Jazz Pharmaceuticals and Zymeworks Present Positive Pivotal Phase 2b Trial Data at ASCO 2023 Evaluating Zanidatamab in HER2-Amplified Biliary Tract Cancers

June 2, 2023

Results presented today at ASCO 2023 and concurrently published in The Lancet Oncology *demonstrate meaningful clinical benefit including antitumor activity, confirmed objective response rate (cORR) of 41.3%, median duration of response (DOR) of 12.9 months, and median progression-free survival (PFS) of 5.5 months (median study follow-up time of 12.4 months)*

Biliary tract cancers (BTC) are an aggressive group of cancers with no currently approved HER2-targeted treatment option

Jazz to host KOL investor webcast June 2, 2023, at 6:45 p.m. CT to review zanidatamab BTC data

DUBLIN and VANCOUVER, BC, June 2, 2023 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) and Zymeworks Inc. (Nasdaq: ZYME) today presented positive pivotal trial data, including new data on progression-free survival (PFS), from the Phase 2b HERIZON-BTC-01 trial of the bispecific antibody zanidatamab in previously treated HER2-amplified biliary tract cancers (BTC). The data were featured as an oral presentation at the American Society of Clinical Oncology (ASCO) Annual Meeting, and the results were concurrently published in *The Lancet Oncology*. The abstract (4008) was also selected to be included in the 2023 Best of ASCO® program, which will be held this summer following the ASCO Annual Meeting.

For the trial's primary endpoint, data from 80 patients with HER2-amplified BTC (defined as in situ hybridization [ISH] positive and immunohistochemistry [IHC] 2+ or 3+) demonstrated a confirmed objective response rate (cORR) of 41.3% [95% confidence interval (CI): 30.4, 52.8] with a Kaplan Meier (KM) estimated median duration of response (DOR) of 12.9 months. The KM estimated median PFS was 5.5 months [95% CI: 3.7, 7.2] with a range of 0.3 to 18.5 months.

"With a confirmed ORR of 41.3 percent, median DOR of 12.9 months and median PFS of 5.5 months, these results for zanidatamab are a significant step forward for second-line treatment of HER2-amplified BTC, where current chemotherapy treatments have been reported to provide only a 5 to 15 percent ORR and median PFS of 1.4 to 4 months," said Shubham Pant, M.D., professor of Gastrointestinal Medical Oncology and Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center. "The HERIZON-BTC-01 trial advances an exciting field of oncology research where we can leverage next-generation sequencing on BTC patients to understand genomic markers of the disease and choose the appropriate targeted therapies for these patients."

"We are thrilled to deliver an oral presentation on the pivotal HERIZON-BTC-01 study results demonstrating zanidatamab's meaningful clinical benefit and tolerable safety profile in patients with HER2-amplified BTC," said Rob Iannone, M.D., M.S.C.E., executive vice president, global head of research and development of Jazz Pharmaceuticals. "We are committed to advancing this program as rapidly as possible to potentially transform the lives of patients in critical need, with the goal of delivering a chemotherapy-free option that is the first-and-only therapy that targets HER2-amplified BTC."

Trial Results

Results of the pivotal HERIZON-BTC-01 trial (NCT04466891) indicate that the HER2-targeted, bispecific antibody zanidatamab demonstrates rapid, durable responses with a manageable safety profile in patients with treatment-refractory HER2-amplified BTC.

The trial evaluated zanidatamab (20 mg/kg IV every 2 weeks) in patients with HER2-amplified, locally advanced unresectable or metastatic BTC (gallbladder cancer, intra-/extra-hepatic cholangiocarcinoma) 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 cORR by independent central review (ICR) in Cohort 1, with secondary endpoints including other efficacy and safety outcomes.

In Cohort 1, cORR was 41.3% [95% CI: 30.4, 52.8] with the KM estimated DOR of 12.9 months (range of 1.5 – 16.9+) by ICR assessment with a median study follow-up time of 12.4 months (range of 7 – 24). The response was more than double the historical response rates of 5 to 15%[1,2] reported for second-line standard of care chemotherapy in patients with BTC. The median PFS in Cohort 1, which is new data presented at ASCO 2023, was 5.5 months [95% CI: 3.7, 7.2], with a range of 0.3 to 18.5 months. Current chemotherapy treatments have shown to provide a median PFS of 1.4 - 4 months in patients with BTC.[1,2]

Among the 33 responding patients at the data cutoff (October 10, 2022), 16 patients (49%) had ongoing responses and 27 patients (81.8%) had a DOR of ≥16 weeks. The median time to first confirmed response was 1.8 months (range, 1.6 – 5.5).

