CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213591Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 124033
Request Receipt Date	June 18, 2019
Product	Capmatinib
Indication	Capmatinib is indicated for the first-line treatment of patients with metastatic NSCLC with a MET exon 14 skipping mutation
Drug Class/Mechanism of Action	Tyrosine kinase inhibitor
Sponsor	Novartis
ODE/Division	OHOP/DOP2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	August 16, 2019

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):**

   Capmatinib is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation.

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," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

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

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

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

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

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

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

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

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

Deny Breakthrough Therapy Designation ☐

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

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

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Capmatinib was granted breakthrough designation in April 2019 for "treatment of patients with metastatic NSCLC with a MET Exon 14 skipping mutation with disease progression on or after platinum-based chemotherapy". The

[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

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BTD was based on the preliminary results from Study CINC280A2201/Cohort 4. This current breakthrough designation request seeks BTD for the first-line treatment of patients with MET Exon 14 skipping mutation based on data from Study CINC280A2201/Cohort 5b. Capmatinib currently has no FDA-approved indications.

Capmatinib is a small molecule adenosine triphosphate (ATP) competitive, reversible inhibitor of the MET receptor tyrosine kinase. MET mutation is a rare alteration accounting for approximately 2-3% of EGFR-wild type NSCLC. Activated MET promotes tumor cell growth, survival, invasion and metastasis, as well as tumor angiogenesis all resulting in poor clinical outcomes.

Lung cancer is the leading cause of cancer and cancer-related mortality world wide[1] and the leading cause of cancer-related deaths in the United States (US)[2]. First-line treatment of patients with metastatic NSCLC with standard platinum-doublet chemotherapy is associated with median progression-free survival (PFS) of 5-7 months and median overall survival (OS) of 10-16 months. Response rates reported for first-line FDA-approved therapies for metastatic NSCLC are listed in Table 1 below.

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.

This request for breakthrough therapy designation is based on preliminary results from Study CINC280A2201. Study CINC280A2201 is a multi-center, open-label, multi-cohort, activity-estimating study designed to evaluate the anti-tumor activity and safety of capmatinib in patients with EGFR wild-type, ALK rearrangement negative, metastatic NSCLC harboring MET amplification (detected by FISH) and/or mutations (detected by RT-PCR).

Specifically, the clinical evidence in support of this BTDR is derived from Cohort 5b, which enrolled treatment-naïve patients with metastatic NSCLC harboring MET Exon 14 skipping mutation (herafter referred to as MET-mutated NSCLC).

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.*

Overall survival (OS), progression-free survival (PFS) and overall response rate (ORR) are all considered clinically relevant endpoints for drugs intended to treat NSCLC. While OS is considered a direct clinical benefit, effects on PFS and ORR may provide evidence of clinical benefit if the magnitude of the treatment effects are very large and/or tumor responses are exceptionally durable.[3]

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.

The primary biomarker relevant to this specific indication is the inhibition of MET signaling at clinically achievable concentrations.

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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.*

The clinical activity of therapies approved for the treatment of patients with NSCLC in the first-line setting are listed in the table 1 below.

Table 1: Available first-line therapies for NSCLC

Regimen	Indication	Study	Endpoint	Treatment effect
Pembrolizumab + pemetrexed + platinum	first-line metastatic non-squamous NSCLC	Pembrolizumab + pemetrexed + platinum versus Pemetrexed + platinum	OS	NE* vs 11.3 mos
			ORR	**48% vs 19%**
Atezolizumab + bevacizumab + carboplatin + paclitaxel	first-line metastatic non-squamous NSCLC	Atezolizumab + bevacizumab + carboplatin + paclitaxel versus bevacizumab + carboplatin + paclitaxel	OS	19.2 vs 14.7 mos
			ORR	**55% vs 42%**
Pemetrexed + cisplatin	metastatic non-squamous NSCLC	Pemetrexed + cisplatin versus gemcitabine + cisplatin	OS	10.3 vs 10.3 mos
			ORR	**27.1% vs 24.7%**
Bevacizumab + carboplatin + paclitaxel	first line unresectable, recurrent, or metastatic non-squamous NSCLC	Bevacizumab + carboplatin + paclitaxel versus carboplatin + paclitaxel	OS	12.3 vs 10.3 mos
			ORR	**29% vs 12.9%**

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Table 1(continued).

