CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761416Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 142519

MEETING PRELIMINARY COMMENTS

Jazz Pharmaceuticals Ireland Limited
Attention: Nina Moore
Associate Director, Regulatory Affairs
3170 Porter Drive
Palo Alto, CA 94304

Dear Nina Moore:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ziihera (zanidatamab).

We also refer to your September 13, 2023, correspondence, requesting a meeting to discuss the proposed content and format of your planned BLA for zanidatamab for treatment of HER2-positive biliary tract cancer.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, an electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call me at (240) 402-4998.

Sincerely,

{See appended electronic signature page}

Rebecca Cohen, R.N., M.P.H., O.C.N.
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO3
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: Thursday, November 2, 2023
Meeting Location: Virtual

Application Number: 142519
Product Name: Ziihera (zanidatamab)

Indication: for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive, locally advanced (unresectable) or metastatic biliary tract cancer (BTC) who have either:

- Received prior systemic chemotherapy for locally advanced (unresectable) or metastatic disease, or
- Developed disease recurrence during or within 6 months of completing adjuvant systemic chemotherapy

Sponsor Name: Jazz Pharmaceuticals
Regulatory Pathway: 351(a) of the Public Health Service Act

FDA ATTENDEES (tentative)
'Lola Fashoyin-Aje, M.D., M.P.H., Deputy Division Director, OOD/DO3
Sandra J. Casak, M.D., Clinical Team Lead, OOD/DO3
Vaibhav Kumar, M.D., M.S., Clinical Reviewer, OOD/DO3
Jason Moore, Pharm.D., Clinical Pharmacology Team Lead, OCP/DCPII
Hairat Sabit, Clinical Pharmacology Reviewer, OCP/DCPII
Matthew Thompson, Ph.D., M.P.H., Nonclinical Team Leader, OOD/DHOT
Joell Gills, Nonclinical Reviewer, OOD/DHOT
Asha Hewarathna, Product Quality Reviewer, OPQ
Hailin (Sheena) Wang, Product Quality Team Leader, OPQ
Yiming Zhang, Ph.D., Statistics Reviewer, OB/DBV
Joyce Cheng, M.D., Ph.D., Statistics Team Lead, OB/DBV
Ashleigh Lowery, PharmD, Team Leader, OSE/DMEPA
Latonia Ford, M.B.A., Safety Regulatory Project Manager, OSE/PMS
Rebecca Cohen, M.P.H., Regulatory Health Project Manager, ORO/DROOD

SPONSOR ATTENDEES
Name Title Discipline/Role
Ercem Atillasoy, M.D./Chief Regulatory and Safety Officer/Regulatory Affairs and Safety
Donnette Staas, Ph.D./V.P., Regulatory Strategy/ Regulatory Affairs

Nina Moore, M.S./ Associate Director, Regulatory Affairs/ Regulatory Affairs
Robert Iannone, M.D./Executive V.P., Research and Development/ Research and Development
Elaina Gartner, M.D./ V.P. Medical, Late-stage Development Clinical Development/ Oncology
Phillip Garfin, M.D., Ph.D./ Senior Medical Director Clinical Development/ Oncology
Ashok Panneerselvam, Ph.D./ Senior Director, Biostatistics/ Biostatistics
George Cai, Ph.D./ Director, Biostatistics/ Biostatistics
Lin Yang, Ph.D./ Associate Director, Biostatistics/ Biostatistics
Joanne Ma, Ph.D./ Executive Director, Clinical Pharmacology/ Clinical Pharmacology
Sheryl Coppola, Ph.D./ Associate Director, Global Clinical Pharmacology & Pharmacometrics/ Clinical Pharmacology
Kedar Vaidya, Ph.D./ Associate Director, Early Development, Oncology Pharmacology/ Nonclinical Pharmacology
Graham Paul, Ph.D./ Director, Toxicology Nonclinical/ Toxicology

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Thursday, November 2, 2023, between Jazz Pharmaceuticals and the Division of Oncology 3. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND
Regulatory
On September 13, 2023, Jazz Pharmaceuticals (Jazz) submitted a request for a Type B, virtual meeting to discuss the proposed content and format of the planned BLA for zanidatamab for the treatment of HER2-positive biliary tract cancer (BTC). On September 18, 2023, a Type B, preBLA meeting was granted.

On December 9, 2019, an End-of-Phase 1 meeting was held to discuss the design of a potential registrational trial for accelerated approval and to discuss the high-level proposal for a confirmatory trial.

