stacie Lindsey, CEO and founder of the Cholangiocarcinoma Foundation. "The approval of *Ziihera* offers a promising treatment option. It provides patients and their loved ones the possibility of more time together and an improved quality of life, which is invaluable for the entire BTC community."

The efficacy of *Ziihera* was evaluated in 62 patients with HER2-positive (IHC 3+ by central assessment) BTC in Cohort 1 of HERIZON-BTC-01, with major efficacy outcome measures of ORR and DOR as determined by ICR according to RECIST (Response Evaluation Criteria in Solid Tumors) v1.1.[1] The study demonstrated an ORR of 52% [95% confidence interval (CI): 39, 65)] with a Kaplan Meier (KM) estimated median DOR of 14.9 months [95% CI: 7.4-not estimable] by ICR.[1]

Boxed Warning for Embryo-fetal toxicity: Exposure to *Ziihera* during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception.[1]

The safety profile for *Ziihera* has been demonstrated in 80 patients in the HERIZON-BTC-01 trial. Serious adverse reactions occurred in 53% of patients who received *Ziihera*. The most common adverse reactions in patients who received *Ziihera* (≥ 20%) were diarrhea, infusion-related reaction, abdominal pain, and fatigue. Serious adverse reactions in > 2% of patients included biliary obstruction (15%), biliary tract infection (8%), sepsis (8%), pneumonia (5%), diarrhea (3.8%), gastric obstruction (3.8%), and fatigue (2.5%). A fatal adverse reaction of hepatic failure occurred in one patient who received *Ziihera*. Permanent discontinuation due to an adverse reaction occurred in 2.5% of patients who received *Ziihera.*[1] See additional safety information below and full prescribing information https://pp.jazzpharma.com/pi/ziihera.en.USPI.pdf.

The confirmatory, global, randomized Phase 3 trial HERIZON-BTC-302 (NCT06282575) is ongoing and is evaluating zanidatamab in combination with standard-of-care therapy versus standard-of-care therapy alone in the first-line setting for patients with HER2-positive BTC. Continued approval for *Ziihera* may be contingent upon verification and description of clinical benefit in this confirmatory trial.

Zanidatamab is also being investigated in a number of additional tumor types, including Phase 3 trials in gastroesophageal adenocarcinomas (GEAs) and metastatic breast cancer (mBC). The HERIZON-GEA-01 trial evaluating the potential of zanidatamab plus chemotherapy with or without tislelizumab as first-line treatment for patients with advanced/metastatic HER2-positive GEAs. The EmpowHER-303 trial is evaluating the potential of zanidatamab in combination with physician's choice chemotherapy for the treatment of HER2-positive mBC for patients who have progressed on, or are intolerant to, previous trastuzumab deruxtecan treatment.

About the Phase 2b HERIZON-BTC-01 Trial
The Phase 2b HERIZON-BTC-01 trial of zanidatamab was an open-label, global Phase 2b study, which enrolled 87 patients with HER2-amplified, locally advanced unresectable or metastatic BTC (gallbladder cancer, intra-/extra-hepatic cholangiocarcinoma) into 2 cohorts and included 62 patients with HER2 IHC 3+ BTC. The trial evaluated zanidatamab (20 mg/kg IV every 2 weeks) in patients who had received prior gemcitabine-containing therapy. Patients with prior HER2-targeted therapy use were excluded from the trial. All patients were required to have HER2 status confirmed with tissue samples by a central lab. Patients (n=87) were assigned into two cohorts based on tumor IHC status: Cohort 1 (n=80) included patients who were IHC 2+/3+ (HER2-amplified) and Cohort 2 (n=7) included patients who were IHC 0/1+. Tumors were assessed every 8 weeks per RECIST v1.1. The primary endpoint was ORR by independent central review (ICR) in Cohort 1, with secondary endpoints including other efficacy and safety outcomes.

Investor Webcast on Wednesday, December 11, 2024
The company will host a webcast on Wednesday, December 11, 2024, at 4:30 p.m. ET / 9:30 p.m. GMT to provide investors an overview of clinical data, patient need and commercialization strategy for *Ziihera*. The webcast will include commentary from a leading BTC expert and the company's senior management.

Audio webcast/conference call:
U.S. Dial-In Number: +1 800 715 9871
Ireland Dial-In Number: +353 1800 943 926
Additional global dial-in numbers are available here.
Passcode: 4898380

A live webcast of the presentation may be accessed from the Investors section of the Jazz Pharmaceuticals website at www.jazzpharmaceuticals.com. Please connect to the website prior to the start of the presentation to ensure adequate time for any software downloads that may be necessary to listen to the webcast. An archive of the webcast will be available for at least one week following the presentation on the Investors section of the company's website at www.jazzpharmaceuticals.com.

