

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218213Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 130465

MEETING MINUTES

Turning Point Therapeutics, Inc.
Attention: Naresh Nayyar, Ph.D., M.B.A., R.A.C.
Vice President Regulatory Affairs
10628 Science Center Drive, Suite 200
San Diego, California, 92121

Dear Dr. Nayyar:¹

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

We also refer to the teleconference between representatives of your firm and the FDA on June 27, 2022. The purpose of the meeting was to discuss your potential new drug application (NDA) submission package and strategy with the Agency.

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

If you have any questions, call me at 240-402-4558 or email opeyemi.udoka@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Opeyemi Udoka DPT, CSM
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic
Diseases for Division of Oncology 2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

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>.

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Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: June 27, 2022, 12:00PM - 1:00PM EST
Meeting Location: Teleconference
Application Number: 130465
Product Name: Repotrectinib (TPX-0005)
Indication: for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) whose tumors are *ROS1*-positive
Sponsor Name: Turning Point Therapeutics, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair: Paz Vellanki
Meeting Recorder: Opeyemi Udoka

FDA ATTENDEES

Harpreet Singh, M.D., Director, Division of Oncology 2 (DO2)
Paz Vellanki, M.D., Ph.D., Acting Cross Disciplinary Team Leader, DO2
Katie Chon, Pharm. D., Clinical Reviewer, DO2
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader, Division of Cancer Pharmacology II (DCPII)
Xiling Jaing, Ph.D., Clinical Pharmacology Reviewer, DCPII
Pallavi Mishra-Kalyani, Ph.D., Biostatistics Team Leader, Division of Biometrics (DBM)
Yi Ren, Ph.D., Biostatistics Reviewer, DBM
Opeyemi Udoka, D.P.T., Regulatory Health Project Manager, Division of Regulatory Operations for Oncologic Diseases (DRO-OD)

SPONSOR ATTENDEES

Athena Countouriotis, M.D., President and Chief Executive Officer
Mohammad Hirmand, M.D., Executive Vice President and Chief Medical Officer
Homa Yeganegi, Senior Vice President, Program Team Leader and Head, Medical Affairs
Naresh K. Nayyar, Ph.D., M.B.A., R.A.C., Senior Vice President, Regulatory Affairs & Quality Assurance
Sybille Sauter, Ph.D., Executive Director, Regulatory Affairs
Ming Lu, Ph.D., Vice President, Clinical Pharmacology
Milbhor D'Silva, M.D., M.P.H., Vice President, Drug Safety
Wilson Wu, Ph.D., Senior Vice President, Biometrics
Armin Graber, Ph.D., Senior Vice President, Companion Diagnostics & Biomarkers
Minal Mehta, M.B.B.S., Executive Director, Clinical Development
Shanna Stopatschinskaja, M.D., Senior Medical Director, Clinical Development
Justine Lam, Ph.D., Executive Director, Clinical Pharmacology

Denise Trone, Executive Director, Biostatistics

BACKGROUND

On April 27, 2022, Turning Point Therapeutics, Inc., (Turning Point) submitted a meeting request to provide topline safety and efficacy data for repotrectinib, and to discuss their potential new drug application (NDA) submission package and strategy with FDA. The meeting package was received on May 27, 2022.

Regulatory

FDA granted Fast Track designation for repotrectinib for the following indications:

- On December 16, 2019, for the treatment of patients with *ROS1*-positive advanced non-small cell lung cancer (NSCLC) who have had disease progression following one prior line of platinum-based chemotherapy and one prior line of a *ROS1* tyrosine kinase inhibitor (TKI).
- On May 12, 2020, for the treatment of patients with *ROS1*-positive advanced NSCLC who have not been treated with a *ROS1* TKI.
- On August 21, 2020, for the treatment of patients with advanced solid tumors that have an NTRK gene fusion who have progressed following treatment with at least one prior line of chemotherapy and one or two prior TRK tyrosine kinase inhibitors and have no satisfactory alternative treatments.
- On August 10, 2021, for the treatment of patients with *ROS1*-positive advanced NSCLC who have been previously treated with one *ROS1* TKI and who have not received prior-platinum-based chemotherapy.

FDA granted Breakthrough Therapy designation for repotrectinib for the following:

- On December 7, 2020, for the treatment of patients with *ROS1*-positive metastatic NSCLC who have not been treated with a *ROS1* TKI.
- On May 9, 2022, for treatment of patients with *ROS1*-positive metastatic NSCLC who have been previously treated with one *ROS1* TKI and who have not received prior platinum-based chemotherapy

Clinical

TPX-0005-01 (TRIDENT-1): dose escalation, dose expansion multicohort study in patients with advanced NSCLC and solid tumors