On September 8, 2021, a Type B meeting was held to discuss the design of ZWI-ZW25-302 entitled "A Randomized, Multicenter, Blinded, Active-controlled, Phase 3 Study of

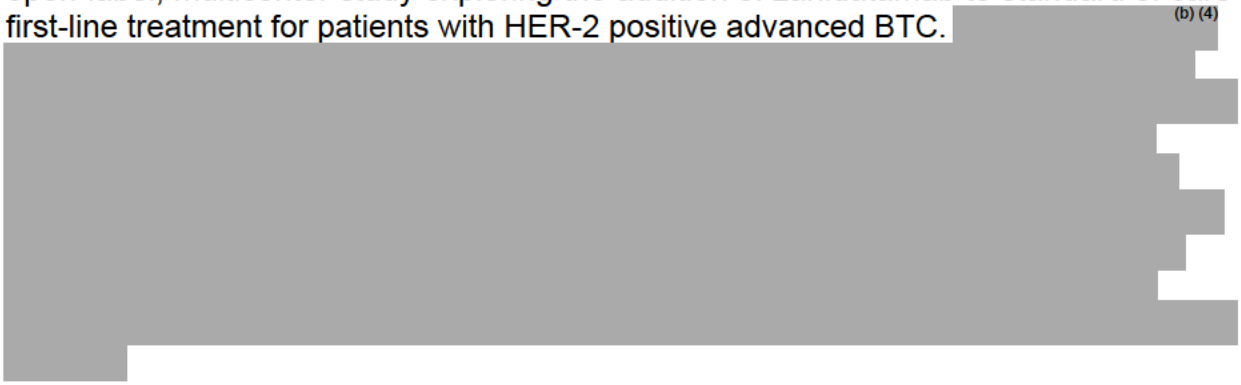
Zanidatamab or Placebo Plus Cisplatin and Gemcitabine (CisGem) Chemotherapy as First-line Treatment for Subjects with Locally Advanced Unresectable or Metastatic HER2-positive Biliary Tract Cancer (BTC)." In preliminary advice, FDA agreed with a side-by-side presentation of efficacy data from studies ZWI-ZW25-203 and ZWI-ZW25-101 and stated that the Summary of Clinical Efficacy (SCE) can serve as the Integrated Summary of Efficacy (ISE) if appropriate data can be included within the space limitations of the SCE.

On April 25, 2022, FDA issued written correspondence discussing analytical comparability data and other chemistry, manufacturing, and control issues needed to support for a BLA.

On May 10, 2023, a Type B meeting was held to discuss the approval pathway of zanidatamab for the treatment of patients with HER2-positive, locally advanced unresectable or metastatic biliary tract cancer, based on data from Study ZWI-ZW25-203 entitled, "A Phase 2b, open-label, single-arm study of zanidatamab (ZW25) monotherapy in subjects with advanced or metastatic HER2- amplified biliary tract cancers." During this meeting FDA stated that the results for Cohort 1 of Study 203 are insufficient to support traditional approval. FDA also stated that a marketing application submission strategy that includes accelerated approval necessitates that the study intended to verify clinical benefit be underway prior to, or within a specified time period after the date of approval of the drug. FDA expressed strong concern that the confirmatory trial ZWI-ZW25-302 discussed with FDA during the September 8, 2021, meeting was not initiated, and reiterated the Agency's position regarding the need for timely initiation of confirmatory studies as part of the evaluation of a marketing application. In addition, FDA questioned whether based on the available data from Cohort 1 of Study 203, the benefit:risk in patients with tumors that are IHC2+ HER2 amplified would be favorable in this population.

On June 9, 2023, ownership of the IND was transferred to Jazz.

On June 26, 2023, a Type B meeting was held to discuss Jazz's revised strategy for the conduct of a randomized controlled study designed to verify the benefit of zanidatamab in patients with previously treated, HER2-positive BTC. Study JZP598-302 is a global, open-label, multicenter study exploring the addition of zanidatamab to standard of care first-line treatment for patients with HER-2 positive advanced BTC. (b) (4)



The following are the main points discussed in the June 26, 2023, meeting:

- FDA reiterated advice on the need to have a confirmatory trial well underway and expressed concerns regarding the preliminary stage of planning for the proposed confirmatory study, given the intended timeline for BLA submission. FDA stated that submission of the planned BLA should occur when enrollment to the proposed confirmatory has commenced and when there is sufficient enrollment to indicate that the projected trial enrollment milestones and goals can be met based on the rate of trial accrual. Furthermore, FDA warned Jazz that premature submission of a BLA for accelerated approval without evidence that the confirmatory trial is underway to achieve the proposed study accrual metrics, may result in a decision to not file the application.

(b) (4)

On July 31, 2023, Jazz submitted Study JZP598-302 to the IND.

FDA granted the following for zanidatamab in biliary tract cancer:

- December 12, 2019, Fast Track Designation
- December 18, 2019, Orphan Drug Designation
- November 27, 2020, Breakthrough Therapy Designation (for the proposed indication below)
- September 1, 2022, iPSP-Initial Agreement

Chemistry, Manufacturing, and Controls

Zanidatamab is a humanized, bispecific, IgG1-like antibody directed against the juxtamembrane extracellular domain and the dimerization domain of HER2 for patients with HER2-expressing cancers. Zanidatamab DS is manufactured (b) (4) Zanidatamab DP is supplied

as a sterile, single-use, preservative-free, lyophilized powder in a glass vial for intravenous infusion.