Regimen	Indication	Study	Endpoint	Treatment effect
Paclitaxel + cisplatin	metastatic NSCLC	Paclitaxel + cisplatin versus etoposide	OS	10 vs. 7.4 mos
			ORR	**35% vs. 12%**
Gemcitabine + cisplatin	locally advanced (stage 3A or 3b) or metastatic NSCLC	Gemcitabine + cisplatin versus cisplatin	OS	9 vs. 7.6 mos
			ORR	**26% vs 10%**
Vinorelbine + cisplatin	unresectable, advanced NSCLC	Vinorelbine + cisplatin versus cisplatin	OS	7.8 vs. 6.2 mos
			ORR	**19% vs. 8%**
Docetaxel + cisplatin	locally advanced or metastatic NSCLC	Docetaxel + cisplatin versus vinorelbine + cisplatin	OS	10.9 vs 10 mos
			ORR	**31.6% vs 24.4%**

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

Crizotinib was granted Breakthrough Therapy designation for MET mutation-positive NSCLC with disease progression on or after platinum-based chemotherapy in May 2018. The ORR for crizotinib-treated patients with exon 14 MET mutation-positive NSCLC was 32% (95% CI: 20, 47), with a median DOR of 8.3 months (95% CI: 6.4, 10.5) across all lines of treatment.

11. Information related to the preliminary clinical evidence:

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

After several ammendments, Study CINC280A2201 comprised the following cohorts/sub- cohorts:

- **Cohort 1:** Previously-treated patients with cMET amplified NSCLC with gene copy number (GCN) ≥ 6, divided into
  - Sub-cohort 1a: Patients with a cMET GCN ≥10 NSCLC, or
  - Sub-cohort 1b: Patients with a cMET GCN ≥ 6 and < 10 NSCLC;
- **Cohort 2:** Previously-treated patients with cMET amplified NSCLC (GCN ≥ 4 and < 6)**;**
- **Cohort 3:** Previously-treated patients with cMET amplified NSCLC (GCN < 4);
- **Cohort 4:** Previously-treated patients with cMET mutation-positive NSCLC regardless of cMET GCN;
- **Cohort 5:** Treatment-naïve patients with cMET dysregulated NSCLC, including:

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

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- Sub-cohort 5a: Patients with a cMET amplified NSCLC (GCN ≥10), or
- Sub-cohort 5b: Patients with cMET mutation-positive NSCLC, regardless of cMET GCN.

- **Cohort 6:** Pre-treated patients with either cMET GCN > 10 without cMET mutations or cMET mutations regardless of cMET GCN;
- **Cohort 7:** Patients with cMET mutations regardless of cMET GCN

Due to a lack of drug response in patients with a level of cMET amplification < 10 GCN (Sub-cohorts 1b, 2, and 3), Novartis permanently closed enrollment in these cohorts. Planned enrollment for Sub-cohorts 1a and Cohort 4 was 69 patients each, while planned enrollment for Sub-cohorts 5a and 5b was 27 patients each. . Cohort 6 will enroll 30 patients with similar eligibility criteria as cohort 4 and was added to the protocol to generate supportive safety and efficacy data in the 2nd line population. Cohort 7 will enroll 27 patients with similar eligibility criteria as cohort 5b and was added to the protocol to generate supportive safety and efficacy data in the 1st line population. As of April 15, 2019, enrollment to Cohorts 4 and 5b were complete.

The BTDR is based upon data for MET-mutated NSCLC patients in the first-line setting (Cohort 5b); tumor histology was adenocarcinoma in the majority of patients (n=25/28, 89.3%). All 28 patients had received no prior treatment for metastatic NSCLC before entering the study.

The primary endpoint is ORR by cohort/sub-cohort per RECIST v1.1 as assessed by blinded independent review committee (BIRC) every 6 weeks (i.e., every 2 cycles) from the first day of treatment with capmatinib until disease progression as determined by investigator and confirmed by BIRC. Duration of response (DOR) per RECIST 1.1 as determined by BIRC is a secondary endpoint.

The confirmed ORR by BIRC in 28 patients with treatment-naïve MET-mutated NSCLC (Cohort 5b) as of the data cut-off date of April 15, 2019, was reported to be 68% (95% CI 48, 84) (one complete response), and 68% of the 19 responders had a DOR $\geq$ 6 months and 53% had a DOR $\geq$ 9 months. Two patients with ongoing responses have a follow up duration > 6 months but less than < 12 months.

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

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

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

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

The maximum tolerated dose (MTD) for capmatinib as single agent is not established and the recommended Phase 2 dose (RP2D) of capmatinib tablets as a single agent is 400 mg twice daily (BID) until disease progression. The RP2D was administered to all 28 patients in Cohort 5b. The safety database for capmatinib 400 mg BID as a single agent comprises 334 patients. A high-level comparison of the safety profiles of single agent capmatinib and 3- and 4-drug combination regimens (available therapy for the first-line treatment of patients with metastatic NSCLC) is summarized below in Table 2.

