Positive HERIZON-GEA-01 Phase 3 Results Support Ziihera® (zanidatamab-hrii) as HER2-Targeted Agent-of-Choice and Ziihera Combination Regimens as New Standard of Care in First-Line HER2-Positive Locally Advanced or Metastatic Gastroesophageal Adenocarcinoma

November 17, 2025

Ziihera plus chemotherapy showed a clinically meaningful and statistically significant improvement in PFS versus trastuzumab and chemotherapy, and a clinically meaningful effect with a strong trend toward statistical significance for OS at the first OS interim analysis

Ziihera plus the PD-1 inhibitor Tevimbra® (tislelizumab) and chemotherapy demonstrated clinically meaningful and statistically significant improvements in OS and PFS versus trastuzumab and chemotherapy

Company plans to submit a supplemental BLA for this indication in first half of 2026

For U.S. media and investors only

DUBLIN, Nov. 17, 2025 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced positive top-line results from the Phase 3 HERIZON-GEA-01 trial evaluating Ziihera® (zanidatamab-hrii) in combination with chemotherapy, with or without the PD-1 inhibitor Tevimbra® (tislelizumab), as first-line treatment for HER2-positive (HER2+) locally advanced or metastatic gastroesophageal adenocarcinoma (GEA), including cancers of the stomach, gastroesophageal junction and esophagus.

- Both *Ziihera* plus chemotherapy and *Ziihera* plus tislelizumab and chemotherapy demonstrated highly statistically significant and clinically meaningful improvements in progression-free survival (PFS) compared to the control arm, trastuzumab plus chemotherapy.
- *Ziihera* plus tislelizumab and chemotherapy also demonstrated clinically meaningful and statistically significant improvements in overall survival (OS), and *Ziihera* plus chemotherapy demonstrated a clinically meaningful effect with a strong trend toward statistical significance for OS compared to the control arm at the time of this first analysis. The trial is ongoing with an additional planned OS interim analysis for *Ziihera* plus chemotherapy currently expected in mid-2026.
- A PFS and OS benefit was observed in the *Ziihera* plus tislelizumab and chemotherapy arm versus the control arm in both PD-L1 positive and PD-L1 negative subgroups.
- Both *Ziihera* plus chemotherapy, and *Ziihera* plus tislelizumab and chemotherapy demonstrated improvements in the key secondary endpoints of objective response rate (ORR) and duration of response (DoR) versus the control arm, and these endpoints were supportive of the primary efficacy endpoints.

"Advanced GEA represents one of the most common tumor types worldwide and remains an aggressive cancer with a poor prognosis," said Dr. Kohei Shitara, director of the Department of Gastrointestinal Oncology, and principal trial investigator at the National Cancer Center Hospital East, Kashiwa, Japan. "Based on the positive results seen in the HERIZON-GEA-01 trial, the zanidatamab plus chemotherapy combination, with and without tislelizumab, has the potential to become the new standard of care for patients in HER2+ first-line locally advanced unresectable or metastatic GEA. This is the first Phase 3 trial to demonstrate a benefit for a novel HER2-targeted therapy compared to trastuzumab as part of a combination regimen in HER2+ first-line GEA."

"We believe these results will be practice changing, and highlight the potential impact of *Ziihera* for patients who are facing a devastating diagnosis and limited options in locally advanced or metastatic GEA," 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. "We expect *Ziihera* to become the new standard of care anti-HER2 therapy for patients with HER2+ first-line metastatic GEA regardless of PD-L1 status. We plan to quickly engage FDA and expect to submit a supplemental Biologics License Application (sBLA) in the U.S. in first half of 2026 to support *Ziihera* as a first-line treatment for patients with HER2+ locally advanced or metastatic GEA for use as part of a standard chemotherapy regimen with and without tislelizumab. We thank the patients and investigators who are involved in this trial."

The safety profile of *Ziihera* in combination with chemotherapy, with or without tislelizumab, was generally consistent with the known safety profile of each agent with no new safety signals observed in the two investigational combination arms and supports the overall benefit risk of *Ziihera* for use in this indication.