Nonclinical
Jazz states Zanidatamab is a bispecific antibody directed against the extracellular domain 4 (ECD4) and the dimerization domain (ECD2) of HER2. These epitopes are the same as those bound by trastuzumab and pertuzumab, respectively. The nonclinical package consists of pharmacology, PK, a tissue cross reactivity study in human tissues, and a 13-week GLP repeat dose toxicology study in cynomolgus monkeys. Jazz is planning to use a weight-of-evidence approach for reproductive risk assessment.

Clinical
As previously discussed, Jazz intends to submit efficacy data from Cohort 1 of Study ZWI-ZW25-203 (Study 203) and supportive data from the BTC cohort of Study ZWI-ZW25-101 (Study 101) to support accelerated approval of zanidatamab for the treatment of HER-2 positive, locally advanced (unresectable) or metastatic BTC who have received prior chemotherapy or had disease recurrence within 6 months of completing adjuvant chemotherapy.

Study 203 is a multicenter, global, open-label, two-cohort, single-arm trial. Patients in Cohort 1 had HER-2 amplified (immunohistochemistry [IHC] 2+ or 3+) advanced (unresectable) or metastatic BTC and have progressed on at least 1 prior regimen of systemic gemcitabine-based therapy. All patients in Cohort 1 (n= 80) received zanidatamab 20 mg/kg intravenously (IV) every 2 weeks (Q2W) until investigator assessed radiographic progression according to RECIST v1.1. The response assessments were conducted every 8 weeks and the primary endpoint is confirmed objective response rate (ORR) by RECIST v1.1 assessed by independent central review (ICR). The study has completed enrollment and at the time of primary analysis with a data cutoff date October 10, 2022, the median follow up was 12.4 months (range: 7, 24) and 17 patients were continuing treatment. Results of the trial have been previously discussed in the May 10, 2023, meeting. The median age of patients in Cohort 1 was 62 years old, 56% were female, 63% of patients were enrolled in Asia and 22.5% in North America, 73% had an ECOG PS of 1, 63% had GBC and 30% ICC; 89% had metastatic disease, 41% had at least 2 prior lines of therapy, and 78% had HER2+ IHC3+. The median treatment duration of zanidatamab for Cohort 1 was 5.6 months (range, 0.5 to 19.8 months). The ICR-assessed ORR was 41.3% (95% CI 30.4, 52.8), with 1 patient (1.3%) having a complete response (CR) and 32 patients (40%) a partial response (PR). The estimated median DOR was of 12.9 months (range, 1.5 to 16.9+ months) and 45% of the responders had ongoing responses of at least 6 months. ORR in patients with IHC3+ was 51.6% (95% CI 38.6, 64.5) (32/62), compared with 5.6% (0.1, 27.3) in patients with IHC2+ (1/18). The investigator-assessed ORR was 41.3% (95% CI: 30.4, 52.8), and an estimated median DOR of 11.1 months (95% CI: 5.59, 14.06). There were no responses in patients in Cohort 2.

Jazz states that for the BLA, a data cutoff of July 28, 2023, will be used (approximately 16 months of follow-up after the last patient was enrolled in Cohort 1 of Study 203). As all patients in Part 2 of Study 101 are off-treatment and with a median follow-up of 27.5 months (range: 13.6–46.9 months), there will be no updates in this 22-patient population.

The proposed safety database will include data for zanidatamab as a single agent from 326 patients with various tumor types at various dose levels from the following studies, including:

- Primary safety data from Study 203 Cohort 1 (n=80)
- Supportive safety data from Study 203 Cohort 2 (n=7) and Study 101 Parts 1 and 2 (n=192).

These data will contribute to the planned pooled analyses.

(b) (4)

As previously discussed, Jazz plans to submit narratives for the events of deaths due to adverse events (AEs) and deaths within 30 days of last dose, serious AEs (SAEs), withdrawals/discontinuations due to an AE, Grade ≥3 diarrhea, and Grade ≥3 AEs of LVEF decrease, heart failure, and interstitial lung disease (ILD)/pneumonitis.

The following is the proposed rolling submission schedule:

Target date	Content
December 2023	**Nonclinical** • Modules 2.4, 2.6s, and Module 4
March 2024	**CMC** • Modules 2.3 and 3 **Clinical** • Modules 2.1, 2.5, 2.7sn and 5 **Regional** • Module 1 (including Assessment Aid)

Jazz states that the CDx development partner, Roche Tissue Diagnostics, is working on the sPMA submissions for the HER2 ISH and IHC assays (related to Q191846 for the ISH assay and Q191846/S001 for the IHC assay) to occur in parallel with the BLA submission (i.e., within 30 days of the final rolling BLA submission).

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

Preamble
FDA refers Jazz to discussions held on May 10, 2023, and June 26, 2023, regarding the conditions for submission of applications for accelerated approval.

1. Does the Agency agree that the proposed efficacy data package, including specific studies and data cutoffs, the proposed side-by-side efficacy presentation, and the use of SCE for ISE, are acceptable for the proposed Original BLA submission for zanidatamab for treatment of HER2-positive BTC?

