U.S. FDA Approves Ziihera® (zanidatamab-hrii) with and without Tislelizumab plus Chemotherapy in First-Line HER2+ Advanced Gastroesophageal Adenocarcinoma

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Ziihera plus tislelizumab and chemotherapy approved for first-line treatment of all HER2+ GEA patients (IHC 3+ and IHC 2+/ISH+) regardless of PD-L1 status, establishing a new standard of care in front-line GEA

Company to host investor webcast on Aug. 25 at 4:30 p.m. ET

For U.S . media and investors only

DUBLIN , Aug. 25, 2026 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced that the U.S. Food and Drug Administration (FDA) approved two Ziihera® (zanidatamab-hrii)-containing regimens for the first-line treatment of adults with unresectable locally advanced or metastatic HER2-positive (HER2+) gastroesophageal adenocarcinoma (GEA): *Ziihera* plus Tevimbra® (tislelizumab-jsgr) and fluoropyrimidine- and platinum-containing chemotherapy (HER2+ IHC 3+ and IHC 2+/ISH+), and *Ziihera* plus fluoropyrimidine- and platinum-containing chemotherapy (HER2+ IHC 3+).

"This approval is a major step forward for people with HER2+ advanced GEA. *Ziihera* is now the first and only bispecific HER2-targeted antibody combined with a PD-1 inhibitor and chemotherapy approved for all HER2+ advanced GEA patients, regardless of PD-L1 status, establishing a new standard of care in first-line treatment," 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 HERIZON-GEA-01 results include the longest median overall survival reported in a Phase 3 trial in this setting, at 26.4 months. We are grateful to the gastric cancer community, including patients, caregivers, investigators and advocacy organizations, whose partnership made this possible."

GEA, which includes gastric, gastroesophageal junction and esophageal cancers, is the fifth most common cancer worldwide and remains associated with poor outcomes despite advances in treatment.[1] Approximately 20% of patients have HER2+ disease.[2,3,4] In the United States , more than 31,000 new stomach cancer cases are diagnosed each year.[5]

"People with advanced HER2+ GEA deserve treatment options that reflect the unique biology of their disease. Understanding what a HER2+ diagnosis means is an important part of navigating treatment decisions and helping patients and families make informed choices about care. Today's approval gives people diagnosed with HER2+ GEA a much-needed new treatment option and more choice in how their cancer is treated," said Martha Raymond, MA, CEO and founder of GI Cancers Alliance .

The approval is based on results from the Phase 3 HERIZON-GEA-01 trial, which were published in the *New England Journal of Medicine* and first presented at ASCO GI 2026, with PD-L1 subgroup data presented at ASCO 2026. The trial remains ongoing, with additional analyses planned.

Key HERIZON-GEA-01 Results

- Progression-free survival (PFS): Both *Ziihera*-containing combinations significantly improved PFS in the overall HER2+ population, reducing the risk of disease progression or death by 35% and extending median PFS to 12.4 months versus 8.1 months with trastuzumab plus chemotherapy.
- Overall survival (OS): In the overall HER2+ population, *Ziihera* plus tislelizumab-jsgr and chemotherapy demonstrated a statistically significant and clinically meaningful OS benefit, reducing the risk of death by 28% compared with trastuzumab plus chemotherapy and achieving a median OS of 26.4 months versus 19.2 months, representing a greater than seven-month improvement and the longest median OS reported in a Phase 3 trial in HER2+ advanced GEA.
- PFS and OS benefits were generally consistent across major prespecified subgroups, including geographic region and PD-L1 status.
- *Ziihera*-containing regimens demonstrated a manageable safety profile consistent with prior zanidatamab studies, with diarrhea as the most common adverse reaction, predominantly early in onset. Loperamide prophylaxis was administered during the first cycle, and diarrhea was managed with antidiarrheals and treatment modifications as needed, resulting in few discontinuations of *Ziihera*.

"This approval represents an important advancement in the treatment of metastatic HER2+ GEA," said Geoffrey Ku, M.D., HERIZON-GEA-01 study co-author and associate attending physician on the Gastrointestinal Oncology Service in the Department of Medicine at Memorial Sloan Kettering Cancer Center . "Importantly, similar outcomes were seen in patients whose tumors were PD-L1 positive or PD-L1 negative, suggesting that this regimen has the potential to benefit a broad range of patients. It further underscores what we have known for more than 15 years: HER2 testing at the time of diagnosis for advanced or metastatic gastroesophageal adenocarcinoma is critical to optimally guide treatment selection."