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Table 2: Safety comparision of capmatinib to (3-and 4-drug) available therapies in first-line NSCLC

Regimen	Most common AEs (≥ 30%)	Most common grade 3-4 AEs (≥ 5%)	Discontinuation Rate and AEs (≥ 1%)	Grade 3-4 ILD Fatal ILD
Capmatinib ***(N=334)***	Edema Nausea	Edema Dyspnea	D/C = 16% Edema (1.8%) Pneumonitis (1.8%) Fatigue (1.8%)	G3-4 = 0.6% 1 fatal ILD
Pembro + pemetrexed + platinum ***(N=405)***	Nausea Fatigue* Constipation Diarrhea	Fatigue* Diarrhea	D/C = 20% Pneumonitis (3%) AKI (2%)	G3-4 = 0 No fatal ILD
Atezolizumab + Bevacizumab + Paclatxel + Carboplatin ***(N=393)***	Neuropathy Fatigue* Alopecia Myalgia/pain Nausea Diarrhea Constipation	HTN Fatigue* Diarrhea	D/C = 15% Pneumonitis (1.8%)	G3-4 = 0.3% No fatal ILD

*includes asthenia

MET exon 14 alterations are found in approximately 3% of patients with NSCLC. Studies in the US and Europe reported disease subgroup frequencies between 2.9-3.8%. Molecular analyses similarly report frequencies between 2.7-4.3% among patients with NSCLC. MET exon 14 alterations result in either deletion or interference with the function of the juxtamembrane domain of MET, which increases MET pathway signaling. Like ALK and ROS1 fusions, MET exon 14 alterations can create a "driver mutation" state leading to MET-positive NSCLC.

Patients with NSCLC whose tumors are positive for MET exon 14 alterations tend to be older than patients with NSCLC whose tumors are not positive for MET exon 14 alterations. MET exon 14 alterations are observed in both adenocarcinoma histology (approximately 70%) and squamous cell histology. There is some limited data that suggests the presence of MET exon 14 mutation is accociated with a worse prognosis in terms of survival compared to MET wild-type tumors.[4] Given that the 5-year survival rate for Stage IV NSCLC is approximately 11%, this subpopulation is also considered to have an unmet medical need.

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

☒ GRANT:

Provide brief summary of rationale for granting:

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

A clinically meaningful improvement in ORR [ORR 68% (95% CI 48-84); 53% of responses durable ≥ 9 months] in the first-line treatment setting was observed in patients who received capmatinib as first-line treatment for MET-mutated NSCLC when compared to ORRs reported for the general population of patients with metastatic NSCLC who received chemotherapy with and without anti-neoplastic agents in clinical trials (ORRs: 19-35%). The improvement in ORR is not likely to be attributable to greater sensitivity to treatment, as MET mutation-

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positive NSCLC has been reported to be associated with a poorer prognosis than MET exon 14 wild-type NSCLC, as noted above.

While the lower limit of the 95% CI of the ORR with capmatinib overlaps with the point estimate of ORR for available therapy with 3-drug (pembrolizumab-pemetrexed-platinum) and 4-drug regimens (atezolizumab-bevacizumab-paclitaxel-platinum), the accompanying significant toxicity of the 3-drug and 4-drug regimens compared to single agent capmatinib tablets favors capmatinib's safety profile. The observed ORR for capmatinib, which is similar or better than that observed with available therapy, together with the better toxicity profile leads the team to recommend granted BTD for this indication.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

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

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

Novartis anticipates filing an NDA for capmatinib for the treatment of patients with MET-mutated NSCLC (planned for 3Q 2019), which will include data for 69 patients in Cohort 4 and 28 patients in Cohort 5b. The data cut-off date for the analysis of cohorts supporting the NDA is April 15, 2019, with primary analysis results for Cohort 4 and Cohort 5b currently available. This data cut off allows for 12 months of follow-up on the majority of responders [(25/28 in the previously treated population (Cohort 4) and 17/19 in the treatment-naïve population (Cohort 5b)] as requested by FDA during a teleconference on September 20, 2018.

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

14. List references, if any:

1. WHO, GLOBOCAN 2012: Estimated Cancer, Incidence, Mortality and Prevalence Worldwide in 2012. http://globocan.iarc.fr/Default.aspx

2. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.

3. Blumenthal GM et al, J Clin Oncol, 2016, 33:1008-1014.

4. Vuong HG et al, Lung Cancer, 2018, 123:76-82.

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):

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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 3/18/19/M. Raggio

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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/

LUCKSON N MATHIEU
07/24/2019 02:07:10 PM

ERIN A LARKINS
07/24/2019 02:22:18 PM

PATRICIA KEEGAN
07/24/2019 02:27:35 PM

IND 124033

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Reena Nadpara, Pharm.D.
Senior Global Program Regulatory Manager
Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Nadpara:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for capmatinib.