More information about *Ziihera*, the Full Prescribing Information, including Boxed Warning and Patient Information, is available **here**.

About Ziihera® (zanidatamab-hrii)
Ziihera (zanidatamab-hrii) is a bispecific HER2-directed antibody that binds to two extracellular sites on HER2. Binding of zanidatamab-hrii with HER2 results in internalization leading to a reduction of the receptor on the tumor cell surface. Zanidatamab-hrii induces complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). These mechanisms result in tumor growth inhibition and cell death in vitro and in vivo.[1] In the United States, *Ziihera* is indicated for the treatment of adults with previously treated, unresectable or metastatic HER2-positive (IHC 3+) biliary tract cancer (BTC), as detected by an FDA-approved test.[1] The U.S. Food and Drug Administration (FDA) granted accelerated approval for this indication 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(s).[1]

Zanidatamab is not approved anywhere else in the world.

Zanidatamab is being developed in multiple clinical trials as a targeted treatment option for patients with solid tumors that express HER2. Zanidatamab is being developed by Jazz and BeiGene, Ltd. (BeiGene) under license agreements from Zymeworks, which first developed the molecule.

The FDA granted Breakthrough Therapy designation for zanidatamab development in patients with previously treated HER2 gene-amplified BTC, and two Fast Track designations for zanidatamab: one as a single agent for refractory BTC and one in combination with standard-of-care chemotherapy for

1L gastroesophageal adenocarcinoma (GEA). Additionally, zanidatamab has received Orphan Drug designations from FDA for the treatment of BTC and GEA, as well as Orphan Drug designation from the European Medicines Agency for the treatment of BTC and gastric cancer.

Important Safety Information

WARNING: EMBRYO-FETAL TOXICITY
Exposure to ZIIHERA during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception.

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity
ZIIHERA can cause fetal harm when administered to a pregnant woman. In literature reports, use of a HER2-directed antibody during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

Verify the pregnancy status of females of reproductive potential prior to the initiation of ZIIHERA. Advise pregnant women and females of reproductive potential that exposure to ZIIHERA during pregnancy or within 4 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception during treatment with ZIIHERA and for 4 months following the last dose of ZIIHERA.

Left Ventricular Dysfunction

ZIIHERA can cause decreases in left ventricular ejection fraction (LVEF). LVEF declined by >10% and decreased to <50% in 4.3% of 233 patients. Left ventricular dysfunction (LVD) leading to permanent discontinuation of ZIIHERA was reported in 0.9% of patients. The median time to first occurrence of LVD was 5.6 months (range: 1.6 to 18.7). LVD resolved in 70% of patients.

Assess LVEF prior to initiation of ZIIHERA and at regular intervals during treatment. Withhold dose or permanently discontinue ZIIHERA based on severity of adverse reactions.

The safety of ZIIHERA has not been established in patients with a baseline ejection fraction that is below 50%.

Infusion-Related Reactions
ZIIHERA can cause infusion-related reactions (IRRs). An IRR was reported in 31% of 233 patients treated with ZIIHERA as a single agent in clinical studies, including Grade 3 (0.4%), and Grade 2 (25%). IRRs leading to permanent discontinuation of ZIIHERA were reported in 0.4% of patients. IRRs occurred on the first day of dosing in 28% of patients; 97% of IRRs resolved within one day.

Prior to each dose of ZIIHERA, administer premedications to prevent potential IRRs. Monitor patients for signs and symptoms of IRR during ZIIHERA administration and as clinically indicated after completion of infusion. Have medications and emergency equipment to treat IRRs available for immediate use.

If an IRR occurs, slow, or stop the infusion, and administer appropriate medical management. Monitor patients until complete resolution of signs and symptoms before resuming. Permanently discontinue ZIIHERA in patients with recurrent severe or life-threatening IRRs.

Diarrhea

ZIIHERA can cause severe diarrhea.

Diarrhea was reported in 48% of 233 patients treated in clinical studies, including Grade 3 (6%) and Grade 2 (17%). If diarrhea occurs, administer antidiarrheal treatment as clinically indicated. Perform diagnostic tests as clinically indicated to exclude other causes of diarrhea. Withhold or permanently discontinue ZIIHERA based on severity.

ADVERSE REACTIONS

Serious adverse reactions occurred in 53% of 80 patients with unresectable or metastatic HER2-positive BTC who received ZIIHERA. Serious adverse reactions in >2% of patients included biliary obstruction (15%), biliary tract infection (8%), sepsis (8%), pneumonia (5%), diarrhea (3.8%), gastric obstruction (3.8%), and fatigue (2.5%). A fatal adverse reaction of hepatic failure occurred in one patient who received ZIIHERA.

