CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219713Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 122347

MEETING PRELIMINARY COMMENTS

AnHeart Therapeutics, Inc.
Attention: Guilin Huang
Senior Vice President, Head of Development
777 Third Avenue, Suite 1704
New York, NY 10017

Dear Guilin Huang:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for taletrectinib (AB-106).

We also refer to your April 24, 2024, correspondence, received April 24, 2024, requesting a meeting to obtain Agency feedback on the overall content and format for the planned new drug application submission of taletrectinib as a treatment for adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer. Specifically, AnHeart would like to align with the Agency on the adequacy of non-clinical and clinical pharmacology packages, and several important clinical and regulatory topics pertaining to dose optimization, data applicability, safety evaluation and companion diagnostic. 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 at 301-796-1755 or Raniya.Al-Matari@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Raniya Al-Matari, Ph.D.
Regulatory Health Project Manager
Division of Regulatory Operations - Oncologic Diseases for Division of Oncology 2
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Preliminary Comments

PRELIMINARY MEETING COMMENTS

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	June 26, 2024 3:00 PM – 4:00 PM, EST
Meeting Location:	FDA will provide zoom details in a later date.
Application Number:	122347
Product Name:	Taletrectinib (AB-106)
Indication:	For the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer.
Applicant Name:	AnHeart Therapeutics, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Erin Larkins, M.D., Associate Supervisory Director, Division of Oncology 2 (DO2)
Gautam Mehta, M.D., Ph.D., Cross Disciplinary Team Lead, DO2
Yufan Liu, Pharm. D., Clinical Reviewer, DO2
Jeanne Fourie Zirkelbach, Ph.D., Master Pharmacokineticist Team Lead, Division of Clinical Pharmacology II (DCPII)
Hairat Sabit, Ph.D., Clinical Pharmacology II Reviewer, DCPII
Xiaoxue Li, Ph.D., Biostatistics Team Lead, Division of Biostatistics V (DBV)
Flora Mulkey, M.S., Biostatistics Reviewer, DBV
Claudia Miller, Ph.D., Nonclinical Team Lead, Division of Hematology, Oncology, Toxicology (DHOT)
Stephanie Aungst, Ph.D., Nonclinical Reviewer, DHOT
Raniya Al-Matari, Ph.D., Regulatory Health Project Manager, Division of Regulatory Operations

SPONSOR ATTENDEES

Jerry Wang, Ph.D., Chief Executive Officer
Lian Li, MD, Ph.D., Chief Medical Officer, SVP
Guilin Huang, M.B.A, SVP, Head of Development
Casey Judge, M.S., Senior Director, Regulatory Strategy
Rose Lai, M.D., Ph.D., VP, Clinical Development
Wei Wang, M.D., Ph.D., Medical Director, Clinical Development
Hanna Dobrowolska, Ph.D., Sr. Director, Translational Medicine
Qinying Zhao, Ph.D., S.V.P., Clinical Pharmacology
Chao Li, Ph.D., Executive Director, Clinical Pharmacology
Michael Chen, Ph.D., Senior Director, Biostatistics

Xianyu (Chris) Zhang, M.S., Principal Statistician, Biostatistics
Utpal Khambholja, M.D., Executive Director, Pharmacovigilance
Jeff Varnes, M.S., Sr. Director, Program Management
Kerry Wentworth, Chief Regulatory Officer, Nuvation Bio
David Liu, M.D., Ph.D., Chief Medical Officer, Nuvation Bio
Liang Fang, Ph.D., V.P., Data Science, Nuvation Bio

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 26, 2024; 3:00 PM – 4:00 PM, EST between AnHeart Therapeutics, Inc. 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. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the 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
On April 24, 2024, AnHeart Therapeutics, Inc. (AnHeart) submitted a meeting request, to obtain the Agency's feedback on the overall content and format for the planned new drug application submission of taletrectinib as a treatment for adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC). Specifically, AnHeart would like to align with the Agency on the adequacy of non-clinical and clinical pharmacology packages, and several important clinical and regulatory topics pertaining to dose optimization, data applicability, safety evaluation and companion diagnostic.

Regulatory
On August 1, 2022, FDA granted Breakthrough Therapy Designation to taletrectinib for the treatment of adult patients with advanced or metastatic receptor tyrosine kinase (ROS1)-positive NSCLC who are ROS1 tyrosine kinase inhibitor (TKI) treatment naïve OR who have been previously treated with crizotinib.

On December 22, 2024, AnHeart submitted a meeting request to obtain our feedback on safety analysis strategy and electronic datasets in support of the planned new drug application for taletrectinib. FDA advised that while the plan to submit a marketing application for taletrectinib appeared reasonable, it would be important for AnHeart to justify the applicability of data from Studies C203 and G208 to U.S. patients and therefore to provide a summary of the efficacy results in U.S. patients side-by-side for comparison with the ex-U.S. patient population.

Nonclinical
Taletrectinib is a small molecule kinase inhibitor against the proto-oncogene tyrosine-protein kinase (ROS1), neurotrophic tropomyosin related kinase (NTRK), and anaplastic lymphoma kinase (ALK). AnHeart has conducted several in vitro and in vivo pharmacology studies, including proof of concept studies with ROS1+ and ROS1 fusion protein cancer cell lines, safety pharmacology studies, GLP-compliant repeat-dose toxicology studies of 4- and 12-weeks in duration in rats and cynomolgus monkeys, embryofetal development studies in rats and rabbits, a phototoxicity study, a full genotoxicity battery, and several pharmacokinetic studies.

Clinical and Statistics
AnHeart is developing taletrectinib for the treatment of adult patients with ROS1-positive advanced or metastatic NSCLC, both in the treatment-naïve and post-ROS1-TKI settings. A summary of the ongoing and completed studies within the clinical development program of taletrectinib for the treatment of ROS1-fusion positive NSCLC are provided below.

