CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219972Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 155685

MEETING PRELIMINARY COMMENTS

Bayer HealthCare Pharmaceuticals Inc.
Attention: Karen Mattessich, PharmD, MHS
Associate Director, Oncology Regulatory Affairs
100 Bayer Blvd
PO Box 915
Whippany, NJ 07981-0915

Dear Dr. Mattessich:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BAY 2927088.

We also refer to your correspondence dated and received November 8, 2024, requesting a meeting to discuss the top line results from the Phase 1/2 trial, Study 21607 (SOHO-01), and obtain the FDA's feedback on Bayer's plan of submitting a new drug application (NDA).

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

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	pre-sNDA
Meeting Date and Time:	January 6, 2025, 3:00pm—4:00pm EST
Meeting Location:	videoconference
Application Number:	155685
Product Name:	BAY 2927088
Indication:	Unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy
Sponsor Name:	Bayer HealthCare Pharmaceuticals Inc. (Bayer)
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Erin Larkins, MD, Director, Division of Oncology 2
Justin Malinou, MD, Cross-Disciplinary Team Lead
Yufan Liu, PharmD, Clinical Reviewer
Jeanne Fourie-Zirkelbach, PhD, Master Pharmacokineticist
Celine Wang, PhD, Clinical Pharmacology Reviewer
Claudia Miller, PhD, Nonclinical Team Lead
Emily Wearne, PhD, Nonclinical Reviewer
Flora Mulkey, MS, Biometrics Reviewer
Olen Stephens, PhD, Product Quality Team Lead
Damien Duveau, PhD, Product Quality Reviewer
Soma Ghosh, PhD, CDRH Team Lead
Rama Kamesh Bikkavilli, PhD, CDRH Reviewer

SPONSOR ATTENDEES

Nicoletta Brega, MD, Global Development Lead Clinical Precision Oncology
Eduard Gasal, MD, Therapeutic Area Head Oncology
Paolo Grassi, MD, Clinical Development Lead, Oncology
Lidia Mongay Soler, MD, PhD, MBA, Clinical Development Lead, Oncology
Alison Maloney, PhD, MBA, Head of Regulatory Affairs North America
Scott Greenfeder, PhD, Head of Oncology Regulatory Strategy Nucleus
Karen Mattessich, PharmD, MHS, US Regulatory Affairs Liaison
Vijaya Makhey, PhD, MBA, PMP, RAC, US Regulatory Affairs Liaison
Jens Leopold, PhD, Regulatory Affairs Strategy, Oncology
Kathleen Simon, PhD, Regulatory Affairs Strategy, IVD
Wendy Sikorski, BS, MBA, Regulatory Affairs, Chemistry, Manufacturing and Controls

Minghua (Michael) Shan, PhD, TA Expert Statistician, Oncology
Weichao Bao, PhD, Principal Statistician, Oncology
Su-Fen Pu, MD, PhD, Pharmacovigilance Benefit Risk Management, Oncology
Bonnie Brennan, PharmD, Clinical Pharmacology, Oncology
Jan Christoph Brase, PhD, Translational Sciences, Oncology

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 January 6, 2025, 3:00pm—4:00pm EST, videoconference between Bayer 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
On January 30, 2024, a Type B EOP1 meeting was held between Bayer and FDA. During the meeting discussion, FDA accepted Bayer's proposal to initiate the planned Phase 2 portion of the first-in-human (FIH) trial, Study 21607, using BAY 2927088 at a dosage of 20 mg twice daily (BID) while continuing to evaluate the 10 mg BID dosage. In addition, FDA advised that Bayer may consider submission of a marketing application based on data from Study 21607 once enrollment in Cohort D is complete with adequate follow-up to characterize duration of response, if there is a positive benefit:risk profile. FDA also stated that once enrollment in Cohort E is complete with adequate follow-up, Bayer could consider filing a separate application based on the results from this cohort.

On February 22, 2024, FDA granted breakthrough therapy designation for BAY 2927088 for the treatment of adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

On May 31, 2024, a Type B meeting was held between Bayer and FDA. During the meeting discussion, FDA acknowledged Bayer's commitment to provide additional follow-up data such that 6 months or greater duration of response information will be available for 100% of responders of Cohort D during the review period and noted that this approach would be acceptable. Bayer also noted that they anticipated having more

mature data for the HER2 antibody-drug conjugate (ADC) refractory population (Cohort E) in Q3 2025. Bayer clarified that they intend to submit these data as supportive for the same indication for patients with HER2 mutant NSCLC following prior systemic therapy. FDA noted that this HER2 ADC refractory population is a population with high unmet medical need and encouraged Bayer to submit objective response and duration of response data from Cohort E to the potential marketing application.