   FDA Response: FDA does not object to the side-by-side presentation of efficacy results from Cohort 1 of Part 2 BTC cohort of Study 203 in the SCE and the SCE to serve as ISE. FDA agrees with Module 5.3.5.3 ISE cross-reference Module 2.7.3 SCE. In the submission, include analysis by HER2 expression (i.e., ICH 3+ vs IHC2+ ISH+) and ensure that the datasets have columns flagging the HER2 status.

2. Does the Agency agree with the proposed safety database at the time of the Original BLA submission, the proposed safety analyses (including safety analysis populations and subgroups) and the use of Summary of Clinical Safety for ISS to support the BLA?

   FDA Response: Generally, safety data cutoff should be within 6 months of submission. However, as only 10 patients are still under treatment, FDA does not object to the proposed safety database, safety analyses and the use of the SCS for ISS. In addition, FDA requests a dedicated analysis of LVEF changes, cardiac events, diarrhea, and ILD/pneumonitis.

3. Based on the updated data cutoff (28 July 2023) for Study 203 for the BLA, does the Agency agree with the proposal that a 90-day safety update is not necessary?

   FDA Response: No, FDA does not agree and requests Jazz to submit the 90-day safety update.

4. Does the Agency agree to waive the recommendation for submission of a retrospective Diversity Plan for pivotal Study 203 to the IND and the BLA for HER2-positive BTC, based on the rarity of the disease and its stage of clinical development?

FDA Response: There are no provisions to grant a waiver for a Diversity Plan. The adequacy of the data to support the applicability of Study 203 to the U.S. population will be a review issue.

5. Does the Agency agree that the proposed Clinical Pharmacology package, including the population pharmacokinetics (popPK) analysis, efficacy and safety ER analysis, C-QT analysis, and immunogenicity is adequate to support the zanidatamab BLA registration for the HER2-positive BTC indication?

FDA Response: In general, the proposed clinical pharmacology package appears reasonable.

6. Does the Agency agree that the executed nonclinical data package for pharmacology, pharmacokinetics and toxicology is adequate to support the BLA filing for zanidatamab for the treatment of HER2-positive BTC?

FDA Response: The proposed nonclinical program appears sufficient to support a future BLA filing. A final determination of the adequacy of the nonclinical data will be a review issue.

The reproductive risk assessment discussed in the meeting background appears reasonable; however, Jazz should remove product-specific information from the risk assessment.

7. Does the Agency agree with the proposed utilization of and timetable for Rolling Review, including the submission of an Assessment Aid, to facilitate the submission, review, and approval of the proposed HER2-positive BTC BLA? In addition, the Sponsor intends to request Priority Review with the BLA submission and will be seeking approval under the accelerated approval pathway.

FDA Response: FDA notes the rolling submission schedule for Module 4 and nonclinical parts of Module 2 is December 2023, but the Assessment Aid submission is planned for March 2024. If a draft of Assessment Aid Section 5 *Nonclinical Pharmacology/Toxicology* is available for the December 2023 submission, submit a draft of Section 5 with *The Applicant's Position* completed to facilitate FDA nonclinical review. Any changes in Section 5 between the draft and final Assessment Aid submitted in March 2024 should be tracked.

8. Does the Agency have any comments on the dossier table of contents, including the proposed location of reports and data formats, for the non-CMC portion of the

BLA?

FDA Response: Jazz's proposal appears acceptable. FDA does not have further comments.

9. Does the Agency agree that the pivotal Study 203, which forms the primary basis of the proposed BLA, is considered the sole covered study for the purpose of BIMO inspection and does the Agency agree with the proposed plan to include BIMO items for Study 203 only in the BLA?

FDA Response: Jazz's proposal appears acceptable.

10. Does the Agency have any preliminary comment on the likelihood of having an advisory committee meeting to support zanidatamab registration for treatment of HER2-positive BTC?

FDA Response: Whether FDA will decide to hold an Oncologic Advisory Committee will be a review issue.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 18, 2023, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[2]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF

[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[3]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating, "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage

[3] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

you to review the labeling review resources on the PLR Requirements for Prescribing Information[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in

eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information, please visit FDA.gov.[7]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[8]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[9]: In general, the data submission should be fully CDISC-compliant to

[7] http://www.fda.gov/ectd
[8] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[9] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program

facilitate efficient review.

- Assessment Aid[10]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

SUBMISSIONS WITH REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.*[11] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

RACE AND ETHNICITY DIVERSITY PLANS

[10] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project
[11] https://www.fda.gov/media/124795/download

Refer to FDA Draft Guidance “Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials- Guidance for Industry” at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/diversity-plans-improve-enrollment-participants-underrepresented-racial-and-ethnic-populations, for recommendations on the approach to develop and submit a Race and Ethnicity Diversity Plan to enroll representative numbers of participants from underrepresented racial and ethnic populations in the United States, in clinical trials during the development of your product. The Diversity Plan should be developed and discussed with FDA early in clinical development, preferably before initiation of any trials intended to support registration.

Although this draft Guidance specifically focusses on race and ethnicity Diversity Plans for the enrollment of members of racial and ethnic populations that have historically been underrepresented in clinical trials, FDA encourages sponsors to consider expanding the Diversity Plan to also account for other underrepresented populations (e.g., based on other demographic characteristics such as sex, age, gender, etc.).