The company will host an investor webcast on Tuesday, August 25, at 4:30 p.m. ET / 9:30 p.m. IST to discuss the FDA approval of *Ziihera* in first-line HER2+ GEA and provide updates on the zanidatamab development program. The webcast may be accessed from the Investors section of the Jazz Pharmaceuticals website at www.jazzpharmaceuticals.com. To ensure a timely connection, it is recommended that participants register at least 15 minutes prior to the scheduled webcast. A replay of the webcast will be available via the Investors section of the Jazz Pharmaceuticals website.

The U.S . Prescribing Information for *Ziihera* contains Boxed Warnings for diarrhea and embryo-fetal toxicity.

Additional Important Safety Information related to *Ziihera* use in GEA is provided below. Please see full Prescription, including Boxed Warnings at https://pp.jazzpharma.com/pi/ziihera.en.USPI.pdf.

About 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.[1,2,3,4] 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 10% for metastatic disease.[6]

About Ziihera® (zanidatamab-hrii)
Ziihera (zanidatamab-hrii) is a bispecific HER2-directed antibody that binds to two extracellular sites on HER2. Binding of zanidatamab with HER2 results in internalization leading to a reduction in HER2 expression of the receptor on the tumor cell surface. Zanidatamab induces CDC, ADCC, and ADCP. These mechanisms result in tumor growth inhibition and cell death in vitro and in vivo.[7]

Gastroesophageal adenocarcinoma (GEA): In the United States, *Ziihera* is indicated for the first-line treatment of adults with HER2+ locally advanced or metastatic gastroesophageal adenocarcinoma (GEA), including cancers of the stomach, gastroesophageal junction and esophagus, in combination with tislelizumab-jsgr and fluoropyrimidine- and platinum-containing chemotherapy (HER2+ IHC 3+ and IHC 2+/ISH+ as detected by an FDA -authorized test); and in combination with fluoropyrimidine- and platinum-containing chemotherapy (HER2+ IHC 3+ as detected by an FDA -authorized test).

Biliary tract cancer (BTC): In the United States , *Ziihera* is also indicated for the treatment of adults with previously treated, unresectable or metastatic HER2+ (IHC 3+) biliary tract cancer (BTC), as detected by an FDA -approved test.[7] Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).[7] *Ziihera* is also approved in the European Union and other countries.

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

The FDA granted three Breakthrough Therapy designations for zanidatamab's development: one as a single agent for previously treated HER2 gene-amplified BTC, one in combination with fluoropyrimidine- and platinum-containing chemotherapy, with or without tislelizumab-jsgr for first-line HER2+ unresectable locally advanced or metastatic gastric, gastroesophageal junction (GEJ), or esophageal GEA, and one for the treatment of adults with previously treated, locally advanced, unresectable, or metastatic HER2+ colorectal cancer (CRC). The FDA also granted 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 GEA. Additionally, zanidatamab has received Orphan Drug designations from the FDA for the treatment of BTC, gastric (including GEJ) cancer, and esophageal cancer, as well as Orphan Drug designations from the European Medicines Agency for the treatment of BTC, gastric/gastroesophageal junction cancer, and esophageal cancer. Jazz continues to pursue additional regulatory approvals for zanidatamab in markets worldwide.

Important Safety Information for ZIIHERA

WARNING: DIARRHEA and EMBRYO-FETAL TOXICITY
ZIIHERA, in combination with fluoropyrimidine- and platinum-containing chemotherapy, with or without tislelizumab-jsgr, can cause severe diarrhea, including life threatening and fatal cases. Use antidiarrheal prophylaxis during the first cycle when ZIIHERA is given in combination with these drugs. Manage with antidiarrheals and supportive measures as clinically indicated. Interrupt, reduce the dose or discontinue ZIIHERA based on severity.
Embryo-Fetal Toxicity: Exposure to ZIIHERA during pregnancy can cause embryo-fetal harm. Advise patients of the risk and need for effective contraception.

Diarrhea: ZIIHERA can cause severe diarrhea.

When ZIIHERA is used in combination with fluoropyrimidine- and platinum-containing chemotherapy with or without tislelizumab-jsgr, severe, life threatening, and fatal cases of diarrhea can occur despite loperamide prophylaxis. The risk of severe and life threatening diarrhea is higher when ZIIHERA is administered with chemotherapy and tislelizumab-jsgr, with a higher risk in patients aged ≥ 65 years compared to younger patients. Advise patients to increase oral fluids, begin antidiarrheals, and notify their healthcare provider immediately if diarrhea occurs.