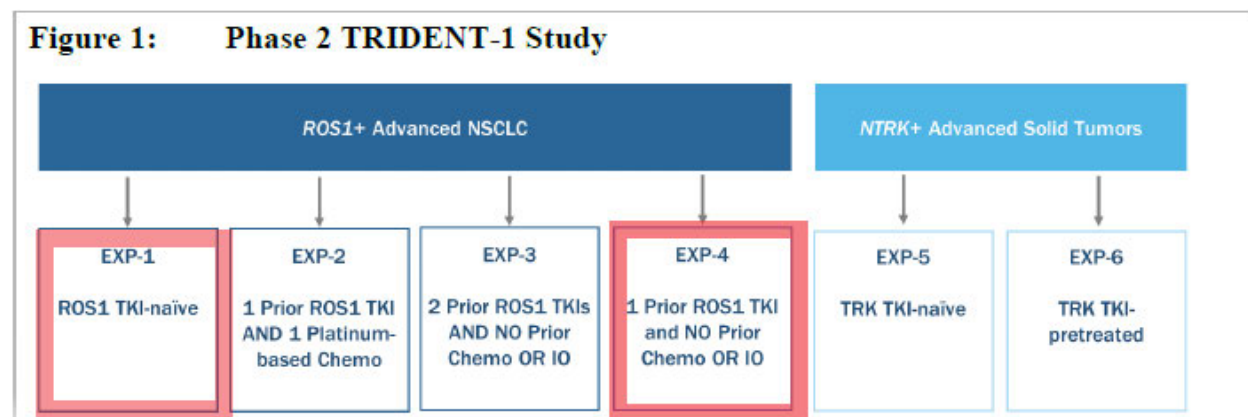
TRIDENT-1 is an ongoing, multicenter, dose escalation, dose expansion trial of repotrectinib in patients with advanced solid tumors harboring *ROS1*, *ALK*, or *NTRK* rearrangements. This is a multiregional clinical trial with patients enrolled from North America, Asia, Western Europe, and Australia. Based on a data cutoff date of January 24, 2022, enrollment to the dose expansion part of the TRIDENT-1 study was highest

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from the U.S. (25% of treated patients), China (17% of treated patients), and South Korea (17% of treated patients).

For the phase 1 dose escalation, food effect, and midazolam drug-drug interaction substudies, patient eligibility for malignancies harboring ALK, ROS1, NTRK1, NTRK2, or NTRK3 gene rearrangements were assessed using local laboratory tests (i.e., NGS, FISH, or IHC). In the phase 2 dose expansion cohorts, tumor tissue was required for either prospective or retrospective central laboratory testing for ROS1 or NTRK1-3 gene fusion. The primary objectives of the phase 1 part of the study were to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of repotrectinib for the treatment of patients with solid tumor malignancies harboring ALK, ROS1, NTRK1, NTRK2, or NTRK3 molecular rearrangement. The primary objective for the multi-cohort expansion part of the study is to determine the confirmed overall response rate (ORR) as assessed by blinded independent central review (BICR) using RECIST v1.1 in each cohort.

Eligibility for individual cohorts is restricted by tumor type (NSCLC or other solid tumors), specific oncogenic driver molecular rearrangement (ROS1 or NTRK), and prior therapy (see study schema below). As of the data cutoff date of February 11, 2022, a total of 380 patients were enrolled into TRIDENT-1.



Source: adapted from page 36 from meeting background package

The Sponsor indicated the RP2D for repotrectinib is 160 mg once daily (QD) for the first 14 days followed by increase to 160 mg twice daily (BID). TP Therapeutics intends to use a data cutoff date of June 20, 2022 and provide two pooled efficacy populations. The first pooled efficacy data will be from 71 TKI-naïve patients with ROS1-positive NSCLC (expansion cohort 1) with measurable disease and at least 6 months of follow-up from first post-baseline scan (or discontinued from study treatment) to support a marketing application. This population will include 8 patients from phase 1, and 63 patients from phase 2. In the second pooled efficacy data will be from 56 patients with 1 prior ROS1 TKI and no prior platinum-based chemotherapy (expansion cohort 4). This population will include 3 patients from phase 1, and 53 patients from phase 2.

As supportive data, TP Therapeutics intends to provide efficacy data from 26 patients with 1 prior ROS1 TKI and 1 prior line of platinum-based chemotherapy (expansion cohort 2) and 18 patients with 2 prior ROS1 TKIs and no prior platinum-based chemotherapy (expansion cohort 3).

In the meeting package, TP Therapeutics presented their efficacy from expansion cohorts 1 and 4 and the safety data from a data cutoff date of February 11, 2022.

	ROS1-positive TKI naive (n=71)	1 prior ROS1 TKI and no prior chemotherapy or anti- PD-(L)1 antibody (n=56)
ORR, % (95% CI) ^a	79% (68, 88)	36% (23, 50)
CR, %	6%	7%
PR	73%	29%
DOR, months (95% CI)	26.7 (14.8, 34.1)	17.8 (7.5, NE)
DOR ≥6 months	73%	57%
DOR ≥9 months	64%	Not provided
DOR ≥12 months	55%	Not provided

^a ORR by BICR and principal investigator

The most common (≥20%) adverse events reported among the 287 RP2D population include anemia (33%), increased ALT (23%), increased AST (22%), dyspnea (25%), fatigue (23%), and nausea (20%). In the safety data in a total of 380 patients, there were 21 patients (5.5%) who experienced TEAEs with a maximum severity of grade 4. There were 20 patients (5.3%) who experienced fatal (grade 5) TEAEs. TEAEs which lead to dose reduction occurred in 32% of patients and 10% of TEAEs which led to dose discontinuation.

Below is a summary of the number of patients intended to support the evaluation of safety in the marketing application.

	Number of patients ^a	Description
TRIDENT-1	380	All patients with at least 1 dose of repotrectinib
	287 ^b	All patients with at least 1 dose of repotrectinib at the RP2D (160 mg QD for 14 days followed by 160 mg BID)
	218 ^c	All patients with ROS1-positive NSCLC with at least 1 dose of repotrectinib at the RP2D

^a Data cutoff date: February 11, 2022

^b 236 (82%) of patients received repotrectinib 160mg QD for the first 14 days with their dose subsequently increased to 160 mg BID.