Study number	Study population	Study design and dose levels	Notes
DS6051-A-U101 (completed) US only N=46; 7 ROS1 fusion positive NSCLC	Patients with advanced solid tumors	First in human, single arm, multiple cohort Dose escalation: 50, 100, 200, 400, 800 or 1200 mg once daily (QD)	MTD identified as 800 mg QD Endpoints: Safety, PK and Preliminary Efficacy
DS6051A-J102 (completed) Japan only N=15	Patients with advanced solid malignant tumors with a ROS1 or NTRK fusion gene	Dose escalation Tested doses of 400, 600 and 800 mg QD	MTD identified as 600 mg QD Endpoints: PK and Safety Pooled efficacy results between U101 and J102

			(N=18): Overall ORR 50%. ROS1-TKI-naïve ORR:67%. ROS1-TKI-pretreated ORR: 33%
AB-106-C203 (ongoing) China only	Patients with locally advanced or metastatic ROS1-fusion positive NSCLC	Single arm study. Enrolled patients which were both crizotinib-naïve and crizotinib pre-treated	Primary endpoint: ORR and DoR by IRC Secondary endpoints: PFS, PK and Safety
AB-06-G208 (ongoing) Global	Patients with advanced/metastatic NSCLC harboring ROS1 fusion gene.	4 cohorts: Cohort 1 (N=55): ROS1 TKI naïve patients (1 prior line of chemo allowed) Cohort 2 (N=50): Prior treatment with 1 approved ROS1 TKI (1 prior line of chemo allowed) Cohort 3 (N=35): Prior treatment with ≥2 ROS1 TKIs (1 prior line of chemo allowed) Cohort 4 (N=20): Patients with ROS1 solid tumors or ROS1 NSCLC not eligible for cohorts 1-3 (Up to 3 prior lines of ROS1 TKIs and up to 2 prior lines	Primary endpoints: ORR by IRC Secondary endpoints: DoR, PFS, Safety and PK

		of chemotherapy allowed)	

In addition to the studies listed above, AnHeart has also completed 5 studies in healthy volunteers (n=134) and a Phase 2 study in patients with advanced solid tumors with NTRK rearrangement (n=14 as of June 2023).

Based on a March 29, 2024 data cutoff, relevant data are provided below from Studies G208 and C203 (106 TKI naïve, 67 ROS1 TKI pre-treated).

Demographics and Baseline Characteristics of Studies G208 and C203

Category (%)		ROS1 TKI Naïve		ROS1 TKI Pre-treated	
		C203 (N=106)	G208 (N=55)	C203 (N=67)	G208 (N=50)
Sex	Male	44%	44%	39%	46%
Age	Median (range), yrs	56 (26, 78)	57 (27, 82)	51 (31, 77)	55 (27, 79)
Race	Asian	100%	66%	100%	46%
	White	-	22%	-	34%
	Other	-	12%	-	20%
Prior Chemo	Yes	21%	20%	34%	36%
Lines of Prior Therapy	0	78%	80%	-	-
	1	21%	15%	81%	60%
	≥2	1%	5%	19%	40%
Prior ROS1 TKI	Entrectinib	-	-	0%	20%
	Crizotinib	-	-	100%	80%
Brain Metastases by IRC	Yes	17%	35%	42%	56%

Source: Table 16 and 17, meeting materials

Efficacy Results by IRC

	ROS1 TKI Naïve		ROS1 TKI Pre-treated	
	C203 (N=106)	G208 (N=54)	C203 (N=66)	G208 (N=47)
Median follow-up (months)	34	14	28	13
cORR, n (%) (95% CI)	91% (83, 95)	85% (73, 93)	52% (39, 64)	57% (42, 72)
mDoR, months (95% CI)	NR (NR, NR)	21 (15, NR)	19 (8, 32)	NR (NR, NR)

Source: Tables 20 and 21, and Figures 26 and 30 meeting materials

Pooled efficacy results from Studies C203 and G208 in the ROS1 TKI Naïve patients include a confirmed overall response rate (ORR) of 89% (95% confidence interval [CI]:

83, 93) with median duration of response (DOR) not reached. In the ROS1 TKI Pre-treated pooled patients, the confirmed ORR was 54% (95% CI:44, 63) with median DOR of 17 (95% CI: 10, 32) months. Subgroup analyses preliminarily show relatively consistent findings to the overall population.

Study G208 enrolled 54% of patients (83/153) from Europe and North America. Six patients (2 US, 4 Canada) were ROS1 TKI naive (Cohort 1) and three (1 US, 2 Canada) were ROS1 TKI pre-treated (Cohort 2) were enrolled from North America. In Cohort 1 there were four responses and in Cohort 2 there was one response. In the pooled efficacy data from both studies the ORR by region are as follows:

- Cohort 1: 21 patients were from Western regions with an ORR of 81% (95% CI: 58, 95) compared with 139 patients from Asia with an ORR of 90% (95% CI: 84, 94)
- Cohort 2: 26 patients were from Western regions with an ORR of 58% (95% CI: 37, 77) vs. 87 patients from Asia with an ORR of 53% (95% CI: 42, 64)

Overview of Safety in Pooled Studies

Category, n (%)	ROS1+ NSCLC 600 mg QD (N=331)	600 mg QD (N=346)
Any ≥Grade 3 TEAEs	167 (51)	174 (50)
Grade 5 TEAEs	24 (7)	27 (8)
Serious TEAEs	95 (29)	99 (29)
Dose interruption TEAEs	132 (40)	138 (40)
Dose reduction TEAEs	92 (28)	97 (28)
Treatment discontinuation TEAEs	19 (6)	19 (6)

Source: Table 22, meeting materials

The most common treatment-emergent adverse events (TEAEs) (≥20%) in the 600 mg QD pool (all patients who received 600 mg QD across the taletrectinib program) included ALT increased (68%), Nausea (45%), Vomiting (44%), Anemia (37%), Constipation (20%), and Dizziness (20%). The only ≥Grade 3 TEAEs occurring in at least 5% of patients were ALT and AST increased (10 and 7% respectively).

NDA plan
AnHeart plans to submit an NDA for taletrectinib for the treatment of adult patients with advanced or metastatic ROS1+ NSCLC based on a June 2024 data cutoff and request priority review. AnHeart will provide a 90-day safety update with a new data cutoff (September 2024), which is approximately within 1 month following the initial NDA submission. AnHeart proposes to participate in rolling review for the planned NDA with noted submissions outlined as follows:

- Part 1 (July 2024): Module 1 (administrative information), Module 2 (Non-clinical overview and summaries) and Module 4 (Non-clinical study reports and deaths)

- Part 2 (August 2024): Module 1 (Labeling and remaining administrative information), Module 2 (QOS, Clinical overview and summaries), Module 3 and Module 5

AnHeart intends to develop a tissue-based companion diagnostic (b) (4) with a potential taletrectinib approval.

