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RESEARCH**

APPLICATION NUMBER:

219839Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 142003
Request Receipt Date	February 6, 2024
Product	Sunvozertinib (DZD9008)
Indication	Sunvozertinib is intended for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations.
Drug Class/Mechanism of Action	Oral tyrosine kinase inhibitor (TKI) Targets EGFR sensitizing mutations, EGFR/HER2 Exon 20 insertion mutations, and EGFR uncommon mutations
Sponsor	Dizal (Jiangsu) Pharmaceutical Co., Ltd.
ODE/Division	OOD/DO2 (Division of Oncology 2)
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	April 6, 2024

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough 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):

Sunvozertinib is intended for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations.

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-threatening¹?

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 BTDR 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>

Section II: 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.**

Drug Description

Sunvozertinib is an oral EGFR tyrosine kinase inhibitor (TKI) which targets EGFR ex20ins mutations. Nonclinical studies indicate sunvozertinib is less potent against wild type EGFR.

Disease Background: EGFR-Positive Exon 20 insertion mutated non-small cell lung cancer

Somatic mutations of EGFR, particularly in exon 18-21, are major oncogenic drivers in NSCLC. They are found in approximately 30%-50% and 10%-20% of patients with NSCLC in Asia/Pacific and Western populations, respectively. Of these patients, approximately 4-10% harbor EGFR ex20ins mutations (Kobayashi 2016). Overall, the incidence of EGFR exon 20ins mutations in all of NSCLC is approximately 2% (Fang 2019).

Various TKI including gefitinib, erlotinib, afatinib, and osimertinib are approved for the treatment of patients with NSCLC harboring EGFR mutations, but the outcome of NSCLC patients with EGFR ex20ins mutations is worse relative to patients whose tumors harbor EGFR exon 19 deletion and L858R mutations when treated with conventional EGFR TKIs (Yasuda 2011).

Regulatory History

Sunvozertinib is not currently approved in the US for any indication.

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 this BTDR, Dizal provided overall response rate (ORR) per RECIST v.1.1 and duration of response (DOR) results from 28 patients from a cohort of patients from an ongoing multicohort global clinical trial, WU-KONG1. WU-KONG28 is also an ongoing, randomized, global trial which is intended to support conversion of a potential accelerated approval to traditional approval. WU-KONG28 is evaluating sunvozertinib versus platinum-based chemotherapy for the first-line treatment of locally advanced or metastatic EGFR ex20ins mutated NSCLC, with a primary endpoint of progression-free survival (PFS) and a key secondary endpoint with Type I error control, of overall survival (OS). (b) (4)

- 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.*

The Division considers ORR of a large magnitude and long duration to be an endpoint reasonably likely to predict clinical benefit in NSCLC and has been used as the basis of accelerated approval for the treatment of patients with NSCLC. Both PFS and OS have been used to support traditional approvals in oncology, including for NSCLC.

- 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.

None.

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.

Currently, there is one FDA-approved therapy for patients with NSCLC with EGFR exon 20 insertion mutations. Amivantamab is a bispecific antibody targeting EGF and MET receptors, which was granted traditional approval in combination with chemotherapy on March 1, 2024, based on the results from a randomized trial, PAPILLON, in 308 adult patients with previously untreated, locally advanced or metastatic NSCLC with EGFR ex20ins mutations. Amivantamab plus carboplatin and pemetrexed demonstrated a statistically significant improvement in PFS compared with carboplatin and pemetrexed with a hazard ratio of 0.40 (95% CI: 0.30, 0.53; p-value<0.0001). The median PFS was 11.4 months (95% CI: 9.8, 13.7) and 6.7 months (95% CI: 5.6, 7.3) in the respective arms. While OS results were immature at the current analysis, with 44% of pre-specified deaths for the final analysis reported, no trend towards a detriment was observed.

Amivantamab is also approved as a single agent based on an ORR 40% (95% CI: 29, 51) with a median DOR of 11.1 months (95% CI:6.1, NE) in 81 patients with EGFR ex20in mutated NSCLC who were previously treated with platinum-based chemotherapy. Amivantamab as a single agent was first granted accelerated approval on May 21, 2021, and was converted to traditional approval on March 1, 2024, based on the results from the PAPILLON trial (described above).

Mobocertinib, an oral kinase inhibitor, was also granted accelerated approval on September 15, 2021, for patients with locally advanced or metastatic, EGFR ex20ins mutated NSCLC, after disease progression on prior platinum-based chemotherapy. Mobocertinib demonstrated an ORR of 28% (95% CI: 20, 37) with a median DOR of 17.5 months (95% CI: 7.4, 20.3) in 114 patients. However, on October 2, 2023, the indication was slated for withdrawal given the confirmatory, randomized trial, EXCLAIM-2, failed to meet

its primary PFS endpoint. Therefore, amivantamab is the only drug that is FDA-approved as a single agent or in combination with chemotherapy for patients with EGFR ex20ins mutated NSCLC.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

Drug or Biologic	Indication and Data to Support BTDR	Outcome
(b) (4)		
Zipalertinib (CLN-801 or TAS6417) an irreversible EGFR inhibitor that selectively targets cells expressing EGFR ex20ins mutations while sparing cells expressing wild type EGFR	For the treatment of patients with locally-advanced or metastatic EGFR ex20ins mutated NSCLC who have been previously treated with platinum-based systemic chemotherapy • ORR 36% (95% CI: 24, 48) in 36 patients • median DOR was > 15 months (95% CI: not reported)	Granted¹ December 24, 2021

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 design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Table 1: Clinical Trial Supporting the BTDR

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

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.

Study ID	Trial Design	Treatment Group	Patient Group	Trial Endpoints
DZ2019E0001 (WU-KONG1) Multiregional trial	Single-arm, study with two parts: Part A dose escalation (n=30)/dose expansion/food effect (n=90 to 110) Part B dose extension (n=206)	DZD9008 200 mg or 300 mg by mouth (PO) daily (QD) Dose extension: Patients randomized to DZD9008 200 mg or 300 mg PO QD	Locally advanced or metastatic NSCLC with EGFR ex20ins mutation, previously treated with ≥ 1 systemic therapy Locally advanced or metastatic NSCLC with EGFR ex20ins mutation previously treated with at least 1 and no more than 3 lines of systemic chemotherapy	<u>Dose escalation</u> : safety and tolerability <u>Dose expansion</u> : ORR and DOR <u>Dose extension</u> : ORR and DOR

The data to support the BTDR is from a cohort of 28 patients in the WU-KONG1 trial with advanced NSCLC with EGFR exon 20ins mutations who are treatment naïve and received sunvozertinib 300 mg QD.

Table 2: Anti-tumor activity of sunvozertinib (DZD9008) in patients evaluable for response

Efficacy parameter	BTDR population N=28
ORR by IRC, n (%)¹ 95% CI	64% (44, 81)
Number of responders Complete response, n Partial response, n	18 2 16
Median DoR, months (95% CI)	NR
Responders with DOR ≥ 6 mos, n (%)	8 (44%)

Data cut-off date: January 4, 2024

Independent Review Committee = IRC; Not Reached = NR

¹ Median follow-up 8.3 months

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

The safety profile of sunvozertinib is similar to other EGFR TKIs. The BTDR included safety data from 182 patients treated with sunvozertinib 300 mg QD. The most common ($\geq 20\%$) treatment emergent adverse events (TEAEs) were:

diarrhea (81%), rash (38%), increased CPK (37%), paronychia (36%), anemia (36%), decreased appetite (35%), nausea (35%), vomiting (33%), and dry skin (24%). Grade ≥ 3 TEAEs occurred in 59% of patients, 4.4% of TEAEs resulted in death, and 34% reported serious adverse events. TEAEs leading to drug interruptions occurred in 51% of patients, TEAEs leading to dose reductions occurred in 27% of patients and TEAEs leading to discontinuation occurred in 12% of patients.