^c 56 of 71 patients (79%) who are TKI-naïve and 80 of 100 patients (80%) who are TKI-pretreated patients have had their dose titrated from 160 mg QD to 160 mg BID.

TP Therapeutics is developing a [REDACTED] (b) (4)

TPX-0005-07 (CARE): dose escalation, dose expansion multicohort study in pediatric and young adults with advanced or metastatic solid tumors, primary CNS tumors, or anaplastic large cell lymphoma (ALCL) with ALK, ROS1, or NTRK alterations

The CARE study is a dose escalation, dose expansion, multicohort study in pediatric and young adults with advanced or metastatic solid tumors, primary central nervous system (CNS) tumors, or anaplastic large cell lymphoma (ALCL) with ALK, ROS1, or NTRK alterations. The primary objective of the dose escalation is to estimate the MTD or maximum administered dose (MAD) and select the pediatric RP2D. The primary objective of the dose expansion is to determine efficacy in pediatric and young adult patients with advanced or metastatic solid tumors, primary central nervous system (CNS) tumors, or anaplastic large cell lymphoma (ALCL) with ALK, ROS1, or NTRK alterations. The study is anticipated to enroll approximately 75 pediatric and young adult patients. As of the data cutoff date of February 11, 2022, a total of 14 patients have been enrolled.

FDA sent Preliminary Comments to Turning Point on June 14, 2022, on June 17, 2022, Turning Point responded and requested to further discuss question 1.

SPONSOR QUESTIONS AND FDA RESPONSES

1. Does the Agency agree that the results from the registrational Phase 1/2 TRIDENT-1 study for repotrectinib provide an adequate basis for approval for an indication relating to the treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC?

FDA Response: We agree with your proposal to submit a marketing application based on your proposed data cutoff date of June 20, 2022. Please confirm that all patients in Phase 1 and Phase 2 of TRIDENT-1 who received at least one dose of repotrectinib are included in the analysis of ORR.

Whether the results from cohorts 1 and 4 of the TRIDENT-1 study will support approval for a specific indication will be determined during the review of the new drug application.

Turning Point Therapeutic Inc's email response on 6/17/22: The Sponsor confirms that the primary efficacy population includes all patients dosed with at least one dose of repotrectinib on or before 15 October 2021 from Phase 1 and Phase 2 of the TRIDENT-1 study who meet the pooling criteria as outlined in the Integrated SAP, shared with the Agency on 20 January 2022. As referenced in the Integrated SAP and in Question #2 and acknowledged by FDA, the pooling

criteria for Phase 1 include similar eligibility criteria of Phase 2, including next-generation sequencing confirmation testing for ROS1 positivity and prior anti-cancer treatments.

Discussion During the 6/27/22 Teleconference: FDA inquired if there are any patients either within Phase 1 or Phase 2, cohorts 1 and 4, who do not meet criteria for inclusion in the primary efficacy population. Turning Point proposed to include patients from Phase 1 and patients from Phase 2. There were patients in Phase 1 who did not meet pooling requirements for the Primary Efficacy population, as they did not have NGS confirmation of the ROS1 alteration. FDA agreed this approach appears reasonable.

2. As referenced in the Integrated Statistical Analysis Plan previously reviewed by the Agency, does the Agency concur with the proposal for the following data integration for the NDA?

FDA Response: The proposed safety populations and plan for pooling efficacy data appear reasonable.

Turning Point Therapeutic Inc's email response on 6/17/22: The Sponsor acknowledges the FDA's comment. No further discussion is needed.

Discussion During the 6/27/22 Teleconference: No discussion occurred.

3. As previously discussed in the Type B Meeting held on 12 April 2021 (Ref ID: 4778104), does the Agency concur that the (b) (4) drug interaction study (b) (4) which evaluates the effects of repotrectinib on the pharmacokinetics of (b) (4) and the hepatic impairment study (protocol TPX-0005-15), which evaluates the pharmacokinetics of repotrectinib in patients with impaired hepatic function, can be submitted as a post-marketing commitment?

FDA Response: It is FDA's expectation that the above-mentioned hepatic impairment study and the DDI study should be complete prior to the NDA submission in order to inform labeling for the specific population. For clinical pharmacology studies that are not be completed prior to NDA submission, adequate information on when, how, and why these studies are not completed, should be included in the NDA submission. The status of any ongoing clinical pharmacology studies should also be provided. The adequacy of the clinical pharmacology package to support an NDA filing will be determined at the time of NDA review.

Turning Point Therapeutic Inc's email response on 6/17/22: The Sponsor acknowledges the FDA's comment. No further discussion is needed.

Discussion During the 6/27/22 Teleconference: No discussion occurred.

4. The Sponsor proposes to use the Summaries of Clinical Efficacy (SCE) and Clinical Safety (SCS) as the narrative portions of the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), respectively. Does the Agency agree with this approach?

FDA Response: Yes, your approach appears reasonable.

Turning Point Therapeutic Inc's email response on 6/17/22: The Sponsor acknowledges the FDA's comment. No further discussion is needed.

Discussion During the 6/27/22 Teleconference: No discussion occurred.

5. Can the Agency confirm that with the agreed initial pediatric study plan, pre-submission pediatric requirements per the amendments made by the FDA Reauthorization Act of 2017 (FDARA) Section 504 to Section 505B of the Federal Food, Drug, and Cosmetic Act regarding molecularly targeted oncology drugs have been met?

FDA Response: The agreed initial pediatric study plan agreement letter dated December 15, 2021, would need to be submitted with your NDA and a determination will be made during the review.