Nonclinical
BAY 2927088 is a kinase inhibitor that targets epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2), including HER2 exon 20 insertion mutations and HER2 point mutations. The nonclinical package for BAY 2927088 includes in vitro and in vivo pharmacology and pharmacokinetic (PK) studies, an in vitro hERG assay, repeat-dose toxicology studies up to 13 weeks duration in rats and cynomolgus monkeys, in vitro and in vivo genotoxicity studies, an in vitro phototoxicity study, and embryofetal development (EFD) studies in rats. Bayer also conducted an in vitro ReproTracker assay using human induced pluripotent stem cells and provided a weight-of-evidence (WOE) assessment for reproductive risk to supplement the rat EFD study. Bayer did not conduct EFD studies in rabbits because clinically relevant BAY 2927088 exposures were not achieved in dose range-finding studies in non-pregnant rabbits. FDA previously agreed to this approach at a Type B post-BTDR meeting on May 31, 2024. In addition, M1 (BAY 3306572) has been identified as a major human metabolite of BAY 2927088, and is present in vitro in human, mouse, rat, dog, and monkey hepatocytes. M1 has also been evaluated in pharmacology studies and was quantified in the 13-week toxicology studies.

Clinical Pharmacology
BAY 2927088 pharmacokinetics (PK) were evaluated in mass balance, food-effect, and drug-drug (DDI) studies. The mass balance study showed 83.6% of the dose was excreted in feces and 10.4% in urine, with a terminal half-life of 5-6 hours. Since Bayer states BAY 2927088 is a highly permeable compound, P-gp and BCRP transporters are not expected to impact absorption, so further P-gp and BCRP inhibitor studies are not planned. The primary metabolite, M1, binds to plasma proteins at a rate of 98.1% but is unlikely to contribute to clinical activity due to low systemic exposure.

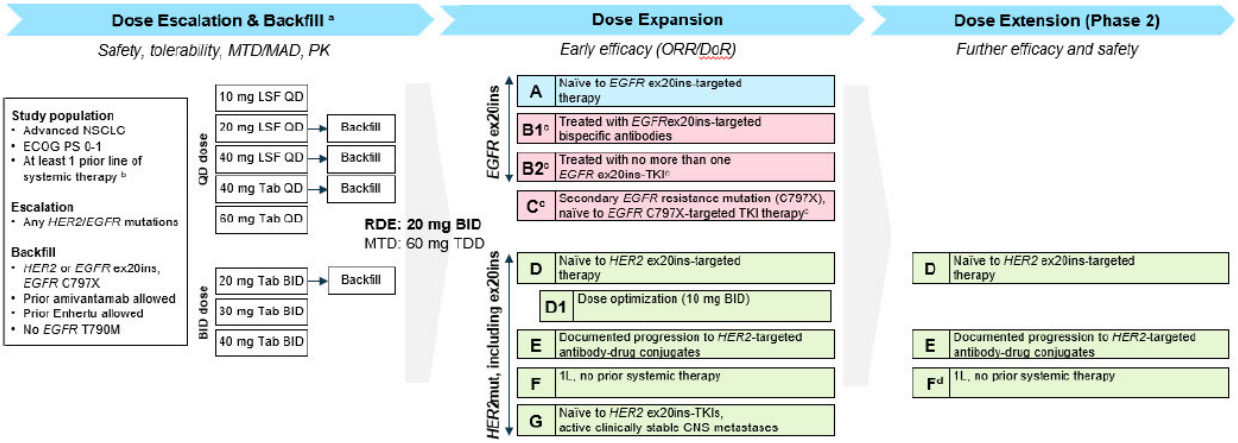
Food-effect studies demonstrated that AUC decreased by 16.1-27.6% and Cmax decreased by 27.8-55.7% with food, while Tmax was delayed to 2-4 hours. To minimize gastrointestinal side effects, the drug is taken with food, regardless of meal type (e.g., low- and high-fat meal). The acid-reducing agent (ARA) study demonstrated co-administration with esomeprazole delayed Tmax from 2 hours to 4 hours and decreased Cmax by 29.3% with no changes in AUC after a low-fat meal, supporting potential co-administration with ARAs.