AnHeart has provided a review of the safety topics of hyperuricemia and skeletal fractures. These toxicities have been observed for other ROS1 TKIs including entrectinib and repotrectinib. AnHeart proposes that review of safety data regarding hyperuricemia does not show a safety risk and warrant any inclusion in the Section 5 of the label. Upon review of the events of skeletal fractures, AnHeart proposes that this topic does not need to be summarized in the NDA submission and should not be included as an adverse event of special interest (AESI).

Clinical Pharmacology
For the planned NDA submission, AnHeart's clinical pharmacology package will include completed and ongoing studies, which will characterize the single-dose, multiple-dose pharmacokinetics (PK), dose proportionality, drug-drug interaction (DDI), absorption, distribution, metabolism and excretion (ADME), food-effect, organ impairment and QT prolongation potential of taletrectinib.

Per FDA's recommendations in the previous discussions, AnHeart amended the protocol for the ongoing Study G208 to include a cohort (Cohort 5) with 40 patients randomized 1:1 to two dose levels (i.e., 400 mg and 600 mg QD) to evaluate the PK, safety, and preliminary anti-tumor activity of taletrectinib.

Per the current meeting package, the interim analysis of this dose randomized trial will be complete in October 2024, but the final analysis will be completed in January/February 2025.

SPONSORS QUESTIONS AND FDA RESPONSES

Nonclinical

1. Does the Agency agree with the adequacy of the nonclinical package to support an NDA submission for taletrectinib as a treatment for adult patients with locally advanced or metastatic ROS1-positive NSCLC?

FDA Response: The nonclinical package appears sufficient to support the submission of a marketing application for taletrectinib in the proposed patient population. We will make a final determination of the adequacy of the data after review of all data included in the NDA submission. See also Nonclinical Additional Comment #15.

Clinical Pharmacology

2. Does the Agency agree the overall clinical pharmacology package, including the planned analyses and the proposed post-marketing study, are adequate to support an initial NDA submission for the proposed indication?

FDA Response: Your overall clinical pharmacology package, including the planned analyses and the proposed post-marketing study, appear acceptable to support an initial NDA submission for the proposed indication. See the following additional comments regarding your clinical pharmacology package:

a. If data from the (b) (4) study (b) (4) become available during the NDA review, we recommend submitting a preliminary report to FDA to inform labeling in this patient population.

b. You should submit a QT/QTc evaluation plan to the FDA IRT team as soon as possible, prior to the NDA submission for QT/IRT review and comment.

The final determination with regards to the adequacy of the proposed studies will be made at the time of the original NDA submission.

Dose Optimization

3. Does the Agency agree with the proposed plan and timing to submit results from dose optimization cohort (Cohort 5) of Study G208 to support 600 mg once daily as a safe and effective dose of taletrectinib for the treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC?

FDA Response: It appears that you are planning to submit your final analysis for the dose randomization trial (Cohort 5) late in the review cycle of your planned NDA submission. As outlined in previous communications, our concerns as to whether 600 mg QD is the optimized dosage-still remain. These include, but are not limited to:

- A limited number of patients have been treated at lower dosages (e.g., 13 patients at < 600 mg QD).
- 35% of patients experienced Grade ≥ 3 TEAEs at the 600 mg QD dose level.

- Exposure-response for efficacy has not been provided.
- Conclusions provided in the current meeting package regarding E-R for safety are mainly based on data from a single dose level.
- In Study AB-106-C203, there was no correlation between C_{trough} and ORR.
- IC90 comparison data for 600 mg QD and 400 mg QD will be considered supportive but the efficacy data from the dose randomization study will be the primary support for the dosage for approval.

The planned interim analysis with 10 patients per dose level may not be adequate to fully support that 600 mg QD is the optimized dosage. Given the small dataset of 10 patients per dose level, the adequacy of the study results will be a review issue.

Submit the data from your final analysis of the completed dose randomization study (Cohort 5) as soon as possible. Based on the adequacy of the study results, additional dosage optimization may be needed as a postmarketing.

Justification of Data Applicability

4. Can the Agency comment on the Applicant's justification regarding the applicability of the pooled data from Studies C203 and G208 to the US representative patient population?

FDA Response: The overall number of patients enrolled from North America in Cohorts 1 and 2 of Study G208 is low. The applicability of the pooled data from Studies C203 and G208 to the U.S. population will be a review issue. In your NDA application, please include a document detailing the rationale for assuming the applicability of foreign data to U.S. population/practice of medicine. This should include the number of patients enrolled in each country for Study G208.

Safety Assessment – Skeletal Fracture and Hyperuricemia

5. Does the Agency agree to the safety assessment for skeletal fracture and hyperuricemia?

FDA Response: We do not agree with your proposal to not characterize hyperuricemia and skeletal fractures as AESIs. Description of these risks should be included in the marketing application, including in the Assessment Aid. An assessment of the safety profile of taletrectinib including safety labeling of skeletal fracture and hyperuricemia will be made during the NDA review.

NDA Content Plan and Rolling Review Request

6. Does the Agency agree with the provided Content Plan for the planned NDA and the Sponsor's proposal to utilize rolling review?

FDA Response: We have no objections to the proposed content and timelines for the pre-submission batches; however, we recommend that submission documents involving Chemistry, Manufacturing, and Controls be included in earlier submission batches if possible to enable a more efficient review.

Risk Evaluation and Mitigation Strategies (REMS)

7. Does the Agency agree that additional risk mitigation activities, such as a Risk Evaluation and Mitigation Strategies (REMS), are not warranted based on the safety profile observed with taletrectinib development program?

FDA Response: Based on the provided safety data, it does not appear a REMS may be necessary; however, a final determination will be made during review of the NDA.

Oncology Drug Advisory Committee (ODAC)

8. Does the Agency agree that an oncology drug advisory committee (ODAC) is not warranted for the review of the planned NDA?

FDA Response: At this time we do not anticipate a need for an ODAC; however, a final decision will be made during the course of the review of the NDA.

Companion Diagnostic

9. AnHeart has partnered with Foundation Medicine (FMI) to co-develop a tissue-based Companion Diagnostic (CDx), FoundationOne®CDx (F1CDx), to identify NSCLC patients with ROS1 fusions who may benefit from treatment with taletrectinib. Can the Agency comment on the anticipated timing of development of the CDx for ROS1-fusions for use with taletrectinib?