		Cohort 1 (n=80)
Confirmed Objective Response Rate, % (95% CI)		41.3 (30.4, 52.8)
Confirmed Best Objective Response, n (%)	Complete Response	1 (1.3)
	Partial Response	32 (40)
	Stable Disease	22 (27.5)
	Progressive Disease	24 (30)
Disease Control Rate, (95%, CI)		68.8 (57.4, 78.7)

Progression Free Survival	Median months: 5.5 (0.3 – 18.5)
Duration of Response Greater than, or Equal to, 16 Weeks	27
Time to First Response	Median months: 1.8 (1.6 – 5.5)

No responses were observed in Cohort 2.

Zanidatamab demonstrated a manageable and tolerable safety profile, with two of the 87 patients (2.3%) experiencing adverse events (AEs) leading to treatment discontinuation. There were no Grade 4 AEs and no deaths were treatment-related. The most common AEs were diarrhea and infusion-related reactions, which were predominately low-grade, reversible and manageable with routine supportive care.

The HERIZON-BTC-01 trial is ongoing and some secondary outcome measures, including overall survival, are not yet mature.

The abstract is available to conference registrants on the ASCO conference website here. (Abstract Number 4008).

Webcast Information

Jazz Pharmaceuticals will host a webcast today, Friday, June 2, 2023, at 6:45 p.m. CT / 7:45 p.m. ET / 12:45 a.m. IST (June 3) to provide a review of the zanidatamab BTC data presented at the 2023 ASCO Annual Meeting. Dr. Shubham Pant, M.D., who is presenting the zanidatamab BTC findings at ASCO, will provide an overview of the data. Dr. Pant is a professor in the Department of Gastrointestinal Medical Oncology with a joint appointment in the Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center.

Interested parties may register for the call in advance here or via the Investors section of the Jazz 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 website at www.jazzpharmaceuticals.com.

About Zanidatamab

Zanidatamab is an investigational bispecific antibody, based on Zymeworks' Azymetric ™ platform, that can simultaneously bind two non-overlapping epitopes of HER2, known as biparatopic binding. This unique design results in multiple mechanisms of action including dual HER2 signal blockade, increased binding and removal of HER2 protein from the cell surface, and potent effector function leading to encouraging antitumor activity in patients. Zymeworks, along with collaborators Jazz and BeiGene, Ltd. (BeiGene), are developing zanidatamab in multiple clinical trials as a targeted treatment option for patients with solid tumors that express HER2.

The U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy designation for zanidatamab in patients with previously treated HER2 gene-amplified biliary tract cancers (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 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 gastric cancer. Zanidatamab was also granted Breakthrough Therapy designation from the Center for Drug Evaluation (CDE) in China.

About Biliary Tract Cancers

Biliary tract cancers (BTC), including gallbladder cancer and cholangiocarcinoma, account for approximately <1% of all adult cancers and are often associated with a poor prognosis.[3,4] Globally, more than 210,000 people are diagnosed with BTC every year[5] and most patients (> 65%) are diagnosed with tumors that cannot be removed surgically. The human epidermal growth factor receptor 2 (HER2) is a well-validated target for anti-tumor therapy in other cancers. About 5% to 19% of patients with BTC have tumors that express HER2[6] and may be positioned for potential benefit from HER2-targeted therapy. Currently no HER2-targeted therapy has been approved for the treatment of BTC.

About Jazz Pharmaceuticals plc

Jazz Pharmaceuticals plc (Nasdaq: JAZZ) is a global biopharmaceutical 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 and novel product candidates, from early- to late-stage development, in neuroscience and oncology. Within these therapeutic areas, we are identifying new options for patients by actively exploring small molecules and biologics, and through innovative delivery technologies and cannabinoid science. Jazz is headquartered in Dublin, Ireland and has employees around the globe, serving patients in nearly 75 countries. Please visit www.jazzpharmaceuticals.com for more information.

About Zymeworks Inc.