Turning Point Therapeutic Inc's email response on 6/17/22: The Sponsor acknowledges the FDA's comment. No further discussion is needed.

Discussion During the 6/27/22 Teleconference: No discussion occurred.;

6. Considering the top line results presented for the proposed indication and that repotrectinib has received two Breakthrough Therapy Designations in ROS1-positive NSCLC patients, the Sponsor seeks participation in the RTOR program for the NDA. The Sponsor plans to submit a formal request to be considered for participation in the RTOR program after the data for the NDA submission become available. Does the Agency agree with this approach?

FDA Response: Yes, your approach appears reasonable.

Turning Point Therapeutic Inc's email response on 6/17/22: The Sponsor acknowledges the FDA's comment. No further discussion is needed.

Discussion During the 6/27/22 Teleconference: No discussion occurred.

Additional Clinical Pharmacology Comments

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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” (available at: <https://www.fda.gov/media/74346/download>). 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:

7. 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.
8. What are the exposure-response relationships for efficacy, safety and biomarkers?
9. What is the effect of repotrectinib on the QT/QTc interval?
10. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
11. 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.
12. 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:

13. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
14. 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.
15. 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.
16. 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>.

17. 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)
18. 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](#).
19. 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.

20. 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
21. Include the following items when you submit your PBPK study report:
 - 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.
 - Provide the study report as PDF files (screenshots can be incorporated if required).
 - Include the model files used to generate the final PBPK simulations. These files should be executable by FDA reviewers using the specified software.
 - Include appropriate supporting documentations such as any special instructions and file definitions.
22. Include the following items when you submit your QT study report:
 - a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
 - b. Electronic copy of the study report
 - c. Electronic or hard copy of the clinical protocol
 - d. Electronic or hard copy of the Investigator's Brochure
 - e. Annotated CRF
 - f. A data definition file which describes the contents of the electronic data sets
 - g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
 - h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
 - i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
 - j. Narrative summaries and case report forms for any:
 - i. Deaths
 - ii. Serious adverse events

- iii. Episodes of ventricular tachycardia or fibrillation
- iv. Episodes of syncope
- v. Episodes of seizure
- vi. Adverse events resulting in the subject discontinuing from the study
- k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- l. A completed Highlights of Clinical Pharmacology Table

Advancing in this field – and possibly reducing the burden of conducting QT studies – depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at <http://cardiac-safety.org/ecg-database/>.

Turning Point Therapeutic Inc's email response on 6/17/22: The Sponsor acknowledges the FDA's Additional comments and Advice sections.

Discussion During the 6/27/22 Teleconference: No discussion occurred.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- FDA will make a final determination regarding the need for REMS during the review of the NDA.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry/multidiscipline pre-submission meeting is scheduled for June 28, 2022. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

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

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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.

We acknowledge your November 16, 2021, submission of an Agreed Initial Pediatric Study Plan, and to our December 15, 2021, letter confirming agreement. This fulfills your requirement at this stage of development to reach an Agreed Initial Pediatric Study Plan with the Agency for products that would trigger PREA at the time of the NDA submission.

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 Information² and Pregnancy and Lactation Labeling Final Rule³ 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

² <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

³ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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.⁴

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.⁵

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,

⁴ <http://www.fda.gov/ectd>

⁵ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

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:

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 356h⁶ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁷. 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

⁶ <https://www.fda.gov/media/84223/download>

⁷ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

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*.⁸

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:

- RTOR⁹: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid¹⁰

⁸ <https://www.fda.gov/media/85061/download>

⁹ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

¹⁰ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

ISSUES REQUIRING FURTHER DISCUSSION

Please refer to the meeting minutes.

ACTION ITEMS

Please refer to the meeting minutes

ATTACHMENTS AND HANDOUTS

repotrectinib, TPT Response to FDA Comments 17June22.pdf

3 Pages 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/

OPEYEMI O UDOKA
07/26/2022 05:07:36 PM



IND 130465

MEETING PRELIMINARY COMMENTS

Turning Point Therapeutics, Inc.
Attention: Naresh K. Nayyar, Ph.D., M.B.A., R.A.C.
Sr. Vice President Regulatory Affairs
10628 Science Center Drive, Suite 200
San Diego, California, 92121

Dear Dr. Nayyar:

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

We also refer to your April 28, 2022, correspondence, received April 28, 2022, requesting a meeting to reach agreement with the Agency on the proposed submission strategy for the new To-be-Marketed (b) (4) 40 mg dosage strength capsule formulation for the NDA.

Specific topics for the meeting include the following:

- Sufficiency of the To-be-Marketed (b) (4) 40 mg capsule formulation for the NDA submission and approval.
- (b) (4)
- Registration strategy including specifications and proposed registration stability plan.
- Adequacy of the proposed dissolution method as a suitable batch release and stability indicating quality control test method.

Our preliminary responses to your meeting questions are enclosed.

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

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call Rabiya Haider, Pharm.D., at (240) 402-6153.