Jazz plans to submit these data for presentation at a major medical meeting in the first quarter of 2026 and for publication in a peer-reviewed journal, and will rapidly submit for adoption in the National Comprehensive Cancer Network® Guidelines (NCCN Guidelines®).

HERIZON-GEA-01 marks the first Phase 3 trial results for *Ziihera*. Ongoing research for *Ziihera* includes the Phase 3 HERIZON-BTC-302 trial evaluating *Ziihera* and CisGem (cisplatin plus gemcitabine) with or without the addition of a PD-1/L-1 inhibitor versus CisGem with or without a PD-1/L1 inhibitor in adult participants with HER2+ biliary tract cancer; the Phase 3 EmpowHER-303 trial evaluating *Ziihera* compared to trastuzumab, each in combination with physician's choice of chemotherapy, for the treatment of participants with metastatic HER2+ breast cancer who have progressed on, or are intolerant to, previous T-DXd treatment; the DiscovHER PAN-206 basket trial evaluating *Ziihera* monotherapy in previously-treated patients with HER2+ (IHC 3+) cancers; and the Phase 2 EmpowHER-208 trial evaluating *Ziihera* in patients with HER2+ neoadjuvant and adjuvant breast cancer.

About the HERIZON-GEA-01 Phase 3 Trial

HERIZON-GEA-01 (NCT05152147) is a global, randomized, open-label Phase 3 trial, conducted jointly with BeOne Medicines, to evaluate and compare the efficacy and safety of *Ziihera* plus chemotherapy, with or without tislelizumab, to the standard of care (trastuzumab plus chemotherapy) as first-line treatment for adult patients with advanced/metastatic HER2+ GEA. The trial randomized 914 patients from approximately 300 trial sites in more than 30 countries. Appropriate patients for this trial had unresectable locally advanced, recurrent or metastatic HER2+ GEA (adenocarcinomas of the stomach or esophagus, including the gastroesophageal junction), defined as 3+ HER2 expression by IHC or 2+ HER2 expression by IHC with ISH positivity per central assessment. Patients were randomized to the three trial arms: *Ziihera* in combination with chemotherapy and tislelizumab; *Ziihera* in combination with chemotherapy; and trastuzumab plus chemotherapy. The trial is evaluating dual primary endpoints, PFS per blinded independent central review (BICR) and OS.

About Gastroesophageal Adenocarcinoma

Gastroesophageal adenocarcinoma (GEA), including cancers of the stomach, gastroesophageal junction, and esophagus, is the fifth most common cancer worldwide, and approximately 20% of patients have HER2+ disease.[1,2,3] HER2+ GEA has high morbidity and mortality, and patients are urgently in need of new treatment options. The overall prognosis for patients with GEA remains poor, with a global five-year survival rate of less than 30% for gastric cancer and about 19% for GEA.[4]

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 in HER2 expression 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.[5] 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.[5] The U.S. 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).[5]

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 BeOne under license agreements from Zymeworks, which first developed the molecule.

The FDA granted Breakthrough Therapy designation for zanidatamab's 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 first-line gastroesophageal adenocarcinoma (GEA). Additionally, zanidatamab has received Orphan Drug designations from the 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 for ZIIHERA

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.

The full U.S. Prescribing Information for ZIIHERA, including BOXED Warning, is available at: https://pp.jazzpharma.com/pi/ziihera.en.USPI.pdf

® TEVIMBRA (tislelizumab) is a registered trademark of BeOne Medicines.

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 potentially 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 Ziihera's potential as a new standard of care in HER2+ first-line GEA and other HER2-expressing cancers, expected timing of OS data from the pivotal Phase 3 HERIZON-GEA-01, plans to submit a sBLA in first half of 2026 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 the successful completion of regulatory activities and uncertain regulatory approval, risks related to failure or delays in successfully initiating or completing clinical trials and assessing patients 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, 2024, as supplemented by Jazz Pharmaceuticals' Quarterly Report on Form 10-Q for the quarter ended September 30, 2025, 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.

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