Zymeworks Inc. (Nasdaq: ZYME) is a global biotechnology company committed to the discovery, development, and commercialization of novel, multifunctional biotherapeutics. Zymeworks' mission is to make a meaningful difference for people impacted by difficult-to-treat cancers and other serious diseases. Zymeworks' complementary therapeutic platforms and fully integrated drug development engine provide the flexibility and compatibility to precisely engineer and develop highly differentiated antibody-based therapeutic candidates. Zymeworks engineered and developed zanidatamab, a HER2-targeted bispecific antibody using Zymeworks' proprietary Azymetric ™ technology. Zymeworks has entered into separate agreements with BeiGene, Ltd. (BeiGene) and Jazz Pharmaceuticals Ireland Limited (Jazz), granting each of BeiGene and Jazz with exclusive rights to develop and commercialize zanidatamab in different territories. Zanidatamab is currently being evaluated in global Phase 1, Phase 2, and pivotal clinical trials as a treatment for patients with HER2-expressing cancers. Zymeworks' next clinical candidate, zanidatamab zovodotin (ZW49), is a HER2-targeted bispecific antibody-drug conjugate (ADC) developed using Zymeworks' proprietary Azymetric ™ and ZymeLink ™ Auristatin technologies. Zanidatamab zovodotin is currently being evaluated in a Phase 1 clinical trial for patients with a variety of HER2-expressing, HER2-amplified or HER2-mutant cancers. Zymeworks is also advancing a deep pipeline of product candidates based on its experience and capabilities in both ADC and multispecific antibodies (MSAT). In addition to Zymeworks' wholly-owned pipeline, its therapeutic platforms have been further leveraged through strategic partnerships with global biopharmaceutical companies. For information about Zymeworks, visit www.zymeworks.com and follow @ZymeworksInc on Twitter.

Jazz Pharmaceuticals plc Caution Concerning Forward-Looking Statements

This press release contains forward-looking statements, including, but not limited to, statements related to leverage next-generation sequencing on

biliary tract cancer patients to understand genetic markers of the disease and choose the appropriate targeted therapies; our goal of bringing to market a new chemotherapy-free option for patients as the first-and-only therapy that targets HER2-positive BTC 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, 2022, as supplemented by our Quarterly Report on Form 10-Q for the quarter ended March 31, 2023, 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.

Zymeworks Cautionary Note Regarding Forward-Looking Statements

This press release includes "forward-looking statements" or information within the meaning of the applicable securities legislation, including Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements in this press release include, but are not limited to, statements that relate to the anticipated clinical data presentations; the potential therapeutic effects of zanidatamab and Zymeworks' other product candidates; the commercial potential of Zymeworks' technology platforms and product candidates; Zymeworks' clinical development of its product candidates and enrollment in its clinical trials; the ability to advance product candidates into later stages of development; anticipated regulatory submissions and the timing thereof; and other information that is not historical information. When used herein, words such as "plan", "believe", "expect", "may", "anticipate", "potential", "will", "continues", and similar expressions are intended to identify forward-looking statements. In addition, any statements or information that refer to expectations, beliefs, plans, projections, objectives, performance or other characterizations of future events or circumstances, including any underlying assumptions, are forward-looking. All forward-looking statements are based upon Zymeworks' current expectations and various assumptions. Zymeworks believes there is a reasonable basis for its expectations and beliefs, but they are inherently uncertain. Zymeworks may not realize its expectations, and its beliefs may not prove correct. Actual results could differ materially from those described or implied by such forward-looking statements as a result of various factors, including, without limitation: future clinical trials may not demonstrate safety and efficacy of any of Zymeworks' or its collaborators' product candidates; clinical trials may not demonstrate safety and efficacy of any of Zymeworks' or its collaborators' product candidates; any of Zymeworks' or its partners' product candidates may fail in development, may not receive required regulatory approvals, or may be delayed to a point where they are not commercially viable; regulatory agencies may impose additional requirements or delay the initiation of clinical trials; the impact of new or changing laws and regulations; market conditions; inability to maintain or enter into new partnerships or strategic collaborations; and the factors described under "Risk Factors" in Zymeworks' quarterly and annual reports filed with the Securities and Exchange Commission, including its Quarterly Report on Form 10-Q for its quarter ended March 31, 2023 (a copy of which may be obtained at www.sec.gov and www.sedar.com).

Although Zymeworks believes that such forward-looking statements are reasonable, there can be no assurance they will prove to be correct. Investors should not place undue reliance on forward-looking statements. The above assumptions, risks and uncertainties are not exhaustive. Forward-looking statements are made as of the date hereof and, except as may be required by law, Zymeworks undertakes no obligation to update, republish, or revise any forward-looking statements to reflect new information, future events or circumstances, or to reflect the occurrences of unanticipated events.

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