Sincerely,

{See appended electronic signature page}

Xing Wang, Ph.D.
Senior Pharmaceutical Quality Assessor, Branch I
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

ENCLOSURE:

Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 28, 2022 from 12:00PM-1:00PM EST
Meeting Location: Teleconference

Application Number: 130465
Product Name: Repotrectinib (TPX-0005)
Indication: Treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC.
Sponsor Name: Turning Point Therapeutics, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Office of Pharmaceutical Quality

Office of New Drug Products (ONDP)

Xing Wang, Ph.D. Senior Pharmaceutical Quality Assessor

Yang Nan, Ph.D. Drug Product Reviewer

Paresma Patel, Ph.D. Branch Chief API

Haripada Sarker, Ph.D. Drug Substance Reviewer

Anitha Govada, Ph.D. Acting Biopharmaceutics Lead

Mei Ou, Ph.D. Biopharmaceutics Reviewer

Office of Translational Sciences/Office of Clinical Pharmacology

Hong Zhao, Clinical Pharmacology Team Leader, Division of Cancer Pharmacology II (DCP II)

Xiling Jiang, Clinical Pharmacology Reviewer, DCP I

Office of Program and Regulatory Operations

Rabiya Haider, PharmD. Sr. Regulatory Business Process Manager

SPONSOR ATTENDEES

Athena Countouriotis, MD

Mohammad Hirmand, MD

President and Chief Executive Officer
Executive Vice President and Chief
Medical Officer

Homa Yeganegi

Senior Vice President, Program Team
Leader and Head, Medical Affairs

Naresh K. Nayyar, PhD, MBA, RAC

Senior Vice President, Regulatory Affairs
& Quality Assurance

Edward Lee, PhD
Sang Lee, PhD
Ming Lu, PhD
Justine Lam, PhD

Senior Vice President, CMC
Director, Regulatory CMC
Vice President, Clinical Pharmacology
Executive Director, Clinical
Pharmacology

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 June 28, 2022, from 12:00PM-1:00PM EST via teleconference between Turning Point Therapeutics, Inc. and the Office of Pharmaceutical Quality. 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. Contact the Regulatory Business Process Manager (RBPM) 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.

1.0 BACKGROUND

On April 28, 2022, Turning Point Therapeutics, Inc., (Turning Point) submitted a meeting to reach agreement with the Agency on the proposed submission strategy for the new To-be-Marketed (b) (4) 40 mg dosage strength capsule formulation for the NDA.

Specific topics for the meeting include the following:

- Sufficiency of the To-be-Marketed (b) (4) 40 mg capsule formulation for the NDA submission and approval.
- (b) (4)
- Registration strategy including specifications and proposed registration stability plan.
- Adequacy of the proposed dissolution method as a suitable batch release and stability indicating quality control test method.

FDA granted Fast Track designation for repotrectinib for the following indications:

- On December 16, 2019, for the treatment of patients with ROS1-positive advanced non-small cell lung cancer (NSCLC) who have had disease progression following one prior line of platinum-based chemotherapy and one prior line of a ROS1 tyrosine kinase inhibitor (TKI).
- On May 12, 2020, for the treatment of patients with ROS1-positive advanced

NSCLC who have not been treated with a ROS1 TKI.

- On August 21, 2020, for the treatment of patients with advanced solid tumors that have an NTRK gene fusion who have progressed following treatment with at least one prior line of chemotherapy and one or two prior TRK tyrosine kinase inhibitors and have no satisfactory alternative treatments.
- On August 10, 2021, for the treatment of patients with ROS1-positive advanced NSCLC who have been previously treated with one ROS1 TKI and who have not received prior-platinum-based chemotherapy.

FDA granted Breakthrough Therapy designation for repotrectinib for the following:

- On December 7, 2020, for the treatment of patients with ROS1-positive metastatic NSCLC who have not been treated with a ROS1 TKI.
- On May 9, 2022, for treatment of patients with ROS1-positive metastatic NSCLC who have been previously treated with one ROS1 TKI and who have not received prior platinum-based chemotherapy

2.0 DISCUSSION

Question 1:

Does the Agency agree

(b) (4)

FDA Response to Question 1:

(b) (4)

Question 2:

(b) (4)

FDA Response to Question 2:

(b) (4)

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/

XING WANG
06/22/2022 11:28:17 AM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 130465
Request Receipt Date	March 11, 2022
Product	Repotrectinib (TPX-0005)
Indication	For the treatment of patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) who have been previously treated with one ROS1 tyrosine kinase inhibitor (TKI) and who have not received prior platinum-based chemotherapy
Drug Class/Mechanism of Action	Tyrosine kinase inhibitor
Sponsor	Turning Point Therapeutics , Inc.(TP)
ODE/Division	Division of Oncology 2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	May 11, 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.

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):

Repotrectinib is indicated for the treatment of patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) who have previously been treated with a ROS1 tyrosine kinase inhibitor (TKI) and who have not received prior platinum-based chemotherapy

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

☐ YES ☒ NO

3. Was the BTDR submitted to a PIND?

☐ YES ☒ NO

If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

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

4. Consideration of Breakthrough Therapy Criteria:

a. Is the condition serious/life-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

Repotrectinib (TPX-0005) is a small molecule, adenosine triphosphate competitive kinase inhibitor of ALK, ROS1, and NTRKA/B/C with activity against some acquired resistance mutations.

Information regarding patients with ROS1 positive NSCLC and the intended population for the proposed indication

ROS1-positive lung cancer is associated with adenocarcinoma, which is the most common type of NSCLC. In total, ROS1 rearrangements are rare occurring in approximately 2% of patients with lung adenocarcinoma. Patients with ROS1 NSCLC tend to be younger (median age 50 years old compared to 70 years old for all cases of NSCLC in the U.S.), never or light smokers, and test negative for other known lung cancer biomarkers (e.g., EGFR, ALK). NSCLC is associated with a poor prognosis in the metastatic setting where the 5 year overall survival (OS) rate is estimated to be approximately 6%.