Submit the Diversity Plan under eCTD Module 1.6 if included in meeting background package, otherwise submit under Module 2.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

REBECCA L COHEN
10/23/2023 01:01:43 PM

IND 142519

MEETING MINUTES

Zymeworks Inc.
Attention: Erica Reeves, Ph.D., P.M.P., R.A.C.
Regulatory Affairs Senior Manager
1215 4th Ave, Suite 2100
Seattle, WA 98161

Dear Dr. Reeves:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Zanidatamab.

We also refer to the telecon between representatives of your firm and the FDA on September 8, 2021. The purpose of the meeting was to discuss the design of Trial ZWI-ZW25-302 entitled "A Randomized, Multicenter, Blinded, Active-controlled, Phase 3 Study of Zanidatamab or Placebo Plus Cisplatin and Gemcitabine (CisGem) Chemotherapy as First-line Treatment for Subjects with Locally Advanced Unresectable or Metastatic HER2-positive Biliary Tract Cancer (BTC)."

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-4998.

Sincerely,

{See appended electronic signature page}

Rebecca Cohen, R.N., M.P.H., O.C.N.
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO3
Office of Regulatory Operations
Office of New Drugs

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

1

Meeting Type: B
Meeting Category: Pre-Phase 3

Meeting Date and Time: September 8, 2021, 3:00-4:00 PM
Meeting Location: Virtual

Application Number: 142519
Product Name: Zanidatamab

Indication: For the treatment of patients with HER2-amplified, locally advanced (unresectable) or metastatic biliary tract cancer (BTC) in combination with cisplatin and gemcitabine

Sponsor Name: Zymeworks Inc.
Regulatory Pathway: 351(a)

FDA ATTENDEES

Steven Lemery, M.D., M.H.S., Director (Acting), OOD/DO3
'Lola Fashoyin-Aje, MD, MPH, Deputy Division Directory, OOD/DO3
Sandra Casak, M.D., Clinical Team Lead, OOD/DO3
Leigh Marcus, M.D., Clinical Reviewer, OOD/DO3
Leslie Doros, M.D., Clinical Reviewer, OOD/DO3
Carmelo Blanquicett, M.D., Ph.D., Clinical Reviewer, OOD/DO3
Vaibhav Kumar, M.D., Clinical Reviewer, OOD/DO3
Matthew Thompson, Ph.D., M.P.H., Nonclinical Team Leader, OOD/DHOT
Catherine Bulik, M.D. Clinical Pharmacology Reviewer, DCPII
Youwei, Bi, Ph.D., Clinical Pharmacology Reviewer, DCPII
Joyce Cheng, M.D., Statistical Team Leader, OB/DBV
Abhishek Bhattacharjee, M.D., Statistical Reviewer, OB/DBV
Rebecca Cohen, R.N., M.P.H., Regulatory Health Project Manager, ORO/DROOD
Christina Leach, PharmD, Regulatory Health Project Manager, ORO/DROOD
Norma Griffin, Chief, Project Management Staff, ORO/DROOD

SPONSOR ATTENDEES

Bhardwaj Desai, M.D., Sr. Medical Director, Clinical Research
Bruce Hart, Ph.D., Sr. Vice President, Regulatory Affairs, Regulatory Affairs
Elaina Gartner, M.D., Executive Medical Director, Clinical Research
Erica Reeves, Ph.D., Sr. Manager, Regulatory Affairs, Regulatory Affairs
Neil Josephson, M.D., Interim CMO & Sr. Vice President, Clinical Research, Clinical Research
Pam Farmer, M.D., Vice President, Global Patient Safety, Pharmacovigilance
Rupert Davies, Ph.D., Sr. Director, Pharmacokinetics, Clinical Pharmacology

Todd Gray, M.S.P.H., Sr. Director, Biometrics, Biostatistics
Anthony Mwatha, M.S., Principal Statistician, Biostatistics

BACKGROUND

Regulatory

July 21, 2021, Zymeworks Inc., (Zymeworks) requested a Type B, pre-Phase 3 meeting to discuss the design of ZWI-ZW25-302 entitled "A Randomized, Multicenter, Blinded, Active-controlled, Phase 3 Study of Zanidatamab or Placebo Plus Cisplatin and Gemcitabine (CisGem) Chemotherapy as First-line Treatment for Subjects with Locally Advanced Unresectable or Metastatic HER2-positive Biliary Tract Cancer (BTC)." On July 27, 2021, a Type B meeting was granted.

On December 4, 2019, an End of Phase 1 meeting occurred, and meeting minutes were issued on December 9, 2019. The meeting was held to discuss the design of a potential registrational trial for accelerated approval and to discuss the high-level proposal for a confirmatory trial.

On December 12, 2019, Fast Track designation was granted for the investigation of ZW25 for the treatment of patients with human epidermal growth factor receptor 2 (HER2) gene-amplified BTC who have either received prior therapy for locally advanced (unresectable) or metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy.

On December 18, 2019, ZW25 was granted Orphan Drug Designation.