FDA Response: Based on the information you provided in the meeting briefing package and during the Type C meeting held on May 2, 2024, you stated that you plan to submit in August 2024 an NDA for taletrectinib to seek full approval for the treatment of locally advanced or metastatic ROS1-postive NSCLC (metastatic indication). Further, you noted that you are working with Foundation Medicine, Inc. (FMI) [redacted] (b) (4) for F1CDx as a tissue CDx for the proposed metastatic indication [redacted] (b) (4) [redacted] (b) (4) In order to support a CDx marketing submission for taletrectinib, given that multiple non-FDA approved devices have been used to enroll patients, a clinical bridging study will be required [redacted] (b) (4) Please be advised that the ascertainment rate of the samples for the clinical bridging study should be sufficiently high to demonstrate robust clinical performance of the CDx device [redacted] (b) (4) Given that studies have been conducted across multiple countries, including China, please ensure that high sample ascertainment will be achieved to support the CDx clinical bridging study to ensure robustness of the study results to demonstrate clinical validation of the device.

ADDITIONAL FDA COMMENTS

Statistics

10. The primary efficacy analysis population should be comprised of all patients receiving at least one dose of therapy and should not be limited by follow-up time on study. A supportive sensitivity analysis may include only patients who have been followed for 14 months (PEAP).

11. In single arm trials, confirmed ORR will be assessed in the context of an adequate DoR; accordingly the timing of the primary analysis should occur at a time when most responders are followed for at least 6 months from initial response in patients who are previously-treated and at least 12 months from initial response for patients who are treatment naïve to accurately estimate DoR.

12. Please summarize the study results for each study and combined in the following patient population:

a. Among ROS TKI Naïve patients, provide subgroup data from patients who have received no prior therapy and from patients who have received prior therapy other than a ROS TKI.

b. Among ROS TKI pre-treated patients, provide subgroup data from patients who have received one line of prior therapy and from patients who have received two or more lines of prior therapy.

13. Death should be included as an event in the DoR analysis and not be censored.

14. When confirming response per RECIST v1.1, we recommend you use a more nuanced determination when the first response is CR and the subsequent response is anything other than CR. Please see and incorporate rules per Table 3 in the following publication: "Best overall response when confirmation of CR and PR required" from Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47. doi: 10.1016/j.ejca.2008.10.026. PMID: 19097774.

Nonclinical

15. In general, for an in vivo genetic toxicology assessment, both sexes should be considered if there is a meaningful sex difference in exposure, metabolism and/or toxicity. In your NDA submission, include a justification for evaluating the genotoxicity potential in males only in your in vivo assays.

Clinical

16. Please clarify if you intend to use an Assessment Aid in your proposed marketing application.

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

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

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

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
- 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

[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

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 INDs not in eCTD format).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential

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

evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[8]

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

[8] 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.

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[9] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[10]*.* Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support*

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[9] https://www.fda.gov/media/84223/download
[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[11] https://www.fda.gov/media/85061/download

Claims.

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

- Assessment Aid[13]

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.*[14] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

SPLIT REAL TIME APPLICATION REVIEW (STAR) PILOT PROGRAM

The FDA is conducting a pilot program, the Split Real Time Application Review (STAR). STAR is a pilot review process allowing earlier patient access to therapies that address an unmet medical need via interactive engagement with the application so that review and analysis of data may commence prior to full supplemental new drug application

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

(sNDA)/supplemental biologics license application (sBLA) submission. An applicant can communicate interest in participating in this pilot program to the FDA review division by submitting a STAR Entry Request if the applicant believes a proposed efficacy supplement fulfills the conditions outlined in the eligibility criteria. Those applicants who do not wish to participate in the pilot program will follow the usual submission process with no impact on review timelines. More information on this pilot program, including eligibility criteria and timelines, can be found at the FDA website for STAR.[15]

[15] https://www.fda.gov/drugs/development-resources/split-real-time-application-review-star

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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/

RANIYA A AL-MATARI
06/24/2024 06:21:39 PM

IND 122347

MEETING PRELIMINARY COMMENTS

AnHeart Therapeutics Inc.
Attention: Casey Judge
Senior Director, Regulatory Strategy
777 Third Avenue, Suite 1704
New York, NY 10017

Dear Casey Judge:[1]

Please refer to your Investigational New Drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Taletrectinib (AB-106).

We also refer to your April 15, 2024, correspondence, received April 15, 2024, requesting a meeting to obtain Agency feedback on the CMC data package for the planned NDA submission of taletrectinib for the treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC.

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.

If you have any questions, please contact Janell Artis, PharmD., Regulatory Business Process Manager at email: Janell.Artis@fda.hhs.gov, or (301) 796 – 6309.

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

[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.

ENCLOSURE:
Meeting Preliminary Comments

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

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B Meeting
Meeting Category:	Pre-NDA
Meeting Date and Time:	June 13, 2024, 11:00a.m. – 12:00p.m. EST
Meeting Location:	Teleconference
Application Number:	IND 122347
Product Name:	Taletrectinib (AB-106)
Indication:	treatment of adult patients with advanced or metastatic ROS1 positive non-small cell lung cancer (NSCLC).
Sponsor Name:	AnHeart Therapeutics, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act

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 13, 2024, 11:00a.m. – 12:00p.m., via teleconference between AnHeart 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. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory business process manager (RBPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the 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

This Pre-NDA Type B Meeting Request was submitted to obtain Agency feedback on the CMC data package for the planned NDA submission of taletrectinib for the treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC.

Taletrectinib was granted breakthrough therapy designation for ROS1+ non-small cell lung cancer (NSCLC) in the US in August 2022. AnHeart intends to submit a New Drug Application (NDA) for taletrectinib in August 2024 to seek traditional approval for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer. The initial NDA will be primarily based on pooled data from two Phase 2 studies, C203 and G208.

2.0 DISCUSSION

Question 1: *Does the agency agree that the proposed drug substance specifications are acceptable to support the NDA submission?*

FDA Response to Question 1:
It is recommended that you tighten the acceptance criterion for the Particle size distribution test (d_{90}) to (b) (4) µm, which is the criterion justified (b) (4) (b) (4) Considering that the Maximum Daily Dose of taletrectinib adipate drug substance is (b) (4) mg (equivalent to 600 mg of taletrectinib free base as per pg. 41 of the briefing package), the elemental impurity limits appear to comply with the Q3D PDE values for each element. Other than the above comment regarding PSD, in general the specification appears reasonable. A final evaluation will be made during the review of the NDA.

Question 2: *Does the agency agree that the proposed drug product specifications are acceptable to support the NDA submission?*

FDA Response to Question 2:
The proposed drug product specification appears reasonable. The final determination will be made upon review of the data submitted to the NDA. Note that acceptance criteria of the drug product specification tests will be an NDA review issue and will be evaluated according to the information provided in your future application.