Administer antidiarrheal prophylaxis with loperamide in cycle 1 for all patients receiving ZIIHERA in combination with fluoropyrimidine- and platinum-containing chemotherapy with or without tislelizumab-jsgr. Begin loperamide at the first loose stool when ZIIHERA is administered in combination with chemotherapy. Administer fluids, electrolytes, and additional antidiarrheal agents as necessary. Before modifying the dose of ZIIHERA, evaluate, modify or discontinue drug(s) contributing to diarrhea in accordance with their respective prescribing information. Withhold, reduce the dose, or permanently discontinue ZIIHERA based on severity.

If treating patients with ZIIHERA in combination with FOLFOX, do not administer the fluorouracil bolus.

ZIIHERA in combination with chemotherapy and tislelizumab-jsgr

Diarrhea was reported in 85% of 330 patients in clinical studies, including Grade 4 (2.1%), Grade 3 (24%), and Grade 2 (31%) events. Fatal outcomes resulting from diarrhea occurred in 1.5% of patients. Diarrhea leading to dose reduction of ZIIHERA occurred in 10% of patients, and permanent discontinuation of ZIIHERA occurred in 3.9% of patients.

In cycle 1, diarrhea at Grade 4 severity occurred in 1.5% and Grade 3 severity occurred in 15% of patients despite use of loperamide prophylaxis. The median time to onset for cycle 1 diarrhea was 6 days and median time to resolution was 18 days.

ZIIHERA in combination with chemotherapy

Diarrhea was reported in 81% of 395 patients in clinical studies, including Grade 4 (1.3%), Grade 3 (20%) and Grade 2 (33%). Diarrhea leading to dose reduction of ZIIHERA occurred in 10% of patients, and permanent discontinuation of ZIIHERA occurred in 1.8% of patients.

In cycle 1, diarrhea at Grade 4 severity occurred in 0.8% and Grade 3 severity occurred in 14% of patients despite use of loperamide prophylaxis. The

median time to onset for cycle 1 diarrhea was 6 days and median time to resolution was 18 days.

Embryo-Fetal Toxicity: Based on the mechanism of action, ZIIHERA can cause fetal harm when administered to a pregnant woman. There are no human or animal data on the use of ZIIHERA in pregnancy. 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 while receiving ZIIHERA and for 4 months following the last dose of ZIIHERA.

Left Ventricular Dysfunction (LVD): ZIIHERA can cause decreases in left ventricular ejection fraction (LVEF).

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 < 50%.

ZIIHERA in combination with chemotherapy and tislelizumab-jsgr

LVEF decrease (an absolute decline in LVEF of > 10%, resulting in a final value of < 50%) was observed in 9% of 330 patients in clinical studies. LVD leading to permanent discontinuation of ZIIHERA was reported in 3% of patients. Fatal outcomes due to LVD occurred in one patient (0.3%). The median time to first occurrence of LVD was 6.9 months (range: 1.2 to 29.1 months). LVD resolved in 78% of patients.

ZIIHERA in combination with chemotherapy

LVEF decrease was observed in 5% of 395 patients. LVD leading to permanent discontinuation of ZIIHERA was reported in 1.0% of patients. The median time to first occurrence of LVD was 6.0 months (range: 1.4 to 15.0 months). LVD dysfunction resolved in 70% of patients.

Infusion-Related Reactions: ZIIHERA can cause infusion-related reactions (IRRs).

Prior to each dose of ZIIHERA, administer premedication 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.

ZIIHERA in combination with chemotherapy and tislelizumab-jsgr

An IRR was reported in 22% of 330 patients in clinical studies, including Grade 4 (0.3%), Grade 3 (1.2%), and Grade 2 (16%) despite use of prophylaxis. IRRs leading to permanent discontinuation of ZIIHERA were reported in 0.3% of patients. IRRs occurred on the first day of dosing in 17% of patients. Of all patients who experienced IRRs, 60% of reactions resolved within the first day.

ZIIHERA in combination with chemotherapy

An IRR was reported in 24% of 395 patients in clinical studies, including Grade 4 (0.3%), Grade 3 (1.5%), and Grade 2 (18%) despite use of prophylaxis. IRRs leading to permanent discontinuation of ZIIHERA were reported in 1.3% of patients. IRRs occurred on the first day of dosing in 22% of patients. Of all patients who experienced IRRs, 83% of reactions resolved within the first day.