The drug's relation to existing therapy(ies)

There are no FDA approved therapies specifically for the treatment of patients with ROS1-positive NSCLC who have had disease progression on a ROS1 TKI. There are very limited data on second-line therapies for ROS1-positive NSCLC so the best comparison for available therapies is uncertain.

For patients with symptomatic disease progression limited to brain metastases, the NCCN guidelines recommends switching therapy to entrectinib if patients were previously treated with crizotinib or ceritinib (NCCN Guidelines Version 3.2022, Non-Small Cell Lung Cancer). Entrectinib received traditional approval for ROS1-positive NSCLC on August 15, 2019, and has better CNS penetration than crizotinib and ceritinib. However, data are very limited on the use of entrectinib after disease progression on another ROS1 TKI. From the available limited data in the STARTRK-1 study of entrectinib for locally advanced or metastatic cancers, there were no responses with entrectinib in the six patients with ROS1-positive NSCLC who were previously treated with crizotinib (Drilon A et al., 2017).

For patients with progression of extracranial metastases with multiple lesions, the NCCN guidelines recommends switching therapy to lorlatinib based on limited data. Lorlatinib is not FDA approved for ROS1-positive NSCLC but in a study of 40 patients previously treated with crizotinib, the ORR was 35% (Shaw et al. 2019).

The NCCN guidelines also recommends platinum doublet chemotherapy with or without an immune checkpoint inhibitor in patients with ROS1-positive NSCLC after disease progression on a ROS1 TKI. Although the exact response rates are unknown for patients with ROS1-positive NSCLC after initial progression on a ROS1 TKI, the response rate for previously untreated, metastatic NSCLC in an unselected population for platinum-doublet chemotherapy is approximately 30%. For platinum-doublet chemotherapy in combination with an anti-PD-(L)1 antibody, the response rate for previously untreated, metastatic NSCLC for an unselected population is approximately 50%.

Relevant regulatory history

Repotrectinib is not approved in the U.S. 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.

The BTDR is supported by overall response rate (ORR) and duration of response (DOR) from the TRIDENT-1 study, an ongoing, multicenter, open-label, dose escalation and multi-cohort expansion study. There are a total of 53 patients who represent the intended population for the proposed indication. Four patients were treated in the dose-escalation part of the study and 49 patients were treated at the selected recommended phase 2 dose (RP2D) in the dose-expansion part of the study in expansion cohort 4.

The primary endpoint of the study in the dose expansion part of the study is ORR per RECIST v1.1 by blinded independent central review (BICR) with DOR as a secondary endpoint. Exploratory endpoints include intracranial tumor response in patients with measurable brain metastases as determined by BICR using modified RECIST v1.1, CNS progression-free survival in patients with measurable brain metastases using modified RECIST v1.1, progression free survival (PFS), overall survival (OS), safety, and pharmacokinetic data collection.

- 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, when large in magnitude and associated with durable responses (e.g., DOR $\geq$ 6 months past onset of response), an endpoint that is reasonably likely to predict clinical benefit for patients with ROS1-positive NSCLC with disease progression on a prior ROS1 TKI.

- 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.

Not applicable

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.*

There are no prior accelerated approvals for patients with ROS1-positive NSCLC who have progressed on ROS1 TKI therapy.

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

There are very limited data on second line therapies for ROS1-positive NSCLC so the best comparison for available therapies is uncertain. Platinum-doublet chemotherapy with or without an immune checkpoint inhibitor are options recommended by the NCCN guidelines. Although the data shown in the table below are for patients with treatment-naïve NSCLC, patients with ROS1-positive NSCLC with prior treatment with a ROS1 TKI may have a similar response to therapy.

Table 1. Standard of Care 2nd Line Therapies for ROS1+ NSCLC (biomarker unselected)

Regimen	Endpoint	Treatment Effect
Platinum doublet chemotherapy (Ref. 4 – 6)	OS ORR	9 – 12 months 26 – 35%
Platinum chemotherapy + IO (nonsquamous NSCLC) (Ref. 7 – 10)	OS ORR	19 – 22 months 38 – 55%

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

Not applicable.

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

Study ID	Trial Design	Treatment Group	Patient Group	Results to support BTDR/ Trial Endpoints
TRIDENT-1	Multicenter, multicohort, open label study	- Dose Escalation (n=4): repotrectinib 120 mg daily (n=1), 160 mg daily (n=2), 160 mg BID (n=1) - Dose Expansion Cohort 4 (n=49): repotrectinib 160 mg daily x 14 days, then 160 mg BID	ROS1-positive NSCLC previously treated with a ROS1 TKI and no prior chemotherapy or an immune checkpoint inhibitor N=53 N= 4 from the dose escalation N= 49 from dose expansion cohort 4	ORR (95% CI) 40% (CI:26, 54) DoR, range (months): 0.8+ to 17.8+ Response: n=21 % DoR ≥6 months = 48% % DoR ≥12 months = 9% Trial endpoints: ORR by BICR per RECIST v1.1 and DOR

Data cut-off date: January 24, 2022, by investigator for expansion cohort 4; July 22, 2019, by BICR for the dose escalation

- 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.*

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.

- *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 Division considers the reported ORR of 40% (95% CI 26, 54), along with evidence of durable responses, preliminary clinical evidence of a substantial improvement over available therapies.

A subgroup analysis based on which ROS1 TKI was received in the first-line setting was performed for the 53 patients relevant to the BTDR in TRIDENT-1. Importantly, repotrectinib had activity in patients who received either prior crizotinib or entrectinib, which are the two FDA- approved therapies for ROS1 NSCLC. Additionally, there were 6 patients who developed the common acquired ROS1 resistance mutation, G2032R, after treatment with crizotinib, and 50% had a response to repotrectinib.