On November 27, 2020, Breakthrough Therapy designation was granted for the treatment of patients with HER2 gene-amplified, locally advanced (unresectable) or metastatic BTC who have either:

- Received prior systemic chemotherapy for locally advanced (unresectable) or metastatic disease, or
- Developed disease recurrence during or within 6 months of completing adjuvant systemic chemotherapy.

Chemistry, Manufacturing, and Controls

Zanidatamab is a humanized, bispecific anti-HER2 IgG1-like antibody. Zanidatamab is directed against 2 distinct HER2 epitopes, the juxtamembrane extracellular domain 4 (ECD4) and the dimerization extracellular domain 2 (ECD2), the epitopes bound by trastuzumab and pertuzumab, respectively. Zanidatamab combines trastuzumab-like and pertuzumab-like activities in a single antibody.

Zanidatamab is supplied as [redacted] (b) (4) lyophilized formulation. [redacted] (b) (4) formulations are for IV administration.

[redacted] The drug product is formulated at [redacted] sucrose, and [redacted] polysorbate 20, at a pH of 4.6.

Lyophilized zanidatamab is supplied as a sterile, lyophilized, single use, preservative free vial containing a nominal fill volume of 6 mL (300 mg). The drug product is formulated at 50 mg/mL in [redacted] sucrose, and [redacted] polysorbate 20, at a pH of 4.6.

Clinical

BTCs comprise approximately 3% of all adult cancers and 10% to 15% of liver cancers (Valle J, 2016). Abnormalities in the ErbB/HER pathway, including HER1, HER2, HER3, and HER4, are also seen across all types of BTC, with HER2 abnormalities more common in GBC (~19%–25%) and ECC (~17%) than ICC (~5%) (Valle 2017).

First line treatment for unresectable, recurrent, or metastatic BTC primarily consists of systemic chemotherapy with the combination gemcitabine and platinum, based on the results of the ABC-02 study, which showed a survival advantage (hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.80; P<0.001) with the combination of gemcitabine and cisplatin (median overall survival 11.7 months) when compared with gemcitabine alone (median overall survival 8.1 months) in patients with previously untreated disease (Valle 2010). Targeted agents have been approved for the second-line treatment of patients with *IDH1* mutations, MSI-H, TMB-H, *NTRK* fusions, and *FGFR2* alterations. There are no targeted therapies approved for the treatment of HER2+ BTC. Choice of second-line treatment in patients who received gemcitabine-cisplatin for first-line treatment is based on performance status. In the randomized ABC-06 trial in the second-line BTC setting comparing a leucovorin, 5-fluorouracil, and oxaliplatin regimen (mFOLFOX) vs. active symptom control (ASC), the median OS in the mFOLFOX treatment arm was 6.2 months vs. 5.3 months with ASC (HR 0.69; 95% CI: 0.50, 0.97; p = 0.031). The ORR with mFOLFOX was 5% but the toxicity was considerable (Lamarca, 2019).

A BTD was granted to zanidatamab for the treatment of patients with HER2 gene-amplified, locally advanced (unresectable) or metastatic biliary tract cancer (BTC) who have either received prior systemic chemotherapy for locally advanced (unresectable) or metastatic disease, or developed disease recurrence during or within 6 months of completing adjuvant systemic chemotherapy based on an ORR of 47% (95% CI 23, 72.2) with a median duration of response of 6.6 months, reported on 17 evaluable patients enrolled in the ZWI-ZW25-101 trial.

Proposed Trial (Study ZWI-ZW25-302)

The proposed trial will be a randomized, blinded study for the first-line treatment of patients with HER2 positive (IHC3+ or IHC2+ with HER2 gene amplification per

9 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated

pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[4]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[5]

[4] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[5] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

REBECCA L COHEN
09/27/2021 05:04:47 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND #	142519 STN# 64
Request Receipt Date	September 30, 2020
Product	Zanidatamab (ZW25)
Indication	Treatment of patients with HER2 gene-amplified, locally advanced (unresectable) or metastatic biliary tract cancer (BTC) who have either: • Received prior systemic chemotherapy for locally advanced (unresectable) or metastatic disease, or • Developed disease recurrence during or within 6 months of completing adjuvant systemic chemotherapy.
Drug Class/Mechanism of Action	Bispecific antibody binding the extracellular domain of the HER2 antigen, ECD4 and ECD2.
Sponsor	Zymeworks Inc.
ODE/Division	OOD/DO3
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	November 27, 2020

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and*** *will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)****.*** *Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

Treatment of patients with HER2 gene-amplified, locally advanced (unresectable) or metastatic biliary tract cancer (BTC) who have either:
• Received prior systemic chemotherapy for locally advanced (unresectable) or metastatic disease, or
• Developed disease recurrence during or within 6 months of completing adjuvant systemic chemotherapy.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

- ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

<u>Section II:</u> If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. **A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.**
   - *Information regarding the disease and intended population for the proposed indication.*
   - *Disease mechanism (if known) and natural history (if the disease is uncommon).*

   Zanidatamab (ZW25) is a bispecific antibody recognizing 2 epitopes of the extracellular domain of the HER2 antigen, ECD4 and ECD2, the same domains bound by trastuzumab and pertuzumab, respectively.