DDI studies showed significant interactions of BAY 2927088 with CYP3A4 inhibitors and inducers. Itraconazole increased AUC by 125% and Cmax by 59.7%, while carbamazepine decreased AUC by 78.8% and Cmax by 57.1%, making concomitant

use with strong CYP3A4 inhibitors or inducers not recommended. BAY 2927088 also increased midazolam exposure, with AUC and Cmax increasing by 95.4% and 78.8%, respectively, after multiple doses. Dabigatran showed a 39% increase in AUC and rosuvastatin had a 24.9% and 36.7% increase in AUC and Cmax, respectively. This suggests caution should be used with concomitant use of BAY 2927088 and sensitive CYP3A4, P-gp, or BCRP substrates.

Clinical
Study 21607 (FIH study)

Study 21607 is an ongoing nonrandomized, open-label, single arm, FIH trial. The study consists of dose escalation, backfill, expansion and extension parts. A study design schema is presented below.



a: Dose Escalation: Starting dose 10 mg with min. 3 DLT evaluable participants/dose level; Backfill: max. 24 participants/cohort.
b: Except for Group F.
c: Development of Groups B1, B2 and C was deprioritized.
d. Dose Extension Group F is not applicable in the US.
Source: Figure 11-3 meeting materials

The primary objectives of the escalation, backfill and expansion parts of the study are to determine the safety and tolerability, determine the maximum tolerated dose (MTD) or maximum administered dose (MAD), and characterize the PK of BAY 2927088. The primary objective of the proposed dose extension part of the study is to determine the efficacy of BAY 2927088 by overall response rate (ORR) per RECIST v1.1 by blinded independent central review (BICR). The primary efficacy population for the proposed NDA would be from Cohort D (patients with NSCLC harboring HER2 activating mutations [including exon 20 insertion] who have received prior systemic therapy but were naïve to HER2 exon 20 insertion targeted therapy), while data from Cohort E (patients with advanced NSCLC harboring HER2 activating mutations who have received prior systemic therapy and had documented progression on HER2-targeted ADCs) would also be provided and considered supportive.

As of October 14, 2024, 136 patients treated with the 20 mg BID dose of BAY 2927088 were evaluable for efficacy in Cohorts D (81 patients) and E (55 patients). In Cohorts D and E, the majority of patients (94% and 78%, respectively) had received prior platinum-based chemotherapy with or without immunotherapy; 4% and 22% of patients in group D and E respectively did not receive immunotherapy or platinum-based chemotherapy. In Cohort D, the confirmed ORR by BICR was 61% (95% CI: 49, 71) with a median duration of response (DoR) of 6.8 months (95% CI: 5.2, 15). The median follow-up was 7.3 months. Based on Kaplan-Meier estimates, the proportion of responders with DoR ≥6 months was 56% (95% CI: [38, 73]), with DoR ≥9 months was 47% (95% CI: [29, 66]), and with DOR ≥12 months was 43% (95% CI: [24, 61]). Of note, 29 of 49 responders were censored at time of analysis.

In Cohort E, the confirmed ORR was 35% (95% CI: 22, 49) with a median DoR of 8.5 months (95% CI:.4.1, NE). The median follow-up was 5.7 months. Based on Kaplan-Meier estimates, the proportion of responders with DoR ≥6 months was 83% (95% CI: [60, 100]) and with DoR ≥9 months was 50% (95% CI: [12, 88]). Of note, 15 of 19 responders were censored at time of analysis.

A summary of the observed safety profile of the 20 mg BID dose (n=268) in Study 21607 is provided below.

Number of patients (%)	All patients receiving 20 mg BID (N=268)
≥Grade 3 TEAEs	45%
TESAEs	27%
TEAE leading to dose reduction	27%
TEAE leading to dose interruption/delay	42%
TEAE leading to discontinuation of study drug	2.2%

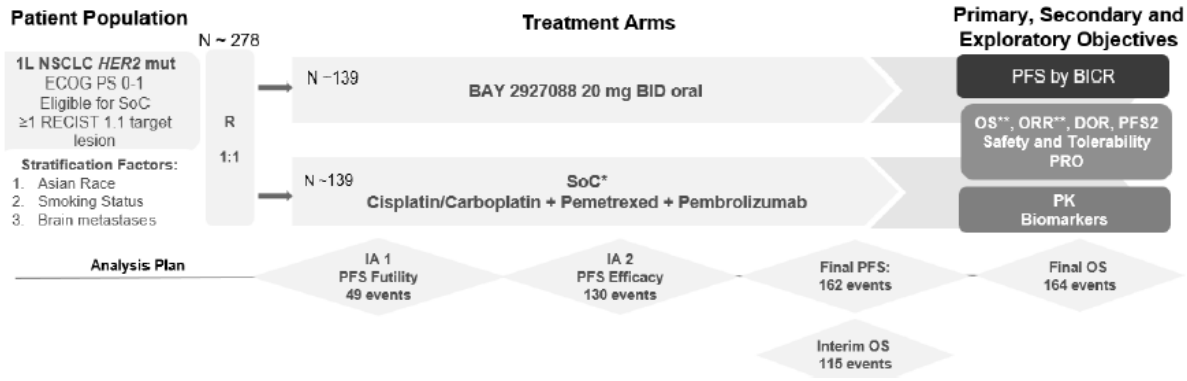
Source: Table 11-36 of Meeting Materials