Adverse Reactions

ZIIHERA in combination with chemotherapy and tislelizumab-jsgr

Serious adverse reactions occurred in 59% of 294 patients in HERIZON-GEA-01. Serious adverse reactions in > 2% of patients included diarrhea (17%), IRR (5%), vomiting (4.8%), hypokalemia (4.4%), acute kidney injury (3.7%), pneumonia (3.7%), nausea (2.4%), decreased appetite (2.4%), and anemia (2.4%). Fatal adverse reactions occurred in 2.4% of patients and included acute kidney injury (N=2), cardiac failure, diarrhea, dehydration, hypovolemic shock and intestinal obstruction (all N=1).

Permanent discontinuation of ZIIHERA occurred in 13% of patients. Adverse reactions that resulted in permanent discontinuation of ZIIHERA in ≥ 1% of patients included diarrhea (4.4%) and ejection fraction decreased (2.7%).

The most common adverse reactions (≥ 20%) were diarrhea (83%), nausea (56%), decreased appetite (46%), vomiting (44%), hypokalemia (39%), fatigue (37%), rash (36%), peripheral neuropathy (27%), and IRR (25%).

ZIIHERA in combination with chemotherapy

Serious adverse reactions occurred in 49% of 305 patients in HERIZON-GEA-01. Serious adverse reactions in > 2% of patients included diarrhea (11%), vomiting (3.3%), decreased appetite (2.6%), pneumonia (2.6%), sepsis (2.6%), hypokalemia (2.3%), and nausea (2.3%).

Permanent discontinuation of ZIIHERA occurred in 10% of patients. Adverse reactions that resulted in permanent discontinuation of ZIIHERA in ≥ 1% of patients included ejection fraction decreased (2.0%), IRR (1.6%), and diarrhea (1.6%).

The most common adverse reactions (≥ 20%) were diarrhea (79%), nausea (54%), vomiting (44%), decreased appetite (40%), fatigue (36%), hypokalemia (33%), peripheral neuropathy (32%), IRR (25%), and rash (22%).

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

Geriatric Use

ZIIHERA in combination with chemotherapy and tislelizumab-jsgr

Of 302 patients randomized to ZIIHERA in combination with chemotherapy and tislelizumab-jsgr in HERIZON-GEA-01, there were 139 (46%) patients aged ≥65 years. One hundred and six (35%) were aged 65-74 years and 33 (11%) were aged ≥ 75 years.

There was a higher incidence of Grade ≥ 3 adverse reactions observed in patients aged ≥ 65 years (87%) as compared to younger patients (80%). The incidence of Grade 3 or 4 diarrhea was higher in patients aged ≥65 years (32%) compared to younger patients (20%).

There was an increased incidence of fatal adverse reactions in patients aged ≥ 65 years (4.4%); including acute kidney injury (N=2), cardiac failure, dehydration, hypovolemic shock and intestinal obstruction (all N=1), compared to younger patients (0.6%), including diarrhea (N=1).

ZIIHERA in combination with chemotherapy

Of 304 patients randomized to ZIIHERA in combination with chemotherapy in HERIZON-GEA-01, there were 130 (43%) patients aged ≥ 65 years. One hundred (33%) were aged 65-74 years and 30 (10%) were aged ≥ 75 years.

No overall differences in safety were observed between patients aged ≥ 65 years and younger adult patients.

Dr. Ku has financial interests related to Jazz Pharmaceuticals .

® TEVIMBRA (tislelizumab-jsgr) 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 life-changing medicines for people with rare disease — often with limited or no therapeutic options. We have a diverse portfolio of medicines, including leading therapies addressing epilepsies, cancers and sleep disorders. Our patient-focused and science-driven approach powers pioneering research and development advancements across our robust pipeline of innovative therapeutics. 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.

Cautionary Note Concerning Forward-Looking Statements
This press release contains forward-looking statements, including, but not limited to, statements related to the potential therapeutic benefits of zanidatamab and of combination therapies with zanidatamab, zanidatamab's potential as a new standard of care in HER2+ first-line GEA and other HER2-expressing cancers 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' Securities and Exchange Commission filings and reports, including Jazz Pharmaceuticals' Annual Report on Form 10-K for the year ended December 31, 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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