Available data indicate that sunvozertinib has a similar ORR compared to currently available, FDA-approved therapy (i.e., amivantamab plus carboplatin and pemetrexed). However, the safety profile of sunvozertinib may have an important safety advantage compared with amivantamab in combination with carboplatin and pemetrexed (further discussed below).

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

GRANT:

Provide brief summary of rationale for granting:

The sunvozertinib ORR of 64% (95% CI: 41, 81) among 28 patients who are treatment naïve is similar to the ORR observed with the currently FDA approved therapy of amivantamab in combination with carboplatin and pemetrexed (ORR 67% [95% CI: 59, 75]). However, sunvozertinib is a single oral drug which may have important safety advantages over amivantamab and chemotherapy, which is a three-drug regimen administered intravenously.

The safety profile of amivantamab in combination with carboplatin and pemetrexed has been evaluated in 151 patients with locally advanced or metastatic NSCLC with EGFR exon 20ins mutations. In cross-trial comparisons of patients with EGFR ex20ins mutated NSCLC treated with sunvozertinib compared to amivantamab plus carboplatin and pemetrexed, sunvozertinib was associated with lower rates of Grade ≥ 3 TEAEs, TEAEs leading to drug interruptions, TEAEs leading to dose reductions, and TEAEs leading to discontinuation. See the table comparing safety results below.

Table 3: Cross-trial comparison of the safety data of sunvozertinib and amivantamab plus carboplatin and pemetrexed in patients with EGFR ex20ins mutated NSCLC

Safety parameter	WU-KONG1 Part A and Part B Sunvozertinib 300 mg QD N=182 %	PAPILLON Amivantamab + Chemo N=151 %
TEAEs Grade ≥ 3	59	77
TEAEs resulting in death	4.4	4.6
Serious Adverse Events (SAEs)	34	38
TEAEs leading to drug interruptions	51	72
TEAEs leading to dose reductions	27	50
TEAEs resulting in discontinuation	12	24
Rash	38	90
Nail Toxicity/Paronychia	36	62
Infusion Related Reactions	0	42
Grade 3 or 4 Laboratory Abnormalities		
Decreased hemoglobin	7	11
Neutropenia	0	36

Dizal has provided preliminary clinical evidence that sunvozertinib may demonstrate substantial improvement over available therapy. As outlined in the *FDA Guidance: Expedited Programs for Serious Conditions – Drugs and Biologics*, an approach to demonstrating substantial improvement over available therapy includes demonstrating an important safety advantage that relates to serious adverse reactions (e.g., those that may result in treatment interruptions) while having similar efficacy.

In summary, sunvozertinib may have important safety advantages with similar efficacy, compared to available therapy (i.e., amivantamab in combination with carboplatin and pemetrexed), based on the following:

- The ORR for sunvozertinib is 64% (95% CI: 41, 81) compared to an ORR of 67% (95% CI: 59, 75) for amivantamab plus carboplatin and pemetrexed.
- Sunvozertinib is associated with lower rates of Grade ≥ 3 TEAEs, TEAEs leading to drug interruptions, TEAEs leading to dose reductions, and TEAEs leading to discontinuation compared to amivantamab plus carboplatin and pemetrexed.
- Compared to amivantamab plus carboplatin and pemetrexed, sunvozertinib is not associated with IRRs, and has lower rates of rash, paronychia, and Grade 3 or 4 lab abnormalities of neutropenia, and decreased hemoglobin.

Therefore, sunvozertinib has provided preliminary clinical evidence to support this BTDR.

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):
- 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:

Dizal has an ongoing randomized trial, WU-KONG 28, which is enrolling patients with locally advanced or metastatic NSCLC with EGFR exon 20ins mutations for the first-line treatment. Patients are randomized to either sunvozertinib or platinum-based chemotherapy. The trial is designed with PFS as the primary endpoint and OS as a key secondary endpoint. The Division had previously discussed with Dizal the design of the randomized trial, WU-KONG28 that enrolled the first patient in December 2022. The comparator arm in the trial is platinum-based chemotherapy as this was standard of care therapy when the trial was designed. [REDACTED] (b) (4)

The Division will be meeting with the Sponsor for a pre-NDA meeting on April 3, 2024, to discuss their planned submission for sunvozertinib for (b) (4) treatment of patients with NSCLC with EGFR ex20ins mutations (b) (4) platinum-based chemotherapy to file an accelerated approval application.

14. List references, if any:

1. Kobayashi Y, Mitsudomi T. Not all epidermal growth factor receptor mutations in lung cancer are created equal: Perspectives for individualized treatment strategy. Cancer Sci. 2016;107:1179-1186.
2. Fang W, et al. EGFR exon 20 insertion mutations and response to osimertinib in non-small-cell lung cancer. BMC Cancer. 2019;19:595. <https://doi.org/10.1186/s12885-019-5820-0>.
3. FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics.

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 } Katie Chon
Team Leader Signature: { See appended electronic signature page } Paz Vellanki
Division Director Signature: { See appended electronic signature page } Harpreet Singh

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/

WONME K CHON
04/03/2024 01:45:45 PM

PAZ J VELLANKI
04/03/2024 01:47:19 PM

BONNIE HARPREET MOORE
04/05/2024 12:58:28 PM



IND 142003

MEETING PRELIMINARY COMMENTS

Dizal (Jiangsu) Pharmaceutical Co., Ltd
c/o Aleon Pharma International, Inc.
Attention: Yen-Ting Shoung, Pharm.D.
Project Manager, Regulatory Affairs
4 Century Drive, Suite 255
Parsippany, NJ 07054

Dear Dr. Shoung:¹

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

We also refer to your correspondence, dated and received February 5, 2024, requesting a meeting to discuss development plan for sunvozertinib.

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, contact me via email at maritsa.stephenson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Maritsa Stephenson, PharmD, BCPS
Regulatory Health Project Manager
Office of Regulatory Operations
Division of Regulatory Operations – Oncologic
Diseases for DO2
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Preliminary Comments



PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: April 3, 2024, 10:00am—11:00am EST
Meeting Location: Videoconference

Application Number: 142003
Product Name: Sunvozertinib (DZD9008)
Indication: adult patients with locally advanced or metastatic NSCLC with EGFR exon20ins, whose disease has progressed on or after platinum-based chemotherapy

Sponsor Name: Dizal (Jiangsu) Pharmaceutical Co., Ltd
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Harpreet Singh, MD, Director, Division of Oncology 2 (DO2)
Paz Vellanki, MD, PhD, Cross-Disciplinary Team Lead
Katie Chon, PharmD, Clinical Reviewer
Hong Zhao, PhD, Clinical Pharmacology Team Lead
Guanming Chen, PhD, Clinical Pharmacology Reviewer
Claudia Miller, PhD, Nonclinical Team Lead
Sachia Khasar, PhD, Nonclinical Reviewer
Anup Amatyia, PhD, Biometrics Team Lead
Michelle Marcovitz, PhD, Biometrics Reviewer
Xing Wang, PhD, Product Quality Team Lead
Tefsit Bekele, PhD, Product Quality Reviewer
Daniel Obrzut, PhD, OPMA Branch Chief
Md Abdullah Mahmud. Ph.D., Pharmaceutical Manufacturing Assessor

SPONSOR ATTENDEES

Xiaolin Zhang, PhD, Chief Scientific Officer, Dizal (Jiangsu) Pharmaceutical Co., Ltd.
Pamela Yang, MD, PhD, Chief Medical Officer, Jiangsu
Li Zheng, MD, PhD, Product Medical Lead, Jiangsu
Kan Chen, PhD, Clinical Pharmacology Head, Jiangsu
Jinwei Zhang, PhD, Clinical Pharmacology Lead, Jiangsu.
Rita Deng, MS, Statistician Director, Jiangsu
Xuemei Huang, MS, Project Statistics Lead, Jiangsu
Weijun Qiao, MS, Head of China Regulatory Affairs, Jiangsu
Paul Tan, MS, Regulatory Affairs Director, Jiangsu
Yun He, MS, Regulatory Affairs Associate Director, Jiangsu
Shih-Ying Chang, PhD, CMC Head, Jiangsu

Qinglin Tang, PhD, Quality, Analytical and CMC RA Head, Jiangsu

Qinghai Guo, Ph,D CMC DP Lead, Jiangsu.