The most common treatment-emergent adverse events (TEAEs) (≥20% of patients) with the 20 mg BID dose were diarrhea (86%), rash (45%), hypokalemia (27%), paronychia (23%) and stomatitis (21%). The most common Grade ≥3 TEAEs (≥5% of patients) with the 20 mg BID dose were diarrhea (15%) and hypokalemia (8%).

Regulatory Plan
Bayer intends to pursue an accelerated approval for BAY 2927088 with the following proposed indication with NDA submission planned in March 2025: BAY 2927088 is indicated for the treatment of adult patients with advanced NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. Bayer intends to request priority review and participation in Project Orbis (requesting Type A participation with Canada, Brazil, United Kingdom and Israel).

In order to verify the clinical benefit of BAY 2927088, Bayer is conducting Study 22615, an open-label, randomized trial to evaluate the efficacy and safety of BAY 2927088 in comparison to pemetrexed-platinum based chemotherapy with pembrolizumab as first-

line therapy in patients with locally advanced or metastatic non-squamous NSCLC, with an activating mutation in the HER2 tyrosine kinase domain. Approximately 278 patients with untreated locally advanced or metastatic nonsquamous NSCLC with HER2 activating mutations will be randomized 1:1 to receive BAY 2927088 or pemetrexed with platinum with pembrolizumab. A study design schema is presented below.



Source: Figure 11-10 meeting materials

For the original NDA, Bayer proposes to provide a 120-day (or 90-day if granted priority review) safety update report with a data cut-off of March 2025. Updated safety data will be provided along with narratives for patients with fatal TEAEs, treatment-emergent serious adverse events (TESAEs), Grade 3 and 4 TEAEs, and TEAEs leading to dose reduction and permanent discontinuation of treatment. Bayer anticipates nearly 100% of the current responders from Group D (based on the database cut-off date of October 14, 2024), will have at least 6 months of follow-up after the initial radiological response in Q2 2025. Bayer also expects having more mature ORR and DoR data from Cohort E by Q2 2025, with nearly all patients expected to have sufficient follow-up to assess potential DoR exceeding 6 months. Given this, Bayer plans to provide additional DoR data by BICR, along with the corresponding ORR data for the current responders as an addendum to the clinical study report (CSR) during the NDA review.

Bayer is working with Thermo Fisher Scientific Inc. to develop the Oncomine™ Dx Target Test (ODxTT; for formalin-fixed, paraffin-embedded [FFPE] tumor tissue samples) and the Oncomine™ Dx Express Test (ODxET; for FFPE tissue samples and liquid biopsy samples) as companion diagnostics (CDx) for BAY 2927088. The ODxTT CDx approval is planned to be concurrent with accelerated approval of the NDA for BAY 2927088, while the ODxET CDx will target an sPMA submission in approximately April 2025.

DISCUSSION OF FDA RESPONES TO SPONSOR QUESTIONS

Clinical Development

1. Does the Agency agree with the proposed indication “Treatment of adult patients with advanced NSCLC whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy”?

   FDA Response: A final determination regarding the wording of the indication statement will be made during the review of the NDA. To aid in our assessment of the appropriateness of the indication statement, in your NDA submission please provide the proportion of patients enrolled in Cohorts D and E who have squamous vs. nonsquamous histology along with efficacy data for these subgroups. In addition, please provide efficacy data for subgroups defined by prior treatments (i.e., prior platinum, immunotherapy) patients have received for Cohorts D and E.

2. Does the Agency agree that the clinical efficacy and safety data from Study 21607 are sufficient to support an NDA filing for BAY 2927088 for the proposed indication?