Prior ROS1 TKI therapy	Second-Line Repotrectinib Overall Response Rate
Crizotinib (n=43)	42% (95% CI: 28,57)
Entrectinib (n=9)	33% (95% CI: 8, 70)
Ceritinib (n=1)	0%

The Sponsor included safety data for 329 patients treated at doses ranging from 40 mg QD to 200 mg BID. There were 226 patients treated with repotrectinib at the selected RP2D (160 mg QD x 14 days then 160 mg BID). In total, 96% of patients were reported to have treatment emergent adverse events (TEAEs), 49% with dose interruptions, 34% with serious adverse events, 33% with dose reductions, and 8% with treatment discontinuation due to TEAEs. The most common ($\geq 30\%$) TEAEs were dizziness (59%), elevated AST/ALT(53%), dysgeusia (44%), constipation (35%), and paresthesia (30%).

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

☒ GRANT:

Provide brief summary of rationale for granting:

The Division considers the observed response rates for patients with ROS1-positive NSCLC who have been treated with a ROS1 tyrosine kinase inhibitor (ORR: 40%, 95% CI: 26, 54), in association with a trend in durable response, preliminary clinical evidence that repotrectinib may demonstrate a substantial improvement in therapy compared to available therapies.

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 TRIDENT-1 study is ongoing and currently there are 49 patients enrolled in expansion cohort 4 for patients with ROS1+ NSCLC who progressed on a prior ROS1 TKI and who have not received prior chemotherapy or IO. Patients are being treated at the RP2D of repotrectinib 160 mg QD for the first 14 days then 160 mg BID. The Sponsor plans to submit an NDA for accelerated approval once data are available in 60 patients enrolled to expansion cohort 4. Overall enrollment for expansion cohort 4 is planned for 120 patients.

To identify patients with the ROS-1 positive rearrangement, the Sponsor has had a pre-submission meeting with CDRH to discuss the development of their (b) (4) as a companion diagnostic.

- 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. NCCN Guidelines Version 3.2022, Non-Small Cell Lung Cancer.
2. Drilon A, Siena S, Ou Si, et al. Safety and Antitumor Activity of the Multitargeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib: Combined Results from Two Phase I Trials (ALKA-372-001 and STARTRK-1). Cancer Discov. 2017 Apr;7(4): 400-409.
3. Shaw AT, Solomon BJ, and Chiari R, et. al. Lorlatinib in advanced ROS1-positive non-small cell lung cancer: a multicenter, open-label, single arm, phase 1-2 trial. Lancet; 2019 (20): 1691-1701.
4. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med 2002; (346): 92-98.
5. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage NSCLC. J Clin Oncol 2008; (26): 3543-3551.
6. Fossella F, Periera JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small cell lung cancer: the TAX 326 study group. J Clin Oncol 2003; (21): 3016 – 3024.
7. Gray J, Rodriguez-Abreu D, Powell SF, et al. Pembrolizumab + Pemetrexed-Platinum vs Pemetrexed-Platinum for Metastatic NSCLC: 4-Year Follow-up From KEYNOTE-189. J Thorac Oncol. 2021 Mar;16(3):S224.

8. U.S. Food and Drug Administration, Merck Sharp Dohme, KEYTRUDA (pembrolizumab) [package insert]. Accessed April 29, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s120lbl.pdf
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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, PharmD, RPh

Team Leader Signature: {See appended electronic signature page}Paz Vellanki, MD, PhD

Division Director Signature: {See appended electronic signature page}Harpreet Singh, MD

Revised 10/13/20 /M. Raggio

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/s/

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05/03/2022 12:51:33 PM
electronically signed by Katie Chon, PharmD, RPh

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05/04/2022 04:53:48 AM

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05/16/2022 10:24:00 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 130465
Request Receipt Date	October 15, 2020
Product	Reprotrectinib (TPX-0005)
Indication	Treatment of patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) who have not been treated with a ROS1 tyrosine kinase inhibitor (TKI)
Drug Class/Mechanism of Action	Tyrosine kinase inhibitor
Sponsor	Turning Point Therapeutics (TP)
ODE/Division	Division of Oncology 2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	December 14, 2020

*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):

Reprotrectinib is indicated for the treatment of patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) who have not been treated with a ROS1 tyrosine kinase inhibitor (TKI)

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 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:

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>

- 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: Not applicable

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.

Drug Description

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>

Reprotrectinib (TPX-0005) is a small molecule, adenosine triphosphate competitive kinase inhibitor of ALK, ROS1, and NTRKA/B/C.

Information regarding ROS1 positive NSCLC and the intended population for the proposed indication

ROS1 lung cancer is associated with adenocarcinoma, which is the most common type of non-small cell lung cancer (NSCLC). The frequency of ROS1 rearrangement is approximately 2% of patients with NSCLC adenocarcinoma, a very small subset of patients, and tend to be of a younger age (median age 50 years old compared to 70 years old for lung cancer), never or light smokers, and test negative for other known lung cancer biomarkers (e.g., EGFR, ALK). NSCLC is associated with a poor prognosis in the advanced and metastatic setting where the 5 year overall survival (OS) rate is estimated to be approximately 6%.