Wenliang Zeng, PhD, CMC RA Associate Director, Jiangsu

Andrew Jiang, MBA, U.S. Regulatory Contact, President, Aleon Pharma International, Inc. (Aleon Pharma)

Shirley Ruan, MBA, Associate Director, Regulatory Affairs, Aleon

Haixia Lin, MD, PhD, Director, Regulatory Affairs, Aleon Pharma

Yen-Ting (Irene) Shoung, PharmD, Project Manager, Regulatory Affairs, Aleon Pharma

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 April 3, 2024, 10:00am—11:00am EST, videoconference between Dizal (Jiangsu) Pharmaceutical Co., Ltd and the Division of Oncology 2. 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 Background

On January 26, 2022, FDA granted Breakthrough Therapy Designation for sunvozertinib (DZD9008) for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion (ex20ins) mutations whose disease has progressed on or after platinum-based chemotherapy.

On February 5, 2024, Dizal requested a Type B Pre-NDA meeting for sunvozertinib for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR ex20ins mutations, whose disease has progressed on or after platinum-based chemotherapy based on single arm data from Part 2 of the WU-KONG1 (DZ2019E0001) clinical trial.

On February 6, 2024, Dizal submitted a Breakthrough Therapy Designation Request for sunvozertinib for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR ex20ins mutations, who are newly diagnosed or have not received prior systemic therapy in the advanced stage.

Chemistry, Manufacturing and Controls (CMC)

The drug product is an oral immediate release tablet containing 150 mg or 200 mg of sunvozertinib. The qualitative compositions of the 150 mg and 200 mg sunvozertinib tablets are the same and the strengths are dose proportional. The manufacturing process (Formulation B) includes (b) (4)

The 150 mg and 200 mg strengths of Formulation B have been used for early phase and late phase clinical trials, as well as primary stability batches, and will be used for PPQ batches and future commercial batches.

Nonclinical

Sunvozertinib is a small molecule, irreversible tyrosine kinase inhibitor (TKI) targeting EGFR sensitizing mutations (ex20ins and T790M resistant mutations) as well as HER2 exon 20 insertion mutations, and has weak activity against wild-type EGFR. Dizal did not include their nonclinical program in the meeting package, however, based on table of contents in Appendix E, their nonclinical program appears appropriate to support an NDA submission pending review. There are no specific nonclinical related questions in the meeting package.

Clinical

As of January 4, 2024, Dizal has initiated nine clinical studies of sunvozertinib as a single agent in patients with NSCLC or in healthy volunteers, as summarized in the table below.

Study Name / Study ID/ Status (at NDA)	Study Design/Population	Dosage, Regimen, Route, Duration	Sample Size (Treated Participants)	Preliminary Efficacy Outcome Measure
WU-KONG1A/ DZ2019E0001, Part A/ Completed Initially enrolling in U.S., Australia, South Korea, and Taiwan	Phase 1, open-label, multi-center, dose escalation, dose expansion and food effect study to evaluate safety, and tolerability of sunvozertinib and define Maximum Tolerated Dose (MTD) and Recommended Phase2 Dose (RP2D) Dose escalation and food effect cohorts: patients with advanced NSCLC with EGFR or HER2 mutations.	Dose escalation: 50 mg, 100 mg, 200 mg, 300 mg and 400 mg. Dose expansion: 200 mg and 300 mg. Food effect: 300 mg. Once daily, orally dosing in 21- day cycles (except Cycle 0 of dose escalation and food effect cohorts), until disease progression, intolerable adverse events (AE), or patient withdrawal	Total: N=113 Dose escalation: N=25 50 mg: n=3; 100 mg: n=6; 200 mg: n=3; 300 mg: n=7; 400 mg: n=6 Dose expansion: N=76 200 mg: n=24 300 mg: n=52 Food effect (300 mg): N=12	Safety n=113

Study Name / Study ID/ Status (at NDA)	Study Design/Population	Dosage, Regimen, Route, Duration	Sample Size (Treated Participants)	Preliminary Efficacy Outcome Measure
	Dose expansion cohorts: patients with advanced NSCLC with EGFR or HER2 exon20ins			
WU-KONG1B/ DZ2019E0001, Part B/ Primary completion U.S., Argentina, Australia, Canada, China, France, Italy, Japan, Malaysia, South Korea, Spain, and Taiwan	Phase 2, open-label, multi- center, dose extension, randomized study to evaluate anti-tumor efficacy of sunvozertinib in NSCLC patients with EGFR exon 20 insertion mutations (exon20ins) Patients with advanced NSCLC harboring EGFR exon20ins, whose disease has progressed on or been intolerant of, at least one prior line with platinum-based chemotherapy	Cohort 1: 200 mg, QD Cohort 2: 300 mg, QD Continuous administration in 21-day cycles, until disease progression, intolerable AE, or participant withdrawal	Total: N=202 Cohort 1 (200 mg): n=91 Cohort 2 (300 mg): n=111	As of a data cut-off date of January 4, 2024, n=89 patients received sunvozertinib 300 mg QD. Confirmed ORR 43% (97.5% CI: 31, 55) Safety n=202
WU-KONG2/ DZ2019E0002/ Completed China only	Phase 1, open-label, multi- center, dose escalation and dose expansion study to evaluate safety, tolerability, PK and preliminary anti-tumor activity of sunvozertinib in Chinese patients with advanced NSCLC with EGFR or HER2 mutations Part A: Patient with advanced NSCLC with EGFR or HER2	Dose escalation: 50 mg, 100 mg, 200 mg, 300 mg and 400 mg Dose expansion: 300 mg and 400 mg Once daily, orally dosing continuously in 21-day cycles (except cycle 0 of escalation cohort), until disease progression, intolerable AE, or participant withdrawal	Total: N=48 <u>Dose escalation:</u> N=18 50 mg: n=3; 100 mg: n=3; 200 mg: n=3; 300 mg: n=6; 400 mg: n=3 <u>Dose expansion:</u> N=30 300 mg: n=19 400 mg: n=11	As of April 3, 2023, data cutoff date, n=74 patients with NSCLC with EGFR exon 20ins mutations who have received prior platinum-based chemotherapy. At all dose levels of sunvozertinib, ORR assessed by investigator was 38%. At sunvozertinib 200 mg and 300 mg, the confirmed ORR was 35% and 45%. Safety n=48