   FDA Response: The clinical efficacy and safety data appear reasonable to support an NDA filing. Please provide the proportion of responders with at least 6 months of follow-up after initial response from Cohorts D and E as of October 14, 2024 (the data cutoff date of the anticipated initial NDA filing). In addition, in your NDA submission (including in the Assessment Aid), when reporting DoR for Cohorts D and E, please provide the actual proportion of responders in each cohort with DoR ≥6 months, DoR ≥9 months, and DoR ≥12 months.

   In addition, we expect the confirmatory trial to be “underway” at the time of action for any accelerated approval application. To be considered "underway" prior to approval, the trial should have an FDA agreed-upon completion date that is consistent with diligent and timely conduct of the trial, considering the nature of the trial’s design and objectives, and show progress towards such date that provides sufficient assurance to expect timely completion of the trial. Given this, please provide the current status of enrollment along with estimated enrollment and readout projections for Study 22615.

3. Does the Agency agree with the proposed safety information to be provided in the 120-Day (or 90-Day if granted Priority Review) safety update report?

   FDA Response: Yes, your proposal appears reasonable.

4. Does the Agency agree that the additional follow-up efficacy data, that will be submitted as an addendum to the CSR for Group D, along with the safety data to be provided in the 120-Day (or 90-Day if granted Priority Review) update report, will be considered for the basis of approval and inclusion in the USPI?

   FDA Response: Yes, the additional follow-up efficacy and safety data will be necessary in our evaluation of benefit:risk and would be considered for the basis of approval and inclusion in the USPI.

5. The Sponsor has conducted a comprehensive clinical pharmacology study program to support the development of BAY 2927088. Does the Agency agree that the completed clinical pharmacology program is adequate to support an NDA filing?

   FDA Response: The clinical pharmacology program appears reasonable, with the following exception. Please provide a response with your plans for addressing the effect of weak and moderate CYP3A inhibitors and moderate CYP3A inducers to allow for adequate labeling in patients for whom concomitant use is needed. Please provide a timeline for completion of the ongoing hepatic impairment study. If the data from this study become available during the NDA review, please submit the preliminary results to inform labeling, even if the final study report will not be available. A final determination on the adequacy of the data to support the clinical pharmacology program will be made during the NDA review.

CMC

6. The Sponsor plans to submit 9 months of stability data for three primary stability batches along with stability data from supportive batches in the initial NDA in March 2025. An additional 3 months of stability data for the registration batches, 12 months in total according to ICH Q1A(R2), will be available during NDA review in June 2025. To confirm the shelf-life proposed in the NDA for the commercial drug product, is it acceptable for the Sponsor to submit the additional stability data at the end of June 2025?

   FDA Response: Yes, your proposal to submit the NDA with 9 months of stability data for the BAY 2927088 10 mg tablets in the initial NDA submission and a stability update in June 2025 is acceptable for filing the NDA. FDA commits to review all data available at the time of filing the NDA and data submitted after the filing date will be reviewed as resources allow. Shelf life will be granted on the basis of the available primary stability data as well as your ability to bridge supportive stability data.

Multidisciplinary

7. Does the Agency agree that the proposed content and organization of the planned NDA are acceptable and that there are no barriers to submission and filing?

   FDA Response: Your proposal appears generally reasonable. However, we could not locate your WOE assessment for reproductive risk in the proposed Table of Contents. Include this WOE assessment in Module 4.2.3.5 of the original NDA submission. In addition, if a large proportion of your enrolled population are from ex-US countries, please provide in your submission rationale for assuming the applicability of foreign data in the submission to the U.S. population.

8. The eCTD NDA submission will contain electronic datasets from Study 21607 and five healthy volunteer studies (22249, 22250, 22251, 22252, and 22253), as described in this pre-NDA briefing package. Does the Agency agree with the proposed scope, format, and documentation of the electronic datasets to be submitted?

   FDA Response: Your proposed scope appears reasonable. However, based on a study start date of October 25, 2021, it appears that you should be using ADaMIG v1.1 for Study 21607. Please refer to the Data Standards Catalog for appropriate versions of SDTM, ADaM, STDMIG and ADaMIG based on trial start dates for each of the trials being submitted: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-standards-catalog.

9. Does the Agency support the Sponsor's request for participation in Project Orbis based on the clinical data from Study 21607 and agree with the Global Submission Plan as presented for Project Orbis?

   FDA Response: We agree it is reasonable to request participation in Project Orbis. Regarding the global submission plan, this is determined by the applicant.

10. Does the Agency agree with the Sponsor's approach to use "BAY 2927088" in the initial submission documents, with the intention to provide the International Nonproprietary Name (INN)/United States Adopted Names (USAN) once it becomes available, given that approval and public release are anticipated by the end of March 2025?