Question 3:
a) Does the agency agree that the provided dissolution development and proposed method are adequate?

b) Does the agency agree that a dissolution acceptance criterion of Q = (b) (4) % at (b) (4) minutes is acceptable for the NDA submission?

FDA Response to Question 3:
a) The current dissolution method [USP Apparatus II (paddles) rotating at 50 rpm, with capsule sinker; 900 mL of 0.05 mol/L acetic acid – sodium acetate buffer, pH 4.0; 37 ± (b) (4) °C] could potentially be acceptable for the QC testing of taletrectinib capsules (200 mg) as (***i***) this method appears to be discriminating for differences in API particle size distribution, which is one of the critical quality attributes that could influence the

Question 5: *Does the Agency agree the Applicant's* [redacted] (b) (4) *assessment is sufficient to support the NDA submission?*

FDA Response to Question 5:
The limited summary of your assessment appears to indicate that you have adequately considered the potential sources of [redacted] (b) (4) impurities in taletrectinib adipate drug substance. Include all details of the [redacted] (b) (4) risk assessment in your NDA, in particular the details of how you determined that there were no [redacted] (b) (4) agents in the manufacturing process for the drug substance. Your assessment of the potential existence of [redacted] (b) (4) compounds in taletrectinib adipate drug substance and the drug product will be evaluated as part of the review of the NDA.

Question 6: *Does the agency agree with the Applicant's plan to provide 6-months and 3-months stability data from a development bridging batch and a formal bridging batch, respectively, in the NDA, with additional stability results from the formal bridging batch to be submitted as available, to bridge to updated product packaging (CRC) and capsule printing?*

FDA Response to Question 6:
We acknowledge the bridging supportive stability studies you propose to submit in the NDA to demonstrate comparability. As reported in FDA's feedback to the Type D meeting request submitted on August 13, 2023, and dated September 19, 2023 (Reference ID 5246758), you should submit at least 6 months long-term and accelerated stability data for the bridging batch with dissolution profile comparison to those of the three registration batches. Review of the data and comparability determination is performed during the NDA review. We note that the purpose of this bridging study is to account for three changes made to the drug product which are capsule count in the storage bottle, [redacted] (b) (4) cap, and addition of an imprint on the capsule shell. The drug product shelf life will be granted on the basis of available stability data submitted in the NDA, and their ability to bridge to supportive stability batches. Your approach to submit additional stability results including 6-month data from the formal bridging batch after original NDA submission appears reasonable. Final determination will be made during the NDA review.

Additional Comment (Biopharmaceutics):

1. In the NDA, include a schematic diagram and/or table to summarize the CMC changes that occurred during pharmaceutical and clinical development of taletrectinib capsules 200 mg, as well as the type/design and results of *in vitro* and/or *in vivo* studies that were appropriately conducted to establish the bridge between the final to-be-marketed drug product and the lots that were evaluated in the clinical, stability and other studies supporting registration. For example, the NDA should contain information to confirm our understanding (e.g., from Table 42 of the meeting package) that there are adequate clinical PK, safety and efficacy data and registration/stability data generated using drug product lots representing the final proposed commercial formulation, manufacturing process, drug substance and drug

product manufacturing sites, supply chain, and controls (with the exception of capsule appearance).

APPEARS THIS WAY ON ORIGINAL

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
06/03/2024 10:38:19 AM

IND 122347

MEETING REQUEST-
WRITTEN RESPONSES

AnHeart Therapeutics Inc.
c/o Parexel International Corporation
Attention: Sowmya Sony Janampally
Regulatory Affairs Consultant
777 Third Avenue, Suite 1704
New York, NY 10017

Dear Sowmya Sony Janampally:[1]

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

We also refer to your submission dated December 22, 2023, containing a meeting request. The purpose of the requested meeting was meeting to obtain our feedback on safety analysis strategy and electronic datasets in support of the planned new drug application for taletrectinib.

Further reference is made to our Meeting Granted letter dated January 3, 2024, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your January 11, 2024, background package.

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

If you have any questions, call me at 301-796-1755.

Sincerely,

{See appended electronic signature page}

Raniya Al-Matari, Ph.D.
Regulatory Health Project Manager
Division of Regulatory Operations - Oncologic Diseases for Division of Oncology 2
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: End of Phase

Application Number: 122347

Product Name: Taletrectinib

Indication: For the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer

Applicant Name: AnHeart Therapeutics, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

BACKGROUND

On December 22, 2024, AnHeart Therapeutics Inc. (AnHeart), submitted a meeting request to obtain our feedback on safety analysis strategy and electronic datasets in support of the planned new drug application for taletrectinib.

Clinical

AnHeart is developing taletrectinib for the treatment of adult patients with receptor tyrosine kinase (ROS1)-positive advanced or metastatic NSCLC, both in the treatment-naïve and post-ROS1-TKI settings. A summary of the ongoing and completed studies within the clinical development program of taletrectinib for the treatment of ROS1-fusion positive NSCLC are provided below.

Study number	Study population	Study design and dose levels	Notes
DS6051-A-U101 (completed) US only N=46; 7 ROS1 fusion positive NSCLC	Patients with advanced solid tumors	First in human, single arm, multiple cohort Dose escalation: 50, 100, 200, 400, 800 or 1200 mg once daily (QD)	MTD identified as 800 mg QD Endpoints: Safety, PK and Preliminary Efficacy
DS6051A-J102 (completed) Japan only	Patients with advanced solid malignant tumors	Dose escalation	MTD identified as 600 mg QD

N=15	with a ROS1 or NTRK fusion gene	Tested doses of 400, 600 and 800 mg QD	Endpoints: PK and Safety Pooled efficacy results between U101 and J102 (N=18): Overall ORR 50%. ROS1-TKI-naïve ORR:67%. ROS1-TKI-pretreated ORR: 33%
AB-106-C203 (ongoing) China only N=173 as of June 2023	Patients with locally advanced or metastatic ROS1-fusion positive NSCLC	Single arm study. Enrolled patients which were both crizotinib-naïve and crizotinib pre-treated	Primary endpoint: ORR and DoR by IRC Secondary endpoints: PFS, PK and Safety Interim analysis conducted on Feb 2022 in 109 patients (67 ROS1 TKI naïve, 42 crizotinib-pretreated) Efficacy ROS1 TKI naïve ORR: 93% (95% CI: 83, 98%), mDoR not reached Crizotinib pretreated ORR: 53% (95% CI: 36-69%), mDoR not reached 11/12 IC-ORR: 92% (95% CI: 62-100%)
AB-06-G208 (ongoing) Global	Patients with advanced/metastatic NSCLC harboring ROS1 fusion gene.	4 cohorts: Cohort 1 (N=53): ROS1 TKI naïve patients (1 prior	Primary endpoints: ORR by IRC