   Biliary tract cancer (BTC) is a term for a group of gastrointestinal tract cancers that include gallbladder cancer (GBC), intrahepatic cholangiocarcinoma (ICC), and extrahepatic cholangiocarcinoma (ECC). BTC accounts for approximately 3% of all adult cancers (Valle 2017). More than 65% of patients with BTC are diagnosed with non-resectable disease and the relapse rate is high, even among patients who undergo potentially curative surgery. The 5-year survival rate is approximately 5–15% for all patients; the estimated 5-year survival rate varies by stage of disease but in advanced unresectable, or metastatic disease the survival rate is less than 1% (Valle 2017). Abnormalities in the ErbB/HER pathway are reported across all types of BTC, with HER2 abnormalities more common in GBC (~19 to 25%) and ECC (~17 %) than ICC (~5%) (Valle 2017), suggesting that HER2-targeted therapy can be of potential relevance for the treatment of BTC. A systematic literature review and meta-analysis of published data in BTC showed that among 38 studies (a total of 3839 subjects) that reported HER2 positivity assessed by immune histochemistry (IHC), the mean HER2 expression rate was 26.5% (95% CI: 18.9, 34.1%) (Galdy 2017). It appears that there are no significant differences in HER2 expression between geographic regions; the mean HER2 expression rate in Asia was 28.4% (95% CI: 14.5, 42.3%) versus 19.7% (95% CI: 10.1, 29.2%) for Western countries.

   Standard of care for unresectable, recurrent, or metastatic BTC consists primarily of a gemcitabine and platinum containing regimen, based on the results of the ABC-02 study, which showed a survival advantage (hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.80; P<0.001) whith the combination of gemcitabine and cisplatin (median overall survival 11.7 months) when compared with gemcitabine alone (median overall survival 8.1 months) in patients with previsouly untreated disease (Valle 2010). Currently, following gemcitabine-based chemotherapy in the frontline setting, treatment options are limited. For patients with FGRF fusions or other rearrangements, pemigatinib has been recently granted accelerated approval based on an objective response rate (ORR) of 36% (95% CI 27, 45), with a median duration of response (DOR) of of 9.1 months (95% CI: 6.0, 14.5). For all other patients, several chemotherapy combinations are used off-label following first-line treatment, with limited or no efficacy. Notably, there are no therapies approved for the treatment of patients with HER2+ BTC.

8. **Information related to endpoints used in the available clinical data:**

   a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

      To support the BTDR, Zymeworks presented ORR and duration of response. ORR was the primary efficacy endpoint of the expansion cohort of Part 2 of Study ZWI-ZW25-101.

   b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

      - *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*

- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*

- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

ORR is an endpoint that directly measures the activity of an intervention on the tumor. In oncology, ORR of a sufficient magnitude and acceptable duration of response may be considered a surrogate endpoint likely to predict clinical benefit or, depending on the disease characteristics, a demonstration of clinical benefit itself. ORR in BTC has been used to support accelerated approval. Specifically, accelerated approval based on ORR and duration of response was granted for pemigatinib for the treatment for patients with recurrent locally advanced or metastatic cholabgiocarcinoma whose tumors express an FGFR fusion or rearrangements, and other FGFR inhibitors are currently under review for the same indication.

For the accelerated approval of pemigatinib, a confirmatory study is being conducted with progression-free survival and overall survival as co-primary endpoints.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

No other biomarker or endpoint would be considered for BTC cancer if it is not accompanied by a demonstration of an effect on the tumor or time-to-event outcomes.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*

- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are no targeted therapies approved for the treatment of HER2+ BTC. Choice of second-line treatment in patients who received gemcitabine-cisplatin for first-line treatment is based on performance status. Second line treatment (all off-label) include capecitabine plus oxaliplatin; capecitabine plus irinotecan; gemcitabine plus oxaliplatin; gemcitabine plus capecitabine; capecitabine plus cisplatin; or fluorouracil plus leucovorin and irinotecan. Overall, these treatment regimens are associated with median OS of approximately 6 to 7 months. In the randomized ABC-06 trial in the second-line BTC setting comparing a leucovorin, 5-fluorouracil, and oxaliplatin regimen (mFOLFOX) vs. active symptom control (ASC), the median OS in the mFOLFOX treatment arm was 6.2 months vs. 5.3 months with ASC (HR 0.69; 95% CI: 0.50, 0.97; p = 0.031). The ORR with mFOLFOX was 5% but the toxicity was considerable and mFOLFOX is not considered standard of care (Lamarca, 2019).