    FDA Response: Yes, your approach appears reasonable.

Nonclinical Development

11. The Sponsor has conducted a comprehensive non-clinical study program to support the development of BAY 2927088. Does the Agency agree that the completed non-clinical program is adequate to support an NDA filing?

FDA Response: The completed nonclinical program appears sufficient to support the filing of an NDA for the proposed indication. We will make a final determination of the acceptability of the nonclinical data to support the filing of an NDA during review of the original NDA submission.

Additional FDA Comments

Clinical Pharmacology

The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format. Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Address the following questions in the Summary of Clinical Pharmacology:

12. What is the basis for selecting the recommended dosage used in the trials intended to support your marketing application? Include a description of the translational evidence, pharmacokinetics, safety, efficacy, dose-response/exposure-response and other information used to support dosage selection as described in the Oncology Dosing Tool Kit.

13. What is the effect of BAY 2927088 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 dosage modifications are recommended?

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

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 with central tendency and intersubject/patient variability or median with maximum and minimum 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.

    a. 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.

    b. Identify individual subjects with dosage modifications; the time to the first and subsequent dose reduction, interruption or discontinuation; and the reasons for dosage modifications in the datasets.

20. Submit the following for the population pharmacokinetic analysis reports:

    a. Standard model diagnostic plots

    b. Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.

    c. Model parameter names and units in tables.

    d. Summary of the report describing the clinical application of modeling results.

    e. Refer to the following pharmacometric data and models submission guidelines.

21. Submit the following information and data to support the population pharmacokinetic analysis:

    a. SAS transport files (*.xpt) for all datasets used for model development and validation.

    b. 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.

c. 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, safety and tolerability) 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.

25. Include the purpose of the simulations, assumptions, detailed process of PBPK model building and verification, summary of model input parameters, version of software, simulation results, and conclusions in the study report.

26. Provide the study report as PDF files (screenshots can be incorporated if required).

27. Include the model files used to generate the final PBPK simulations. These files should be executable by FDA reviewers using the specified software.

28. Include appropriate supporting documentations such as any special instructions and file definitions.

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.[2]

FDARA REQUIREMENTS

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

Sponsors 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.[3]

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 Information[4] and Pregnancy and Lactation Labeling Final Rule[5] 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

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

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

randomization ratio imbalances, study populations, etc.).

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

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

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

SECURE EMAIL COMMUNICATIONS

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

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

INDs not in eCTD format).

ONCOLOGY PILOT PROJECTS

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

- RTOR.[8] In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[9]

REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.*[10] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

[8] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[9] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project
[10] https://www.fda.gov/media/124795/download

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
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CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	155685
Request Receipt Date	December 21, 2023
Product	BAY 2927088
Indication	Treatment of adult patients with unresectable or metastatic non small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy
Drug Class/Mechanism of Action	HER2 and EGFR Tyrosine Kinase Inhibitor (TKI)
Sponsor	Bayer
ODE/Division	OOD/Division of Oncology 2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	February 19, 2024

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

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

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

   BAY 2927088 is indiated for the treatment of adult patients with unresectable or metastatic non small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy.

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

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

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

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

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

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 therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

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

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

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

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

Deny Breakthrough Therapy Designation ☐

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

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

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

Drug Description

According to the Sponsor, BAY 2927088 is a reversible tyrosine kinase inhibitor that inhibits mutated HER2 and EGFR receptors. BAY 2927088 displays high potency towards HER2 ex20ins mutations and HER2 point mutations.

Information regarding unresectable or metastatic HER2 mutated NSCLC and the intended population for the proposed indication

Lung cancer is the second leading cause of cancer and leading cause of cancer-related mortality worldwide[1] and the leading cause of cancer-related deaths in the US[2].

Approximately 40% of lung cancers are of adenocarcinoma histology[3]. HER2 activating mutations are oncogenic driver mutations in approximately 2 – 4% of lung adenocarcinomas and are typically mutually exclusive from other driver oncogenic aberrations[4]. HER2 mutations are most common in patients who are Asian, women, and nonsmokers.

The drug's relation to existing therapy(ies)

Currently there is no available targeted therapy for patients with NSCLC with activating HER2 mutations who have a received a prior systemic therapy. There is one targeted therapy (fam-trastuzumab deruxtecan-nxki [trastuzumab deruxtecan]) that has been granted accelerated approval for patients with NSCLC with activating HER2 mutations who have a received a prior systemic therapy.