Study Name / Study ID/ Status (at NDA)	Study Design/Population	Dosage, Regimen, Route, Duration	Sample Size (Treated Participants)	Preliminary Efficacy Outcome Measure
	mutations, failed prior standard treatment Part B: Patient with advanced NSCLC with EGFR exon20ins or HER2 exon20ins, failed prior standard treatment			
WU-KONG6/ DZ2020E0001/ Completed China only	Phase 2, open-label, multi-center study to evaluate anti-tumor activity, safety, tolerability and PK of sunvozertinib in patients with advanced NSCLC with EGFR exon20ins Patient with advanced NSCLC harboring EGFR exon20ins, whose disease has progressed on, or after or been intolerant to platinum-based chemotherapy.	300 mg orally, once daily, continuously in 21-day cycles, until disease progression, intolerable AE, or participant withdrawal	N=104	As of the April 3, 2023 data cutoff date, n=97 patients ORR 61% (95% CI: 50, 71) Median DoR: 8.3 months (95% CI: 5.6, 10.4) Safety n=104
WU-KONG28*/ DZ2022E0005/ Ongoing* U.S., Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Czech Republic, France, Germany, Italy, Poland, Spain, and Turkey.	Phase 3, open-label, randomized, multi-center study of DZD9008 versus platinum-based doublet chemotherapy as first-line treatment for patients with locally advanced or metastatic NSCLC with EGFR exon20ins Patients who are newly diagnosed or have not received prior systemic treatment for locally advanced or	DZD9008 arm: 300 mg orally, once daily, continuously in 21-day cycle, until disease progression, intolerable AE, or participant withdrawal	See footnote ^(b)₍₄₎ % of patients enrolled (n= ^(b)₍₄₎)	No data available

Study Name / Study ID/ Status (at NDA)	Study Design/Population	Dosage, Regimen, Route, Duration	Sample Size (Treated Participants)	Preliminary Efficacy Outcome Measure
	metastatic NSCLC harboring EGFR exon20ins			
WU-KONG7/ DZ2021E0008/ Completed U.S.	Phase 1, single-center, nonrandomized, open-label, 2- part, fixed-sequence, drug-drug interaction study to assess PK of DZD9008 when orally administered alone, when co-administered with itraconazole, and when co-administered with carbamazepine in healthy adult participants Healthy adult participants	Part A: At single doses of 100 mg (Formulation B tablet) orally Part B: At single doses of 300 mg (Formulation B tablet) orally	Total: N=40 Part A (100 mg): N=20 Part B (300 mg): N=20	Not applicable.
WU-KONG11/ DZ2021E0003/ Completed U.S.	Phase 1, single-center, non-randomized, open-label pharmacokinetic and mass balance study of oral-administrated [¹⁴ C]-DZD9008 in healthy male participants Healthy male participants	Single oral dose of 100 mg [¹⁴ C] DZD9008 suspension	N=8	Not applicable.
WU-KONG12/ DZ2021E0004/ Completed	Phase 1 study with 4 parts. Part A is randomized, double-	Part A: dose escalation with a single oral dose of 50 mg, 100 mg, 200 mg, 300 mg and 400 mg DZD9008 (Formulation A or	Total: N=78 (Including placebo N=10) Part A: N=40 50 mg, 100 mg, 200 mg, 300 mg, 400 mg: N=8	Not applicable.

Study Name / Study ID/ Status (at NDA)	Study Design/Population	Dosage, Regimen, Route, Duration	Sample Size (Treated Participants)	Preliminary Efficacy Outcome Measure
U.S.	blind, placebo-controlled study to assess the safety, tolerability and PK of DZD9008 following single ascending dose, Part B and D are randomized, two-sequence studies to evaluate the effect of low-fat and high-fat meal on single oral dose PK of DZD9008, Part C is to evaluate the PK of DZD9008 suspension formulation. Healthy adult participants	Formulation B tablet) Part B: single doses of 300 mg DZD9008 (Formulation B tablet) orally under fasted and low-fat fed Part C: single doses of 100 mg DZD9008 orally with tablet (Formulation A tablet) and suspension Part D: single doses of 300 mg DZD9008 (Formulation B tablet) orally under fasted and high-fat fed	for each dose cohort (including N=2 with placebo) Part B: N=12 Part C: N=6 Part D: N=20	
WU-KONG19/ DZ2021E0009/ Completed (Estimated) China only	Phase 1, open-label, non-randomized study to assess the effect of DZD9008 on PK of the cocktail probes representative for CYP3A4, P-gp, BCRP and OATP1B1 in patients with EGFR or HER2 mutant advanced NSCLC Patients with advanced NSCLC harboring EGFR or HER2 mutations, and have progressed from, been refractory to or are intolerant to prior standard therapy without preferred alternative Therapy	All at 300 mg DZD9008 (Formulation B tablet). A single dose followed by 1 day washout, then orally, once daily for consecutive 27 days.	N=31 (Planned)	Not applicable.

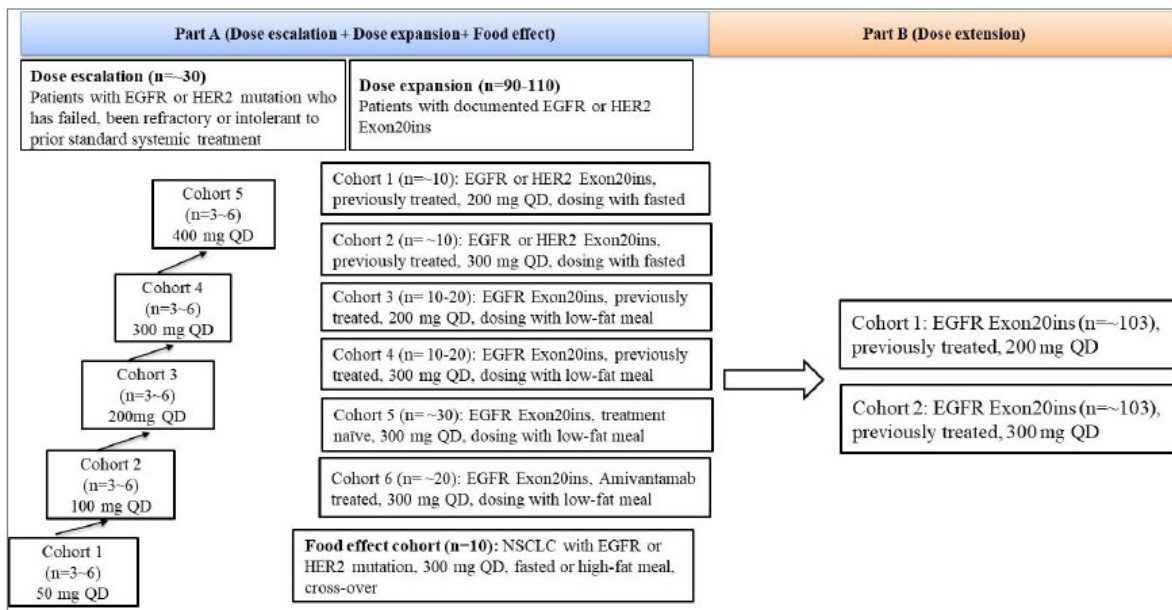
Study Name / Study ID/ Status (at NDA)	Study Design/Population	Dosage, Regimen, Route, Duration	Sample Size (Treated Participants)	Preliminary Efficacy Outcome Measure
WU-KONG27/ DZ2022E0007/ Ongoing U.S.	Phase 1, single-dose, non-randomized, open-label study to investigate the effect of hepatic impairment on the pharmacokinetics, safety, and tolerability of DZD9008	10 participants with moderate hepatic impairment (10 subjects with Child-Pugh B classification as entry criteria for moderate hepatic impairment group; 6 of the 10 subjects with moderate hepatic impairment also meet the NCI-ODWG Group C criteria) and 10 matched subjects with normal hepatic function (control group) All at a single dose of 200 mg DZD9008 (Formulation B tablet)	N=20 (Planned)	Not applicable

* WU-KONG28 is a phase 3, randomized trial. No predefined interim analysis is planned, and thus the study status will be updated at NDA submission while it is not included in the pooled efficacy and safety summary.