N=150 at 600 mg QD as of 06/2023		line of chemo allowed) Cohort 2 (N=46): Prior treatment with 1 approved ROS1 TKI (1 prior line of chemo allowed) Cohort 3 (N=35): Prior treatment with ≥2 ROS1 TKIs (1 prior line of chemo allowed) Cohort 4 (N=20): Patients with ROS1 solid tumors or ROS1 NSCLC not eligible for cohorts 1-3 (Up to 3 prior lines of ROS1 TKIs and up to 2 prior lines of chemotherapy allowed)	Secondary endpoints: DoR, PFS, Safety and PK Efficacy Inv. Assessed ORR in 20 TKI naïve patients: 90% (95% CI: 68-99%). Inv. Assessed ORR in 18 patients treated with 1 ROS1 TKI previously: 61% (95% CI: 36-83%) 20 of the 64 patients enrolled thus far are from Europe and North America

In addition to the studies listed above, Anheart has also completed 5 studies in health volunteers (n=134) and a Phase 2 study in patients with advanced solid tumors with NTRK rearrangement (n=14 as of June 2023).

Proposed Elements of Potential NDA

Anheart intends to submit an NDA for taletrectinib in August 2024 with a data cutoff date of March 2024 to seek traditional approval for the treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC. A pre-NDA meeting is planned for the end of Q2 2024. In this meeting package, Anheart proposes the following for the NDA:

- The NDA would have 2 pooled safety populations: 1) an overall safety population (n=418) comprised of all patients with cancer, irrespective of tumor type who received at least 1 dose of taletrectinib, irrespective of dose levels and 2) a ROS1-positive NSCLC 600 mg safety population (n=326)

- Anheart will provide all content elements required by 21 CFR within the summary of clinical safety. Thus, the SCS will serve as the narrative portion of the ISS. All safety tables, figures, and listings referred to in the SCS will be provided in Module 5, Section 5.3.5.3 instead of as an appendix to the SCS. The SCS will provide a cross reference to the safety data in Module 5, Section 5.3.5.3.

- Anheart proposes the following as adverse events of special interest (AESIs) or other special events of interest (OSEI) to be included in the ISS: Hy's Law cases, liver-related events, interstitial lung disease (ILD), QT-related events, gastrointestinal events, nervous system disorders.

- Anheart proposes the following safety subgroups: age (<65 years, ≥65 years to <75 years and ≥75 years), sex (male and female), brain metastases (yes and no), race (Asian, White, Other), region (US, Asia and Rest of World as one comparison and China and Rest of World as a second comparison)

- Narratives and CRFs will be provided for deaths (within 30 days after last dose, and those occurring after 30 days after last dose if treatment related), TESAEs (within 30 days after last dose, and those occurring after 30 days after last dose if treatment related), AESIs, and TEAEs leading to treatment discontinuation.

- Anheart will provide a 90-day safety update with a new data cutoff of approximately within 1 month following the initial NDA submission. The submission will include updated or new safety narratives and CRFs along with an updated duration of response with approximately 18 months of duration follow-up.

QUESTIONS AND RESPONSES

FDA Preamble

As previously communicated, your plan to submit a marketing application for taletrectinib appears reasonable. However, it will be important for you to justify the applicability of data from Studies C203 and G208 to U.S. patients with ROS1 fusion-positive NSCLC. Given this, please provide a summary of the number of U.S. patients enrolled from the G208 study as well as a listing of the numbers of patients enrolled from all other countries. You should also provide a summary of the efficacy results in U.S. patients side-by-side for comparison with the ex-U.S. patient population.

Safety Pooling Strategy

1. Does the Agency agree with the proposed pooling strategy for safety populations to support the NDA submission?

FDA Response: In general, we agree with your proposed pooling strategy for the safety populations; however, we recommend that you include a third pool of patients which includes all cancer patients who received taletrectinib at the 600 mg QD dose.

Location of ISS

2. Does the Agency agree to split the ISS across eCTD Module 2.7.4 Summary of Clinical Safety (SCS) and Module 5?

FDA Response: As outlined in in *FDA's Guidance for Industry - Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document* (available at: https://www.fda.gov/media/75783/download), there may be situations in which Section 2.7.4, Summary of Clinical Safety (SCS) would be sufficiently detailed to serve as the narrative portion of the ISS while still concise enough to meet the suggested size limitations for Module 2. This situation is rare, but can occur if an application is small and consists of a single study or a number of small studies. In such situations, the ISS can be split across Module 2 and Module 5, with the narrative portion located in section 2.7.4 and the appendices of tables, figures, and datasets located in Module 5. If the ISS is split across modules in this way, it is critical to include a clear explanation of where all components are located. This explanation should be placed in Module 2 (section 2.7.4) and in Module 5 (section 5.3.5.3).

AESI and OSEI

3. Does the Agency agree with the proposed AESI and OSEI for taletrectinib?

FDA Response: We generally agree with your proposed AESI and OSEIs for taletrectinib. You may also consider providing a summary of the following safety risks given known class effects for ROS1 drugs: skeletal fractures and hyperuricemia.

Subgroups

4. Does the Agency agree with the proposed subgroups for safety analyses?

FDA Response: We generally agree. We recommend including ECOG performance status as a subgroup as well.

Narratives and Case Report Forms (CRFs)

5. Does the Agency agree that the narratives and CRFs that will be provided are sufficient for inclusion in the NDA?
FDA Response: Yes, we agree.

90-Day NDA Safety Update

6. Does the Agency agree with the plan for the 90-day NDA Safety Update?

FDA Response: Yes, we agree. While it would be acceptable to provide updated efficacy data in the 90-day safety update report, previous assessments of response should not be re-adjudicated. This means that ORR results should not change unless a new response occurred after the original data cut-off date and updated duration of response for responses documented prior to the original cut-off date should be based on date of response used for the initial BLA submission.

Clinical Datasets

7. Does the Agency agree with the proposal for the format and content of the electronic datasets to be included in the NDA?

FDA Response: Yes, we agree.