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

None.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

ZWI-ZW25-101 (NCT02902123)	Ongoing, 3-part, first-in-human, study to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, and potential anti-tumor activity of zanidatamab as a single-agent and in combination with selected chemotherapy agents in patients with locally advanced (unresectable) and/or metastatic HER2 expressing tumors. Part 1 of the study is a standard 3+3 dose-escalation that identified the recommended dose for zanidatamab monotherapy (10 mg/kg IV weekly and 20 mg/kg IV every 2weeks [Q2W]). Part 2 of the study further characterizes the safety, tolerability, and preliminary anti-tumor activity of single-agent zanidatamab in multiple indication-specific expansion cohorts; Cohort 5 includes 20 patients with BTC (all HER2-high expressing, defined as IHC3+ or IHC2+/FISH+, confirmed by central review) treated with zanidatamab 20 mg/kg Q2W. Patients were heavily pretreated with a median number of prior systemic cancer regimens of 2.5 (range, 1 to 8), and 5 patients (25%) had received prior treatment with trastuzumab. Per protocol, response rates were assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Of the 20 BTC patients treated with zanidatamab, 17 were evaluable for response (patients with measurable disease who have had at least one post-baseline disease assessment or discontinued study treatment prior to reassessment due to death from any cause or clinical progression). Eight patients had confirmed partial responses (PR), with an ORR of 47% (95% CI 23, 72.2). Durable responses were observed, ranging from 1.9 to 12.9 months; the median DOR was 6.6 months (95% CI: 3.2, not estimable [NE]).

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*

  Eight of 17 patients with disease progression after prior systemic treatment had confirmed PRs (second scan at least 4 weeks after onset of response), with an ORR of 47% (95% CI 23, 72.2). Durable responses were observed, with observed duration of response ranging from 1.9 to 12.9 months; the median DOR was 6.6 months (95% CI: 3.2, not estimable [NE]). These data compares favorably with the ORR 5% observed with mFOLFOX6 in the ABC-06 study. A systematic literature review of the second-line systemic chemotherapy for patients with advanced biliary cancer (Lamarca 2014) in 761 patients across 25 studies and showed a response rate of 7.7% (95% CI: 4.6, 10.9).

[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

In a cohort of patients who received zanidatamab monotherapy in Study 101, 30 evaluable patients with HER2-positive gastroesophageal adenocarcinoma and had received prior trastuzumab treatment had a confirmed ORR of 23%, with responses ranging from 1.7 to 11 months.

- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

  In addition to the 8 responses, 3 patients had tumor shrinkage that did not qualify as a response (<30% decrease in tumr size) and stable disease. In the 20-patient cohort, three patients were non-evaluable: one who withdrew from the study before being dosed and 2 patients who are currenty receiving treatment but have not yet been assessed for response.

- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

  Of the 149 patients treated in the Parts 1 and 2 (all HER2+ solid tumors), 145 (97%) experienced at least one adverse event (AE). Adverse events of special interest (AESIs) are defined as infusion related reactions (IRRs) and cardiac events including decreases in left ventricular ejection fraction and symptomatic heart failure (known toxicities of HER2 inhibition). Overall, AESIs were reported for 47 patients (32%), the majority of which were infusion-related reactions (30%). The overall safety profile was similar for BTC and non-BTC subjects. In BTC patients, the most common (all grades) AEs were diarrhea (50%), infusion-related reactions (25%), anemia (20%), vomiting (20%), and ALT/AST increased (20%); Grade 3-4 AEs were GGT increased, blood alkaline phosphatase increased (15%), cholangitis (10%), anemia, pneumonia, diarrhea, and increased bilirubin (one patient each). The AEs observed are consistent with the patient population (cholangitis, bilirubin, alkaline phosphatase, transaminases, etc.) and expected HER2-inhibition related AEs (diarrhea).

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting: In Study 101, the ORR by RECIST 1.1 as determined by investigators in patients with advanced/refractory HER2+ BTC was 47%; these responses were durable (median duration of response was 6.6 months) and clinically meaningful. The ORR observed with zanidatamab far exceeds the ORR observed with the standard of care (5-7%). The safety profile of zanidatamab is consistent with the known HER2 inhibition-related AEs and study population. The magnitude of ORR and the durability of responses represent clinical evidence that zanitadimab provides a substantial improvement on clinically significant endpoints over available therapies for the treatment of patients with unresectable or metastatic HER2+ BTC with disease progression after prior systemic therapy.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for

traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

DO3 will advise the Sponsor to request a meeting to further discuss the development of a randomized controlled study comparing zanitadimab against standard of care in HER2 positive BTC assessing time-to event (PFS and OS) endpoints, which may be conducted in the first-line setting. Consideration for expansion of the current cohort for submission of data based on ORR will be discussed.

DO3 met with Zymeworks on October 20, 2020 to discuss the development of zanitadimab in gastroesophageal carcinoma. Zymeworks stated in the briefing package for this meeting that they are collaborating with Roche Diagnostics in the development of IHC and in situ hybridization (ISH) assays for identification of HER2+ subjects with carcinomas of the digestive system including gastric, esophageal, and gastroesophageal junction adenocarcinomas, biliary tract cancers, and colorectal carcinomas. Presubmission meetings between CDRH and Roche Diagnostics regarding development of the assays were held November 20, 2019, and May 29, 2020

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 10/13/20 /M. Raggio

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SANDRA J CASAK
11/12/2020 08:38:05 AM