Refer to Section 9 below for a summary of conventional systemic therapies that are currently available for NSCLC regardless of HER2-mutation status.

Relevant regulatory history

None

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.

Overall response rate (ORR) per RECIST v1.1 and duration of response (DoR) from the Sponsor's open label, single arm, multi-cohort Phase 1 study were submitted to support this breakthrough therapy designation.

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.*

Both overall survival and progression-free survival have been used to support approvals in NSCLC. Additionally, clinically meaningful overall response rate (ORR) with adequate duration of response has been considered a

predictor of clinical benefit and has been used to support accelerated approvals. In cases of tumors with low incidence, including NSCLC harboring less common genomic tumor aberrations, ORR of large magnitude associated with durable responses has been accepted to support traditional approval

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.*

Conventional therapies used in clinical practice

Currently there are no available targeted therapies under traditional approval for patients with HER2 mutated NSCLC.

Patients with advanced NSCLC and tumors harbouring HER2 mutations are treated with conventional systemic therapies that are available for NSCLC irrespective of HER2 mutation status, including first-line platinum-based chemotherapy and/or an anti-PD(L)1 antibody. There is conflicting data on whether patients with tumors with driver mutations benefit from immunotherapy.

Upon progression, subsequent available therapies include: single agent anti-PD(L)1 antibody (e.g., nivolumab, pembrolizumab if not received in frontline) and single agent chemotherapy (e.g., docetaxel) or docetaxel in combination with ramucirumab. A summary of trials and endpoints are shown in the following tables below.

Table 1. Biologics/Drugs for 2nd-line Metastatic NSCLC

	Clinical Trial	Endpoints (with 95% CI)
Single Agent Checkpoint Inhibitor		
Pembrolizumab	RCT of pembrolizumab vs docetaxel for PD-L1 positive metastatic NSCLC (KEYNOTE-010) N=689	Pembrolizumab 10 mg/kg vs. docetaxel mOS **12.7** vs. 8.5 mo (HR 0.61 [0.49, 0.75]) mPFS **4** vs. 4 mo (HR 0.79 [0.66, 0.94]) ORR **19% (15, 23)** vs. 9% (7, 13)
Single Agent Chemotherapy		
Docetaxel	RCT sotorasib vs. docetaxel (Codebreak 200) N=345	mOS 10.6 vs. **11.3** mo (HR 1.01 [0.77, 1.33]) mPFS 5.6 vs. **4.5** mo (HR 0.66 [0.51, 0.86]) ORR 28% (22, 35) vs. **13% (9, 19)**
Combination Therapy		
Docetaxel plus ramucirumab	RCT Ramucirumab/docetaxel vs. placebo/docetaxel (REVEL) N=1253	mOS **10.5** vs. 9.1 mo (HR 0.86 [0.75, 0.98]) mPFS **4.3** vs. 3 mo (HR 0.76 [0.68, 0.86]) ORR **23% (20, 26)** vs. 14% (11, 17)

Targeted therapies under accelerated approval

Trastuzumab deruxtecan has received accelerated approval for the treatment of unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA-approved test, and who have received a prior systemic therapy. Approval was based on a non-randomized multi-cohort study of 52 patients in which trastuzumab deruxtecan demonstrated a confirmed ORR of 58% (95% CI 43, 71) and median DoR of 8.7 months (95% CI 7.1, not estimable [NE]).

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

Trastuzumab deruxtecan received breakthrough therapy designation in patients with metastatic NSCLC whose tumors have a HER2 mutation and had disease progression on or after platinum-based therapy on May 14, 2020. Data to support the breakthrough designation were derived from an ongoing, open-label, parallel-cohort study. Objective responses were observed in 16 of 38 patients (ORR 42%, 95% CI 26, 59). The median DoR was NE with 31% of patients experiencing a response of ≥ 6 months. All patients received prior platinum-based chemotherapy.

11. Information related to the preliminary clinical evidence:

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

Data to support this BTDR are from the ongoing Phase I 21607 study, which was designed to evaluate the safety, preliminary efficacy and determine the maximum tolerated dose of BAY 2927088 in patients with locally advanced or metastatic NSCLC. The study is comprised of multiple expansion cohorts including patients with NSCLC harboring an activating HER2 mutation. All patients enrolled must have had disease progression on at least 1 prior systemic therapy for advanced disease. BAY 2927088 was administered orally daily at a dose of 20 mg twice daily for these patients.