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

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

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

Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[4]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards.
Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.
For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.3 eCTD Sample Submission pg. 44) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[6]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[7].

[6] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

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.[8]

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.[9]

SECURE EMAIL COMMUNICATIONS

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[10]

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product

[8] http://www.fda.gov/ectd
[9] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[10] 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.

development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling changes.

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:
- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21

CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

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

- Assessment Aid[12]

SUBMISSIONS WITH REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.*[13] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

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

SPLIT REAL TIME APPLICATION REVIEW (STAR) PILOT PROGRAM

The FDA is conducting a pilot program, the Split Real Time Application Review (STAR). STAR is a pilot review process allowing earlier patient access to therapies that address an unmet medical need via interactive engagement with the application so that review and analysis of data may commence prior to full supplemental new drug application (sNDA)/supplemental biologics license application (sBLA) submission. An applicant can communicate interest in participating in this pilot program to the FDA review division by submitting a STAR Entry Request if the applicant believes a proposed efficacy supplement fulfills the conditions outlined in the eligibility criteria. Those applicants who do not wish to participate in the pilot program will follow the usual submission process with no impact on review timelines. More information on this pilot program, including eligibility criteria and timelines, can be found at the FDA website for STAR.[14]

[14] https://www.fda.gov/drugs/development-resources/split-real-time-application-review-star

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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/

RANIYA A AL-MATARI
03/01/2024 05:19:18 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	122347
Request Receipt Date	6/2/2022
Product	Taletrectinib
Indication	Taletrectinib for the treatment of adult patients with advanced or metastatic ROS1 positive non-small cell lung cancer (NSCLC) who are ROS1 tyrosine kinase inhibitor (TKI) treatment naïve OR previously treated with crizotinib.
Drug Class/Mechanism of Action	Tyrosine kinase inhibitor
Sponsor	AnHeart Therapeutics
ODE/Division	OCE/DO2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	8/1/2022

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):**

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

[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

reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

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

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

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

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

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

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

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

Deny Breakthrough Therapy Designation ☐

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

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

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.

- *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: Taletrectinib is a small molecule tyrosine kinase inhibitor (TKI) of ROS proto-oncogene 1 (ROS1).

Disease Background: ROS1 mutated NSCLC
ROS1 alterations are found in 1-2% of patients with advanced NSCLC. The majority of pathological mutations occur in the form of gene fusions that produce oncogenic fusion proteins. ROS1-mutated NSCLC typically occurs in patients who were never smokers, and this subset of NSCLC tends to have a poor response to immune checkpoint inhibitors (D'Angelo 2020).

Regulatory history
Taletrectinib 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 overall response rate (ORR), as assessed by independent review committee (IRC), and duration of response (DOR) data from Studies J102, C203, and U101, and safety data from Studies J102, C203, U101, C205, and G208, described in Table 3.

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 accepts endpoints as clinically significant outcome measures for patients with metastatic NSCLC and considered adequate to support traditional approval include an improvement in overall survival (OS) or a large, clinically meaningful improvement inprogression free survival (PFS). ORR of large magnitude and long duration is considered to be an endpoint reasonably likely to predict clinical benefit in NSCLC and has been considered adequate to support accelerated approval for the treatment of patients with NSCLC with targetable genomic alterations (Blumenthal 2015). ORR and DOR have also supported regular approval of targeted therapies for patients with NSCLC with rare targetable genomic alterations.

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.*

Table 1 summarizes available therapies for patients with ROS1-mutated NSCLC. Entrectinib and crizotinib are TKIs with activity against ROS1 alterations.Platinum-based chemotherapy with or without an anti-PD-(L)1 agent is a standard of care treatment regimen for patients with NSCLC irrespective of oncogenic driver mutation status. Platinum-based chemotherapy with or without an anti-PD-(L)1 agent is typically used as a second-line therapy following progression on a ROS1 TKI in this patient population.

Table 1. Available therapies for patients with ROS1 positive NSCLC

Drug/Regimen	Approval type/Endpoint	Treatment effect
FDA-approved therapies for previously untreated patients		
Entrectinib	Regular; n=51 Primary endpoint: ORR Secondary endpoint: DOR	**ORR 78% (95% CI: 65, 89)** DOR, range: 1.8, 36.8+ % DOR ≥ 12 mos: 55%
Crizotinib	Regular; n=50 Primary endpoint: ORR Secondary endpoint: DOR	**ORR 66% (95% CI: 51, 79)** mDOR 18.3 mos (95% CI 12.7, NR)
Therapies for patients with progression on a prior ROS1 TKI		
Platinum-based chemotherapy[1]	N/A Primary endpoint: OS	OS: 9-12 months **ORR: 26-35%**
Platinum-based chemotherapy + anti-PD(L)1 agent[2]	Regular Primary endpoint: OS Secondary endpoints: ORR, DOR	OS: 19-22 months **ORR: 38-55%**

1: Fossella 2003; Scaggliotti 2008; Schiller 2002
2: Gray 2021; USPI KEYRUDA; USPI TECENTRIQ

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

Table 2: Drugs granted BTDR for the same indication(s)

Therapy/Date of BTDR	Study design/N	Results supporting BTDR
For the treatment of previously untreated patients		
Repotrectinib December 2020	Dose escalation/dose expansion N=19	**ORR 95% (95% CI: 74, 99)** DoR, range (months): 1.2+ to 35+ % DoR ≥6 months = 67%
For the treatment of patients with progression on prior therapy		
Repotrectinib May 2022	Dose escalation/dose expansion; patients with progression on ROS1 TKI N=53	**ORR 40% (95% CI: 26, 54)** DoR, range (months): 0.8+ to 17.8+ % DoR ≥6 months = 48%
Crizotinib March 2016	Dose escalation/dose expansion; most patients with progression on chemotherapy N=50	**ORR 72% (95% CI: 58, 84)** mDOR (months): 17.6 (95% CI 14.5, NR)

11. Information related to the preliminary clinical evidence:

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

1. 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.