Source: adapted from pages 21-25 from meeting background package

DZ2019E001 (WU-KONG1, Part B): ongoing single arm study of sunvozertinib for EGFR exon20 insertion mutated NSCLC after prior platinum-based chemotherapy

Clinical trial DZ2019E0001 (WU-KONG1) is a two-part, ongoing multiregional trial evaluating the safety, tolerability, pharmacokinetics (PK), and anti-tumor activity of sunvozertinib administered orally once daily (QD) in patients with advanced or metastatic NSCLC. The dose escalation portion of the study in Part A enrolled patients with EGFR or HER2 mutations who are refractory, relapsed, or intolerant to prior systemic therapy. The dose expansion portion of the study in Part A enrolled patients with EGFR- or HER2- ex20ins mutations and the dose extension portion of the study in Part B enrolled patients with EGFR ex20ins mutations who have received at least 1 prior line but no more than 3 lines of systemic therapy. The study schema is provided below.

Figure 7 Study Design of WU-KONG1 (Protocol Code: DZ2019E0001, Version 12.0)

Source: page 55 from meeting background package

In Part B of the study, patients were randomized to either the DZD9008 200 mg QD or 300 mg QD dose cohorts. Randomization was stratified by baseline brain metastasis (yes vs no) and number of prior systemic anti-cancer therapies (<3 vs 3). The primary endpoint is objective response rate (ORR) per RECIST v1.1 by independent review committee (IRC). Secondary endpoints include duration of response (DOR), progression-free survival (PFS), and overall survival (OS). The primary endpoint will be analyzed within each dose cohort independently. The Bonferroni method was employed to control the family-wise type I error (at one-sided 0.025). Under a Simon two stage design, a sample size of 103 within each dose cohort is required to test a null hypothesis of $H_0: ORR \leq 0.17$ versus an alternative hypothesis of $H_1: ORR \geq 0.3$ with a one-sided significance level of 0.0125 and 80% power. In the first stage, 39 patients will be enrolled in each dose cohort. If the number of responses is less than or equal to 7 out of 39 patients ($ORR \leq 18\%$) in the first stage, then the dose cohort will be stopped. If the arm proceeds to the second stage, an additional 64 patients will be enrolled for a total of 103 patients per cohort. If 27 or more responses are observed, then the null ORR of 0.17 will be ruled out by the lower limit of a 95% confidence interval.

As of a data cutoff (DCO) date of January 4, 2024, 202 patients were enrolled and received at least one dose of sunvozertinib at 200 mg (n=91) and 300 mg (n=111). This includes 91 patients who were randomized to receive sunvozertinib 200 mg, 93 patients who were randomized to receive sunvozertinib 300 mg, and 18 patients who were enrolled to the overall 300 mg cohort (b) (4)

Trial enrollment is complete. A total of 191 patients (84 patients in the 200 mg randomized cohort and 107 patients in the overall

300 mg cohort, including 89 patients in the 300 mg randomized cohort) had at least one tumor assessment or dropped out of the study before the first tumor assessment and are included in the full analysis set (FAS).

The efficacy results for WU-KONG1B are presented in the table below.

Efficacy Parameter	Sunvozertinib 200 mg QD N=84	Sunvozertinib 300 mg QD N=89	Sunvozertinib 300 mg - overall N=107
Confirmed ORR (97.5 % CI)	39% (28, 52)	43% (31, 55)	36% (26, 48)
Complete Response, n	3	2	2
Partial Response, n	30	36	37
Median Duration of Response, months	NE (6.9, NE)	10.9 (5.6, NE)	10.9 (5.6, NE)

NE=not estimable

Source: adapted from page 62 from meeting background package

The safety results for WU-KONG1B are presented in the table below.

Safety Parameter	Sunvozertinib 200 mg QD N=91	Sunvozertinib 300 mg QD N=93	Sunvozertinib 300 mg - overall N=111
Grade $\geq$ 3 TEAE	48%	58%	58%
SAE	36%	31%	32%
TEAE leading to drug interruption	40%	53%	53%
TEAE leading to dose reduction	15%	37%	37%
TEAE leading to drug discontinuation	10%	11%	10%
TEAE with Fatal Outcome	2.2%	5%	4.5%

Source: adapted from page 94 from meeting background package

The most common ($\geq$ 20%) treatment emergent adverse events (TEAEs) reported in the 300 mg cohort (n=111) were diarrhea (84%), increased blood creatine phosphokinase (45%), anemia (43%), rash (42%), vomiting (39%), decreased appetite and nausea (36% each), paronychia (34%), increased blood creatinine (30%), dry skin (26%), and asthenia and pruritus (21% each).

Dizal indicated results from WU-KONG1B would be submitted in a future marketing application for accelerated approval. The planned DCO date for the NDA package is June 2024, when the last responder of WU-KONG1B has been followed up for at least 6 months from the first documented response. Dizal also proposes a 90-day Safety Update rather than 120-Day safety update.

The planned safety analysis for the proposed NDA will include patients from WU-KONG1B from the 300 mg cohort (n=111). Patients will also be pooled from WU-

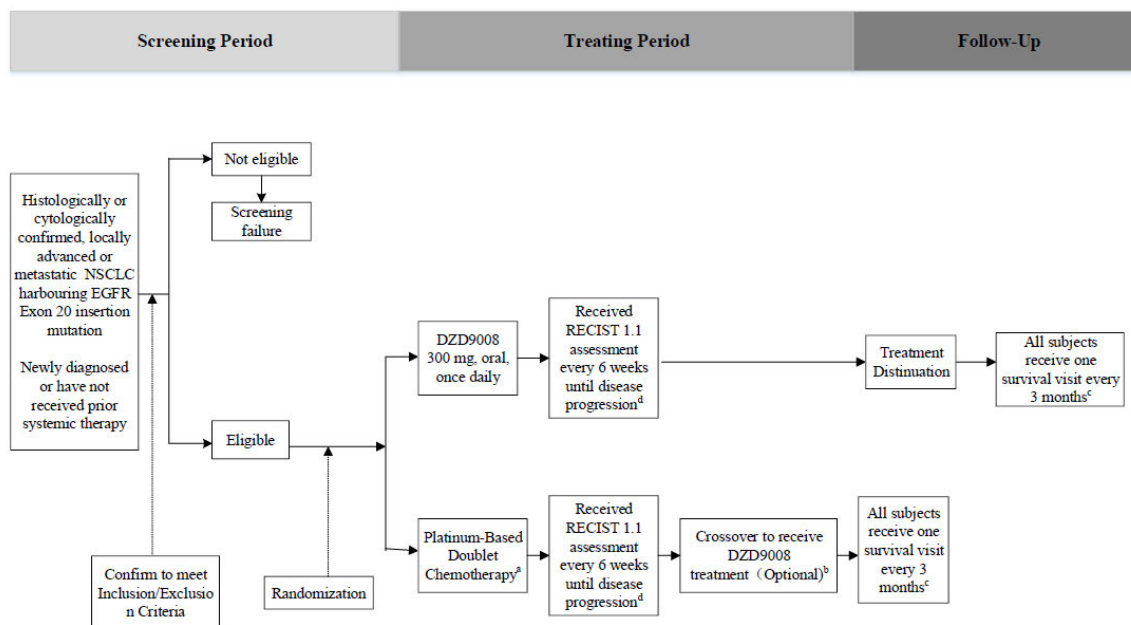
KONG1A, WU-KONG1B, WU-KONG2, and WU-KONG6 for a safety analysis set of patients treated at 300 mg QD (n=311) and for an overall safety analysis set of patients treated at any dose (n=467). WU-KONG28 data (discussed below) are not proposed to be included in the pooled safety datasets.