As of a cut of date of December 4, 2023, of the 65 total patients enrolled, 59 patients were included in the efficacy analysis set (enrolled patients who had 1 post baseline efficacy assessment). Of the 59 patients, 42 patients were naïve to HER2 ex20ins mutation therapy and 17 received previous treatment with HER2 ADC therapy. Of the 42 patients who were naïve to HER2 ex20ins mutation therapy, 41 received prior platinum-based chemotherapy with or without immunotherapy and 1 patient received prior immunotherapy only. Of the 17 patients who received previous treatment with HER2 ADC therapy, 12 received prior platinum-based chemotherapy with or without immunotherapy.

Table 2. Clinical Data Supporting BTDR

Studies	Trial Design(s)	No. of Patients	Treatment	Results to support BTD
21607	Multiple cohort, activity estimating	59 patients N=42; NSCLC patients with HER2 activating mutations naïve to HER2 ex20ins targeted therapy (HER2 treatment naïve)	BAY 2927088 20 mg orally twice daily	ORR and mDoR for HER2 treatment-naïve: 69% (95% CI: 53, 82) and 5.3 mos. (95% CI: 3.1, NE) ORR and mDoR for HER2 previously treated: 24% (95%

[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.

		N=17; NSCLC patients with HER2 activating mutations treated with prior HER2 targeting ADCs (Prior HER2 treatment)		CI: 7, 50) and NE (all responses ongoing)

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.*

ORR was consistent between patients who received prior platinum without immunotherapy and prior platinum with immunotherapy. Although cross-trial comparisons of single-arm data have inherent limitations, these outcomes compare favorably to existing available therapies under traditional approval described in Table 1.

Of the 17 patients who were previously treated with HER2 ADCs, 4 (ORR 23%, 95% CI, 7, 50) patients had a confirmed response. The median duration of response was not calculable as all responses were ongoing at the time of the data cut-off. All 4 responders had received prior platinum-based chemotherapy.

Safety data were provided for 105 patients from the expansion cohorts who received BAY 2927088 at the 20 mg twice daily dose. Of the 105 patients, 41% experienced Grade ≥3 treatment emergent adverse events (TEAEs) including 6% of patients experiencing a fatal TEAE. Of the fatal TEAEs, half were considered due to disease progression and none were assessed as related to study treatment by investigator. In addition, 3% of patients experienced a TEAE resulting in treatment discontinuation. The most common TEAEs (all grade ≥20%) were diarrhea (81%), Rash (34%), Nausea (27%), Paronychia (23%), Decreased appetite (21%) and Dry skin (20%).

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

☒ GRANT:

Provide brief summary of rationale for granting:

The Division notes that currently there is no available targeted therapy for patients with HER2 mutated NSCLC. The Division considers the ORR of 69% (95% CI 53, 82) with a median DoR of 5.3 months (95% CI: 3.1, NE) in patients who have progressed on at least 1 prior systemic therapy and are naïve to HER2 exon20ins therapy to be preliminary clinical evidence of a substantial improvement over currently available therapies. The ORR of 24% (95% CI 7, 50) in patients who have progressed on at least 1 prior systemic therapy and received previous treatment with a HER2 ADC comprise a smaller population, but are supportive and represent a population of interest that warrants further evaluation.

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 Division supports the Sponsor's ongoing efforts to continue enrollment in Study 21607 to further characterize the safety and efficacy of BAY 2927088. In meeting materials provided for a January 30, 2024 Type C meeting, the Sponsor intends to work towards a potential accelerated approval once an adequate number of patients in both treatment populations are enrolled in Study 21607 with adequate follow-up for duration of response. The Sponsor plans to conduct a confirmatory Phase 3 trial in a 1st line treatment-naïve patients with HER2 mutant metastatic NSCLC indication. The Division looks forward to providing advice on the Sponsor's development plan.

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. WHO, GLOBOCAN 2018: Estimated Cancer, Incidence, Mortality and Prevalence Worldwide in 2020. http://gco.iarc.fr/today/home
2. NCI, Surveillance, Epidemiology, and End Results Program: Cancer Stat Facts, 2023 https://seer.cancer.gov/statfacts/html/lungb.html
3. Chen Z at al. Non-small-cell lung cancers: a heterogeneous set of diseases. *Nat Rev Cancer*, Aug 1, 2014; 14 (8): 535-546
4. Hirsch FR et al. Lung cancer: current therapies and new targeted treatments. *Lancet*, January 21, 2017; 389 (10066): 299-311.
5. Mazieres J et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. *J Clin Oncol*. June 1, 2013; 31(16): 1997-2003.

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

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

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

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

Revised 10/13/20 /M. Raggio

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

/s/

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