The most common adverse reactions in 80 patients with unresectable or metastatic HER2-positive BTC who received ZIIHERA (≥20%) were diarrhea (50%), infusion-related reaction (35%), abdominal pain (29%), and fatigue (24%).

USE IN SPECIFIC POPULATIONS

Pediatric Use

Safety and efficacy of ZIIHERA have not been established in pediatric patients.

Geriatric Use

Of the 80 patients who received ZIIHERA for unresectable or metastatic HER2-positive BTC, there were 39 (49%) patients 65 years of age and older. Thirty-seven (46%) were aged 65-74 years old and 2 (3%) were aged 75 years or older.

No overall differences in safety or efficacy were observed between these patients and younger adult patients.

About Biliary Tract Cancer
BTC, including gallbladder cancer and intrahepatic and extrahepatic cholangiocarcinoma, account for <1% of all adult cancers globally and are often associated with a poor prognosis.[2,3] The human epidermal growth factor receptor 2 (HER2) is a well-validated target for antitumor therapy in other

cancers. Across the U.S., Europe, and Japan, approximately 12,000 people are diagnosed with HER2+ BTC annually.[4,5,6,7]

About Jazz Pharmaceuticals
Jazz Pharmaceuticals plc (Nasdaq: JAZZ) is a global biopharma company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing life-changing medicines for people with serious diseases—often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines, including leading therapies for sleep disorders and epilepsy, and a growing portfolio of cancer treatments. Our patient-focused and science-driven approach powers pioneering research and development advancements across our robust pipeline of innovative therapeutics in oncology and neuroscience. Jazz is headquartered in Dublin, Ireland with research and development laboratories, manufacturing facilities and employees in multiple countries committed to serving patients worldwide. Please visit www.jazzpharmaceuticals.com for more information.

Jazz Pharmaceuticals plc Caution Concerning Forward-Looking Statements

This press release contains forward-looking statements, including, but not limited to, statements related to the potential to transform the current treatment paradigm for BTC, our goal of delivering a potential chemotherapy-free option to more patients living with other HER2-expressing solid tumors, the planned date for commercial availability in the U.S., the potential for the Phase 3 trial HERIZON-BTC-302 to serve as a confirmatory trial and other statements that are not historical facts. These forward-looking statements are based on Jazz Pharmaceuticals' current plans, objectives, estimates, expectations and intentions and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, risks and uncertainties associated with pharmaceutical product development, and other risks and uncertainties affecting Jazz Pharmaceuticals and its development programs, including those described from time to time under the caption "Risk Factors" and elsewhere in Jazz Pharmaceuticals plc's Securities and Exchange Commission filings and reports (Commission File No. 001-33500), including Jazz Pharmaceuticals' Annual Report on Form 10-K for the year ended December 31, 2023, as supplemented by our Quarterly Report on Form 10-Q for the quarter ended September 30, 2024, and future filings and reports by Jazz Pharmaceuticals. Other risks and uncertainties of which Jazz Pharmaceuticals is not currently aware may also affect Jazz Pharmaceuticals' forward-looking statements and may cause actual results and the timing of events to differ materially from those anticipated. The forward-looking statements herein are made only as of the date hereof or as of the dates indicated in the forward-looking statements, even if they are subsequently made available by Jazz Pharmaceuticals on its website or otherwise. Jazz Pharmaceuticals undertakes no obligation to update or supplement any forward-looking statements to reflect actual results, new information, future events, changes in its expectations or other circumstances that exist after the date as of which the forward-looking statements were made.

Dr. Harding has financial interests related to Jazz Pharmaceuticals and Zymeworks.

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References:

[1] ZIIHERA (zanidatamab-hrii) Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.
[2] Valle JW, et al. Lancet 2021; 397:428-44
[3] Siegel RL, et al. CA Cancer J Clin 2022; 72;7-33
[4] BTC overall diagnosed patients as per SEER 22.
[5] Assumes anatomic subsites intrahepatic CCA, extrahepatic CCA, gallbladder cancer, and BTC unspecified.
[6] Assumes HER2 positivity rates per anatomical subsite from Galdy, S., Lamarca, A., McNamara, M.G. et al. Cancer Metastasis Rev 36, 141–157 (2017), Nobuyoshi Hiraoka, et al. Human Pathology, Volume 105, 2020, Pages 9-19
[7] Major markets: UK, France, Germany, Spain, Italy. Note: HER2+ BTC patients in Jazz-controlled commercial territories, which includes Japan, and excludes other certain Asia Pacific countries licensed to BeiGene, Ltd

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