DZ2022E0005 (WU-KONG28): ongoing randomized trial of sunvozertinib versus platinum-based chemotherapy for first-line treatment of EGFR ex20ins mutated NSCLC

The ongoing WU-KONG28 trial is a multiregional, open-label, randomized trial of sunvozertinib versus platinum-based chemotherapy in patients with locally advanced or metastatic NSCLC with EGFR exon 20ins mutations who are treatment-naïve. The trial plans to enroll approximately 320 patients. Patients will be randomized 1:1 to receive either sunvozertinib 300 mg QD or platinum-based chemotherapy. Randomization will be stratified by baseline brain metastasis (with or without).

Patients randomized to platinum-based chemotherapy were permitted to crossover to sunvozertinib following confirmation of disease progression. The primary endpoint is PFS per BICR, and OS is a key secondary endpoint. A total of 219 PFS events will provide ~80% power at a one-sided significance level of 0.025 to detect a hazard ratio (HR) of 0.684 corresponding to a 3-month improvement in median PFS (9.5 months for sunvozertinib and 6.5 months for platinum-based chemotherapy, respectively). The study schema is provided below.

Figure 1 Study Design



Source: Clinical Study Protocol

DISCUSSION OF FDA RESPONSES TO SPONSOR QUESTIONS

Clinical

1. Does the Agency agree that the results from Study WU-KONG1 (DZ2019E0001) Part B, the phase 2 pivotal study, are adequate to support the submission of an NDA under the accelerated approval regulations (21 CFR 314 Subpart H) for sunvozertinib as a treatment for adult patients with locally advanced or metastatic NSCLC harboring EGFR exon20ins whose disease has progressed on or after platinum-based chemotherapy?

FDA Response: Preliminary efficacy data suggest that it may be reasonable to submit a marketing application after all responders in WU-KONG1B has been followed for at least 6 months from the first documented response by IRC per RECIST v1.1. Whether the data support an accelerated approval will depend on the confirmed overall response rate (ORR) and durability of response in the 111 patients treated with at least one dose of sunvozertinib (b) (4) mg QD, in the context of an overall benefit-risk assessment.

2. Does the Agency agree with the proposed plan for integrated summary of efficacy (ISE) and format of result presentation to support the NDA submission?

FDA Response: Yes, your proposal appears reasonable.

3. Does the Agency agree with the proposed integrated summary of safety (ISS) and format of result presentation to support the NDA submission?

FDA Response: The ISS dataset should contain all patients dosed with sunvozertinib regardless of dose. Please use flags to reflect which patients received sunvozertinib at the (b) (4) mg dose.

In addition, we were not able to locate the narratives and case report forms (CRFs) that you plan to provide in a future NDA submission. Narratives and CRFs should be provided for the following:

- All deaths on study or within 30 days of the last dose
- All serious adverse events occurring during treatment or within 30 days of last dose
- All adverse events leading to discontinuation of treatment

- All adverse events of special interest
- Pregnancy
- Overdose

We may request additional narratives during the review of the NDA.

4. Does the Agency agree with the proposed DCO for the sunvozertinib NDA submission?

FDA Response: Yes, we agree that all patients who had a response with sunvozertinib (b) (4) mg should be followed for at least 6 months post onset of response. A 90-day safety update may be reasonable; further determination will be made after review of topline efficacy and safety data in the (b) (4) patients who received at least one dose of sunvozertinib (b) (4) mg QD and after all responders have had at least 6 months of follow-up post onset of response.

5. Does the Agency agree with the following items proposed on the prescribing information?

FDA Response: A final determination on labeling will be made during the review of the original NDA.

6. Does the Agency agree with the proposed contents and format of the submission data?

FDA Response: The Study Data Standardization Plan (SDSP) appears reasonable.

Clinical Pharmacology

7. Does the Agency agree that the clinical pharmacology package is adequate to support the NDA submission?

FDA Response:

Dosage selection was previously discussed at the Type D meeting on May 19, 2023, (SDN 240) under IND 142003. At that time, we expressed concerns

(b) (4)

Additionally,

adequate clinical data should be included in a future NDA to justify the dosage selection.

Besides dosage selection, we agree that the proposed clinical pharmacology package is adequate to support the NDA submission. Refer to FDA Additional Comments for questions to be addressed in the Summary of Clinical Pharmacology in a future marketing application.

CMC

8. Dival plans to conduct Process Performance Qualification (PPQ) of sunvozertinib tablets in (b) (4), with the (b) (4) separated from all the previous steps, and validate the (b) (4) independently. Does FDA agree with the proposed validation design?

FDA Response:

Your proposal of performing Process Performance Qualification (PPQ) of sunvozertinib tablets in (b) (4), with the (b) (4) separated from all the previous step, appears reasonable.

However, we cannot comment on the execution and acceptability of your PPQ approach and results. We do not review or approve PPQ protocols or specify the number of batches to be included in PPQ protocol. The acceptability of executed PPQ protocols, acceptance criteria, study outcomes and supportive development and qualification studies will be evaluated during an inspection of the manufacturing facility. It is your responsibility to conduct all studies necessary to assure that the commercial manufacturing process is capable of consistently delivering quality product. Be advised that the purpose of PPQ is to demonstrate the robustness of the manufacturing process and therefore additional controls, in-process tests, enhanced sampling, and performance monitoring acceptance criteria should be a part of PPQ protocol.

Regulatory

9. Does the Agency agree that the proposed contents and formats of the planned NDA for sunvozertinib as outlined in the Table of Contents are adequate?

FDA Response: [Yes with the exception that the Assessment Aid is submitted under module 1.11.4 Multiple module information amendment (rather than module 1.2 as currently proposed).

10. The Sponsor plans to request Priority Review at the time of the initial NDA submission. Does the Agency agree with Dizal's rationale for requesting Priority Review?

FDA Response: It is your choice to request Priority Review with the initial NDA submission. On March 1, 2024, amivantamab with carboplatin and pemetrexed was granted traditional approval for the first-line treatment of locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations. A Priority Review request for sunvozertinib should include justification for Priority Review in the context of the current treatment landscape (e.g., improved efficacy, different route of administration, different or improved toxicity profile compared to available therapy). Please refer to the FDA Guidance on Expedited Programs for Serious Conditions². A final decision regarding Priority Review would be made at the time of an NDA filing.

Additional comments

Clinical Pharmacology

In the Pre-NDA submission, address the following question in the Summary of Clinical Pharmacology:

11. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
12. What are the exposure-response relationships for efficacy, safety and biomarkers?
13. What is the effect of sunvozertinib on the QT/QTc interval?
14. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
15. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
16. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

² <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics>

17. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
18. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean $\pm$ standard deviation) and median with minimum and maximum values as appropriate.
19. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
 - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
20. Submit the following for the population pharmacokinetic analysis reports:
 - Standard model diagnostic plots
 - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.
 - Model parameter names and units in tables.
 - Summary of the report describing the clinical application of modeling results.
 - Refer to the following pharmacometric data and models submission guidelines
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.
21. Submit the following information and data to support the population pharmacokinetic analysis:
 - SAS transport files (*.xpt) for all datasets used for model development and validation.
 - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
22. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population. Refer to Guidance for Industry for [population PK](#), [exposure-response relationships](#), and [pharmacometric data and models submission guidelines](#).

23. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.
24. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.

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 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 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.

Meeting 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

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>

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 you to review the labeling review resources on the PLR Requirements for Prescribing Information⁵ and Pregnancy and Lactation Labeling Final Rule⁶ 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

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>

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.

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**,

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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 *for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.⁸

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

⁷ <http://www.fda.gov/ectd>

⁸ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁹ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*¹⁰. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.¹¹

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

⁹ <https://www.fda.gov/media/84223/download>

¹⁰ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

¹¹ <https://www.fda.gov/media/85061/download>

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:

- RTOR¹²: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid¹³

¹² <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

¹³ <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/

MARITSA T STEPHENSON
04/01/2024 07:34:06 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 142003
Request Receipt Date	November 30, 2021
Product	DZD9008
Indication	DZD9008 is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon20 insertion whose disease has progressed on or after platinum-based chemotherapy
Drug Class/Mechanism of Action	Oral tyrosine kinase inhibitor (TKI) Targets EGFR sensitizing mutations, EGFR/HER2 Exon 20insertion mutations, and EGFR uncommon mutations
Sponsor	Dizal (Jiangsu) Pharmaceutical Co., Ltd.
ODE/Division	OOD/DO2 (Division of Oncology 2)
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	January 29, 2022

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough 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.

DZD9008 is indicated for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon20 insertion whose disease has progressed on or after platinum-based chemotherapy.

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):
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-threatening¹? YES NO

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

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>

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 therapy²/ 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 BTDR 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}

Section II: 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.

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>

Drug Description

DZD9008 is an oral EGFR tyrosine kinase inhibitor which targets Exon 20 insertion mutations and nonclinical studies indicate DZD9008 is less potent against wild type EGFR.

Disease Background: EGFR-Positive Exon 20 insertion mutated non-small cell lung cancer

Somatic mutations of EGFR, particularly in exon 18-21, are major oncogenic drivers in NSCLC. They are found in approximately 30%-50% and 10%-20% of patients with NSCLC in Asia/Pacific and Western populations, respectively. Of these patients, approximately 4-10% harbor EGFR ex20ins mutations (Kobayashi 2016). Various tyrosine kinase inhibitors (TKI) including gefitinib, erlotinib, afatinib, and osimertinib are approved for the treatment of patients with NSCLC harboring EGFR mutations, but the outcome of NSCLC patients with EGFR ex20ins mutations is worse relative to patients whose tumors harbor 'classical' mutations when treated with conventional EGFR TKIs (Yasuda 2011). Additionally, administration of currently approved EGFR TKIs can result in significant toxicities related to the inhibition of wild-type (WT) EGFR, including rash and diarrhea (Lacouture 2006).

Regulatory History

DZD9008 is not currently approved in the US for any indication.

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 this BTDR, the Sponsor provided overall response rate (ORR) per RECIST v.1.1 and duration of response (DOR) results from two dose escalation and cohort expansion studies. The Sponsor plans to use ORR as a primary endpoint in a randomized, dose extension part that is included in one of these studies. The Sponsor is in the process of planning randomized trial(s) using a time-to-event endpoint (progression-free survival and/or overall survival) as the time-to-event endpoint.

- 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.*

The Division considers ORR of large magnitude and long duration to be an endpoint reasonably likely to predict clinical benefit in NSCLC and has been considered adequate to support accelerated approval for the treatment of patients with NSCLC (Blumenthal 2015). Two EGFR exon 20 insertion-targeted drugs have received accelerated approval based on the demonstration of durable ORRs in single arm studies of patients with previously treated EGFR exon 20 insertion mutation-positive NSCLC.

- 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.

None.

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.*

Targeted therapies under accelerated approval

There have been two recent accelerated approvals of therapies targeting EGFR exon 20 insertion mutations based on single arm studies with primary endpoints of ORR. A summary of the approvals is provided in the table below.

Table 1: Targeted therapies for the treatment of patients with NSCLC with EGFR exon 20 insertion mutations with progression on prior platinum-based chemotherapy

	Clinical Trial	Approval Endpoint	Notes
Mobocertinib EGFR TKI Approval date: 9/15/2021	Non-randomized, multicohort study N=114	ORR 28% (95% CI 20, 37) mDOR 17.5 mos (95% CI 7.4, 20.3)	BTD granted 4/27/2020 based on ORR 43% (95% CI 25, 63) in 28 patients mDOR 10.2 months (95% CI: 5, 14)
Amivantamab Anti-EGFR-MET bispecific antibody Approval date: 5/21/2021	Non-randomized, multicohort study N=81	ORR 40% (95% CI 29, 51) mDOR 11.1 mos (95% CI 6.1, NE)	BTD granted 3/10/2020 based on ORR 41% (95% CI 24, 61) in 29 patients mDOR 6.8 months (range 1.1+, 16.1)

Conventional therapies used in clinical practice

There are no therapies targeting EGFR exon 20 insertion mutation-positive tumors in NSCLC that have received regular approval. Patients with advanced NSCLC with EGFR exon 20 insertion mutations are treated with systemic therapies that are available for EGFR wild-type tumors, including first-line platinum containing chemotherapy and/or an anti-PD(L)1 antibody. Upon progression, subsequent available therapies include single agent anti-PD(L)1 antibodies (nivolumab, pembrolizumab or atezolizumab) and single agent chemotherapy (docetaxel, pemetrexed) or docetaxel in combination with ramucirumab. A summary of the trial and approval endpoints are shown in the following table.

Table 2. Biologic/Drug Approved for 2nd-line metastatic NSCLC (biomarker unselected)

	Clinical Trial	Approval Endpoint
Single Agent checkpoint inhibitor		
Nivolumab	RCT* of nivolumab vs. docetaxel for nonsquamous NSCLC (Checkmate-057)	median OS 12.2 vs. 9.4 mo [HR 0.72 (0.60, 0.89)] mPFS 2.3 vs. 4.2 mo [HR 0.92 (0.77, 1.11)] ORR 19% (95% CI 15, 24) vs. 12% (95% CI 9, 17)
Pembrolizumab	RCT of pembrolizumab vs. docetaxel for PD-L1 positive metastatic NSCLC (KEYNOTE-010)	Pembrolizumab 10 mg/kg vs. docetaxel mOS 12.7 vs. 8.5mo [HR 0.61 (95% CI 0.49, 0.75)] mPFS 4.0 vs. 4.0 mo [HR 0.79 (0.66, 0.94)] ORR 19% (95% CI 15, 23) vs. 9% (95% CI 7, 13)
Atezolizumab	RCT of atezolizumab vs. docetaxel for metastatic NSCLC (OAK)	mOS 13.8 vs. 9.6 mo [HR 0.74 (95% CI 0.63, 0.87)] mPFS 2.8 vs. 4.0 mo (HR 0.95 (0.82, 1.10)) ORR 14% (95% CI 11, 17) vs. 13% (95% CI 10, 17)
Single Agent Chemotherapy		
Docetaxel	RCT docetaxel vs. vinorelbine/Ifosfamide (TAX320 trial)	mOS 5.7 vs. 5.6 mo (Risk Ratio, Mortality 0.82 (95% CI 0.63, 1.06)) mTTP 8.3 vs. 7.6 weeks ORR 5.7% (95% CI 2.3, 11.3) vs. 0.8% vs. (95% CI 0.0, 4.5)
Pemetrexed	RCT pemetrexed vs. docetaxel (study JMEDI)	Exploratory OS analysis by histology (non-squamous) mOS 9.3 vs. 8.0 [HR 0.89 (95% CI 0.71-1.13)]
Combination Therapy		
Docetaxel plus ramucirumab	RCT ramucirumab/docetaxel vs. placebo/docetaxel (REVEL study)	N=1253 mOS 10.5 vs. 9.1 m (HR 0.86 (95% CI 0.75, 0.98)) PFS 4.5 v.s 3.0 months [HR 0.76 (0.68, 0.86)] ORR 23% (95% CI 20, 26) vs. 14% (95% CI 11, 17)

*RCT, randomized, controlled trial

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

In addition to the breakthrough therapy designation requests for mobocertinib and amivantamab, described in Table 1, there have been two additional small molecules, (b) (4) and CLN-081 that have requested BTDR.