The drug's relation to existing therapy(ies)

There are two FDA approved therapies specifically for the treatment of patients with metastatic NSCLC whose tumors are ROS1 positive. On March 11, 2016, crizotinib, a first generation kinase inhibitor was approved for the treatment of patients with metastatic NSCLC whose tumors are ROS1 positive. Crizotinib demonstrated an overall response rate (ORR) of 66% (95% CI: 51,79) and a median duration of response (DOR) of 18.3 months (95% CI: 12.7, NR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1 as assessed by independent radiology review (IRR) committee. Then on August 15, 2019, entrectinib, another kinase inhibitor was approved for the treatment of patients with metastatic NSCLC whose tumors are ROS1+. Entrectinib demonstrated an ORR of 78% (95% CI: 65, 89) and a DOR range of 1.8 to 36.8+ months. Both applications were traditional/regular approvals.

Relevant regulatory history

Reprotrectinib is not 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.

The BTDR is supported by objective response rate (ORR and duration of response [DoR]) by principal investigator from the TRIDENT-1 study, an ongoing, multicenter, open-label, dose escalation and multi-cohort expansion study. Eleven patients are from Phase 1 and eight patients are from Phase 2.

The primary endpoint of the study is ORR per RECIST v1.1 by blinded independent central review, and secondary endpoints include DOR, time to response (TTR), clinical benefit rate (CBR), intracranial tumor response in patients with measurable brain metastases, as determined by BICR using modified RECIST v1.1, CNS progression-free survival in patients with measurable brain metastases using modified RECIST v1.1, progression free survival (PFS), overall survival (OS), safety, and pharmacokinetic data collection.

An objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 of 95% (95% CI: 74, 99) with a duration of response, range from 1.2+ to 35+ months.

- 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 overall response rate (ORR), when large in magnitude and/or associated with durable responses (DOR ≥ 12 months past onset of response), an endpoint that is reasonably likely to predict clinical benefit for patients with ROS1 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.

Not applicable

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.

Study ID (drug)	Trial Design	Treatment Group	Patient Group	Results to support approval
PROFILE 1001 (Crizotinib)	Multicenter, single-arm, study	Patients with ROS1-positive metastatic NSCLC	N=50	ORR (95% CI) 66% (CI: 51, 79) DoR, (95% CI (months)): Median 18.3 (12.7, NR)
ALKA, STARTRK1, STARTRK2 (Entrectinib)	Multicenter, single-arm, study	Patients with ROS1-positive metastatic NSCLC	N=51 3 pooled studies	ORR (95% CI) 78% (CI:65, 89) DoR, range (months): 1.8 to 36.8+ % DoR ≥ 9 months = 70% % DoR ≥ 12 months = 55% % DoR ≥ 18 months = 30%

NR = not reached

- 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.

Crizotinib and entrectinib are FDA approved therapies, and the NCCN guidelines provides an option to use ceritinib, a kinase inhibitor, for ROS1 positive NSCLC patients. While chemotherapy and/or immunotherapy are treatment options, these are not preferred options over ROS1 TKI therapy.

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

Crizotinib received breakthrough therapy designation on April 17, 2015, ROS1 positive NSCLC.

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 1: Clinical Trial Supporting the BTDR

Study ID	Trial Design	Treatment Group	Patient Group	Results to support BTDR
TRIDENT-1	Multicenter, multicohort, open label study	Expansion cohort 1: Patients with ROS1-positive NSCLC not previously treated with a ROS1 TKI Repotrectinib RP2D	ROS1-positive NSCLC not previously treated with a ROS1 TKI N=19 N=11 from Ph1 N=8 from Ph2	ORR (95% CI) 95% (CI:74, 99) DoR, range (months): 1.2+ to 35+ Response: n=18 % DoR ≥6 months = 67% % DoR ≥12 months = 33% % DoR ≥18 months = 28%

- 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 Division considers the reported ORR of 95% (95% CI 74, 99), along with evidence of durable responses, constitutes preliminary clinical evidence of a substantial improvement over available therapies.

Repotrectinib demonstrates a toxicity profile similar to other kinase inhibitors.

As the TRIDENT-1 trial is still ongoing, additional data will be forthcoming.

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

☒ GRANT:

Provide brief summary of rationale for granting:

The Division considers the observed response rates for patients with ROS1 positive NSCLC who have not been treated with a ROS1 tyrosine kinase inhibitor (ORR: 95%, 95% CI: 74, 99) in association with a trend in durable response indicates that repotrectinib may demonstrate a substantial improvement in therapy compared to available therapies.

We acknowledge the relatively small sample size and the fact that the lower limit of the 95% CI for ORR with repotrectinib overlaps the point estimate of ORR reported for entrectinib. However, given the rarity of the disease, for

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.

which prior approvals have been granted based on data from approximately 50 patients, we believe the sample size is reasonable to assess for BTDR, and we consider the fact that 18 of 19 patients exhibited a confirmed response impressive enough to support BTDR. While we did not include this info in the template, the sponsor has also indicated that the next two patients in this subgroup have unconfirmed responses (awaiting next scan to confirm response); if confirmed, the ORR would hold at 95% (95% CI 76, 100) .

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 plans to discuss the development of the companion diagnostic for ROS1. We had a meeting with the sponsor in July 2020 to discuss this development program and anticipate meeting with them again when additional data is available. .

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

14. List references, if any:

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

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

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}Katie Chon, PharmD, RPh
Team Leader Signature: {See appended electronic signature page}Erin Larkins, MD
Division Director Signature: {See appended electronic signature page}Harpreet Singh, MD

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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12/03/2020 01:13:06 PM
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