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

Table 3: Clinical Trials Supporting the BTDR

Study ID/Location	Trial Design	ROS1 mutated Tumor Type	Trial Endpoint
DS6051-A-U101 U.S. 10/2014 – 3/2019	First in human Dose escalation: 50, 100, 200, 400, 800, or 1200 mg once daily (QD)	Advanced solid tumors	MTD: 800 mg Safety, PK Preliminary effi
DS6051-A-J102 Japan Initiated 2/2016,ongoing	Dose escalation: 400, 600, or 800 mg QD 1: ROS1-TKI naïve (n=11) 2: Prior crizotinib (n=4)	NSCLC	MTD: 600 mg PK, Safety
AB-106-C203 China Initiated 7/2020,ongoing	Part 1, dose comparison: 400 mg or 600 mg (n=6) Part 2, dose expansion: 600 mg 1: ROS1-TKI naïve (n=67) 2: Prior crizotinib (n=42)	Stage IIIb/c or IV NSCLC	1º: ORR by IRC 2º: DOR, PFS,

Tables 4 and 5 below provide pooled anti-tumor activity results in treatment-naïve and ROS1 TKI/crizotinib pretreated patients, respectively, who receieved taletrectinib in Studies J102, U101, and C203. Results are shown from patients who received the intended dose for expansion (600 mg QD) and for patients who received any dose of talectrectinib in the respective studies.

Table 4. Anti-tumor activity of taletrectinib in patients with ROS1-mutated NSCLC who are ROS1 TKI naïve.

Efficacy parameter	Patients treated with **taletrectinib 600 mg QD** in Studies J102 (n=4) & C203 (n=64) **Total N=68**	Patients treated with **taletrectinib 400, 600, or 800 mg QD** in Studies J102 (n=9) & C203 (n=67) **Total N=76**
ORR by IRC (%) 95% CI	90 (83, 97)	90 (80, 95)
mDOR, range (months) DOR ≥ 6 months, n (%)	NR (1.3+, 16.6+) 46 (72)	NR (1.3+, 62.2+) 53 (78)

CI: confidence interval; DOR; duration of response; IRC: independent review committee; TKI: tyrosine kinase inhibitor; NR: not reached. J102 cut-off date: August, 19, 2021; C203 cut-off date: February 23, 2022.

Table 5. Anti-tumor efficacy of taletrectinib in patients with ROS1-mutated NSCLC who have received prior crizotinib.

Efficacy parameter	Patients treated with **taletrectinib 600 mg QD** in Studies J102 (n=1) & C203 (n=38) **Total N=39**	Patients treated **taletrectinib 400, 600, or 800 mg QD** in Studies U101 (n=3), J102 (n=3) & C203 (n=38) **Total N=44**
ORR (%) 95% CI	51 (35, 67)	48 (33, 63)
mDOR, range (months) DOR ≥ 6 months, n (%)	NR (1.4+, 12.3+) 11 (28)	NR (1.4+, 51.0+) 12 (57)

CI: confidence interval; DOR; duration of response; IRC: independent review committee; TKI: tyrosine kinase inhibitor. J102 cut-off date: August, 19, 2021; C203 cut-off date: February 23, 2022.

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.*

Patients with ROS1 mutated NSCLC who are ROS1 TKI naïve
The Division considers the reported ORR of 90% (95% CI 80, 95) and the evidence of durable responses, with 78% of responders experiencing a DOR of at least 6 months, to be preliminary clinical evidence of a substantial improvement over available therapies, which include entrectinib and crizotinib, with ORRs ranging from 66-78%. Given the rarity of ROS1 mutated NSCLC, with most approvals being granted based on results from populations of 50 patients, the 76 patients who comprise the primary pooled efficacy population is a robust sample size that provides additional support for the data provided.

Patients with ROS1 mutated NSCLC previously treated with crizotinib
The Division considers the reported ORR of 48% (95% CI 33, 63) and the evidence of durable responses, with 57% of responders experiencing a DOR of at least 6 months, to be preliminary clinical evidence of a substantial improvement over available therapies, which include platinum-based chemotherapy with or without an anti-PD-(L)1 agent, with ORRs ranging from 26%-55%. There are no ROS1 TKIs approved for this indication.

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

  In a pre-BTDR meeting held with AnHeart on May 3, 2022, FDA requested additional justification for the selected dose of taletrectinib 600 mg QD including data on toxicology, pharmacokinectics, pharmacodynamics, and safety data. FDA recommended an additional meeting with clinical pharmacology to discuss dose optimization.

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

  Based on a pooled analysis of 170 patients who received at least one dose of taletrectinib across Studies C203, U101, and J102, the most common (≥ 20%) treatment-emergent adverse events (TEAEs) were diarrhea (65%), increased AST (56%), nausea (49%), increased ALT (49%), vomiting (48%), and anemia (29%). A total of 47% of patients had a ≥ Grade 3 TEAE and 18% had a serious AE. TEAEs led to treatment interruption, dose reduction, or discontinuation in 38%, 14%, and 5.9% of patients respectively. A total of 5 patients (2.9%) had a TEAE leading to death.

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 are previously untreated and for those who have been treated with prior crizotinib (ORRs 90% [95% CI 80, 95] and 48% [95% CI 33, 63]), in association with a trend in durable responses, to be preliminary clinical evidence that taletrectinib may demonstrate a substantial improvement in therapy compared to available therapies for both indications.

☐ DENY:

Provide brief summary of rationale for denial:

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):

At a Type C guidance meeting held on May 3, 2022 to discuss the taletrectinib development program, the Division advised the Sponsor that results from a proposed global study (Study G208) of taletrectinib in patients with advanced ROS1 mutated NSCLC would be required to support a marketing application for taletrectinib given that Study C203 was conducted entirely in China, but that results of Study C203 could be provided as supportive evidence of efficacy. The Division recommended that the Sponsor request a meeting to discuss the topline results when the majority of responders from Study G208 have been followed for ≥ 6 months past onset of response to discuss the adequacy of the data to support marketing applications for the proposed indications.

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. Blumenthal GM, et al. Overall response rate, progression-free survival, and overall survival with targeted and standard therapies in advanced non-small-cell lung cancer: US Food and Drug Administration trial-level and patient-level analyses. J Clin Oncol. 2015 Mar 20;33(9):1008-14.
2. D'Angelo A, Sobhani N, Chapman R, Bagby S, Bortoletti C, Traversini M, Ferrari K, Voltolini L, Darlow J, Roviello G. Focus on ROS1-Positive Non-Small Cell Lung Cancer (NSCLC): Crizotinib, Resistance Mechanisms and the Newer Generation of Targeted Therapies. Cancers (Basel). 2020 Nov 6;12(11):3293.
3. 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.
4. 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.
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. 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.
7. 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
8. U.S. Food and Drug Administration, Genentech Inc, TECENTRIQ (atezolizumab) [package insert]. Accessed April 29, 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761034Orig1s042lbl.pdf

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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07/28/2022 02:54:49 PM

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