(b) (4)

On October 22, 2021, breakthrough therapy designation was requested for CLN-081, an oral TKI, for an indication similar to that being requested for DZD9008. BTDR was granted on December 24, 2021, for the treatment of patients with locally advanced or metastatic NSCLC harboring EGFR ex20ins mutations who have previously received platinum-based chemotherapy based on an ORR of 36% (95% CI 21, 54) in 36 patients treated at the RP2D, with a median DOR >15 months and 43% of patients with DOR ≥6 months..

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

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 design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Table 3. Clinical Trial Supporting the BTDR

Study ID	Trial Design	Treatment Group	Patient Group	Trial Endpoints
DZ2019E0001 Multiregional trial	Single-arm, study with two parts: Part A dose escalation (n=30)/dose expansion/food effect (n=90-110) Part B dose extension (n=206)	DZD9008 200 mg or 300 mg po daily for 28 day cycles Dose extension: Randomize patients to DZD9008 200 mg or 300 mg po daily for 28 day cycles	Locally advanced or metastatic NSCLC with EGFR Exon 20 insertion mutation, previously treated with ≥ 1 systemic therapy Locally advanced or metastatic NSCLC with EGFR Exon 20 insertion mutation previously treated with at least 1 and no more than 3 systemic chemotherapy	<u>Dose escalation:</u> safety and tolerability <u>Dose expansion:</u> ORR and DOR <u>Dose extension:</u> ORR and DOR
DZ2019E0002 China only	Single arm, dose escalation and dose expansion	DZD9008 Dose escalation (n=15-30) Dose expansion (n=30)	Locally advanced or metastatic NSCLC with EGFR Exon 20 insertion mutation previously treated with ≥ 1 systemic therapy	<u>Dose escalation:</u> safety and tolerability <u>Dose expansion:</u> ORR and DoR

The RP2D population supporting the BTDR includes 38 patients with advanced NSCLC with EGFR exon 20 insertion previously treated with platinum-based chemotherapy, treated at doses of 200 mg once daily (QD) (n=9) or 300 mg QD (n=29) in Study DZ2019E0002 and Part A of Study DZ2019E0001. Both of these doses have been selected as RP2Ds for further study (in Part B of Study DZ2019E0001).

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.

Table 4. Anti-tumor activity of DZD9008 in patients evaluable for response

Efficacy parameter	<u>RP2D BTD population</u> <u>N=38[‡]</u>	<u>RP2D (Platinum + IO naïve)</u> <u>N=24</u>
ORR by BICR, n (%) 95% CI	47% (31, 64)	42% (22, 63)
Number of responders	18	10
% with DOR ≥ 6mos	39%	50%

[‡] 200 mg (n=9), 300 mg (n=29); ORR was similar across both doses with overlapping 95% CI

Data cut-off date: July 30, 2021; CI = confidence interval

RP2D (platinum + IO naïve) is a subgroup of the 38 patients in the RP2D BTD population

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

The safety profile of DZD9008 is similar to other EGFR TKIs. The BTDR included safety data for 75 patients treated at the RP2Ds (n=18 at 200 mg QD, n=57 at 300 mg QD). The most common treatment-emergent adverse events (TEAEs) were diarrhea, rash, anemia, nausea, decreased appetite, paronychia, fatigue, vomiting, mouth ulceration, headache, pneumonia, dry skin and constipation. Grade ≥3 TEAEs were 22% at 200 mg QD and 53% at 300 mg QD. Grade ≥3 TEAEs occurring in ≥5% of patients treated at 200 mg QD were increased AST, increased ALT, increased lipase, and anemia (6% each). Grade ≥3 TEAEs occurring in ≥5% of patients treated at 300 mg QD were increased creatine phosphokinase (9%), anemia (9%), and diarrhea (5%). There were no discontinuations due to AE at 200 mg QD, while 10.5% of patients treated at 300 mg QD discontinued treatment due to AE.

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

GRANT:

Provide brief summary of rationale for granting:

The ORR of 47% (95% CI 31, 64) with DOR ≥6 months in 39% of responders among patients treated at the RP2Ds and ORR 42% (95% CI 22, 63) with DOR ≥6 months in 50% of responders in the subgroup of patients who received prior platinum-based chemotherapy but had not been previously treated with an anti-PD-(L)1 antibody immune checkpoint inhibitor demonstrate a substantial improvement over currently available second-line therapies. The ORR observed for DZD9008 is similar to the ORRs that supported BTD for both mobocertinib and amivantamab, which are currently approved under the accelerated approval pathway.

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):

The Sponsor plans to conduct Part B of their ongoing clinical trial Study DZ2019E0001 study, a randomized comparison of two different doses of DZD9008 (200 mg QD versus 300 mg QD), to potentially support an accelerated approval based on ORR. In addition, the Sponsor will be requesting a meeting with FDA to discuss proposal(s) for (b) (4)

a randomized study comparing DZD9008 to platinum-based chemotherapy in newly diagnosed (treatment-naïve) patients.

- 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:

1. Oxnard GR, Lo PC, Nishino M, Dahlberg SE, Lindeman NI, Butaney M, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. *J Thorac Oncol.* 2013;8:179-184.
2. Blumenthal GM, et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses. *J Clin Oncol.* 2015 Mar 20;33(9):1008-14.
3. Kobayashi Y, Mitsudomi T. Not all epidermal growth factor receptor mutations in lung cancer are created equal: Perspectives for individualized treatment strategy. *Cancer Sci.* 2016;107:1179-1186.
4. Yasuda H, Kobayashi S, Costa DB. EGFR exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinical implications. *Lancet Oncol.* 2012 Jan;13(1):e23-31. doi: 10.1016/S1470-2045(11)70129-2. Epub 2011 Jul 19. Erratum in: *Lancet Oncol.* 2011 Dec;12(13):1182.
5. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nat Rev Cancer.* 2006 Oct;6(10):803-12. doi: 10.1038/nrc1970. PMID: 16990857.

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 } Katie Chon
Team Leader Signature: { See appended electronic signature page } Erin Larkins, Supervisory Associate Director
(acting)
Division Director Signature: { See appended electronic signature page } Harpreet Singh

Revised 10/13/20 /M. Raggio

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/

WONME K CHON
01/24/2022 04:31:06 PM
electronically signed by Katie Chon, PharmD, RPh

ERIN A LARKINS
01/24/2022 05:51:26 PM

B HARPREET SINGH
01/24/2022 08:49:00 PM