We also refer to the teleconference between representatives of your firm and the FDA on July 22, 2019. The purpose of the meeting was to present the results from Cohorts 4 and 5B in Study CINC280A2201 and to discuss the proposed filing strategy for the NDA seeking a proposed indication for "treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation as detected by an FDA approved test" relying on the evidence of anti-tumor activity in these single-arm cohorts.

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

If you have any questions, call me at (301) 796-7910.

Sincerely,

{See appended electronic signature page}

Shubhangi (Gina) Mehta, PharmD
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
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 Minutes

Reference ID: 4468648

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	July 22, 2019
Meeting Location:	Teleconference
Application Number:	IND 124033
Product Name:	Capmatinib
Indication:	Capmatinib is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation as detected by an FDA approved test
Sponsor/Applicant Name:	Novartis

Meeting Chair:	Patricia Keegan
Meeting Recorder:	Norma Griffin

FDA ATTENDEES

Patricia Keegan	Division Director
Erin Larkins	Clinical Team Lead
Luckson Mathieu	Clinical Reviewer
Olen Stephens	CMC Reviewer
Pallavi Mishra-Kalyani	Statistical Team Lead
Arup Sinha	Statistical Reviewer
Norma Griffin	Lead Regulatory Project Manager
Soma Ghosh	CDRH Reviewer

SPONSOR ATTENDEES

Mikhail Akimov, MD, PhD	Global Program Head, Oncology Clinical Development
Monica Giovannini, MD	Global Program Clinical Head, Oncology Clinical Development
Maeve Waldron-Lynch, MD	Clinical Development Medical Director
Alaknanda Joshi, PhD	Global Project Biostatistics Head, Oncology Global Development
Sylvie Le Mouhaer	Trial Statistician, Oncology Global Development
Sabine Glaser	Senior Principal Statistician, Oncology Global Development
Samson Ghebremariam	Senior Principal Statistician, Oncology Global Development
Xiaoming Cui, PhD	Director, Clinical Pharmacology, Oncology Clinical Development

Oezlem Tanriverdi, MD	Brand Safety Lead, Chief Medical Office / Patient Safety
Banu Sankaran	Precision Medicine Leader, Oncology Precision Medicine
Aastha Kohli	Global Program Regulatory Director, Regulatory Devices
Rich Steinbach	Regulatory CMC Director, Oncology Global Development
Joseph Posluszny, PhD	Vice President, US Regional Head, Oncology Regulatory Affairs
Beth DiDomenico, PhD	Global Therapeutic Area Lead, Oncology Regulatory Affairs
Benedicte Chauvin	Global Program Regulatory Director, Oncology Regulatory Affairs
Reena Nadpara, PharmD	Senior Global Program Regulatory Manager, Oncology Regulatory Affairs
Sadia Afrin	Global Program Regulatory Manager, Oncology Regulatory Affairs

BACKGROUND

Regulatory

Regulatory History

- The development of capmatinib (INC280) was initiated under IND 116691 (DOP1) for the treatment of patients with advanced c-met dependent advanced solid tumors. The IND-enabling study was Study CINC280X2102, “A Phase I Open-Label Dose Escalation Study with Expansion to Assess the Safety and Tolerability of INC280 in Patients with c-MET dependent Advanced Solid Tumors.” The study was allowed to proceed December 12, 2012.

- On October 15, 2014, a Type B pre-IND/Pre-phase 2 meeting request was submitted to pre-IND 124033 to discuss the overall design a clinical trial of capmatinib for the treatment of patients with NSCLC, Study CINC280A2201; the clinical pharmacology development program; and the preclinical safety package.

- IND 124033 was submitted on January 29, 2015 and was allowed to proceed February 27, 2015.

- A February 7, 2017, Type C teleconference was planned to obtain Agency guidance on the characterization of the pharmacokinetic profile of capmatinib in order to support the filing of a planned NDA for capmatinib. Upon review of the Preliminary Comments, Novartis elected to cancel the teleconference.

- On March 1, 2017, a Type B End-of-Phase 2 meeting was held to discuss clinical data intended to support a planned NDA submission, specifically, data from Study CINC280A2201.

- On January 17, 2018, a meeting was held between Novartis and the Center for Devices and Radiological Health to discuss Novartis' proposed Analytical Validation plan and Accuracy Study, where FDA agreed on using the FoundationOne CDx as the comparator assay and agreed that bridging is likely not required.

- On June 20, 2018, Novartis submitted a Preliminary Breakthrough Therapy Designation Advice request for capmatinib for the treatment of patients with MET Exon 14 skipping mutated advanced or metastatic NSCLC in both the 2nd/3rd line and treatment-naive setting. A teleconference was held between FDA and Novartis on July 5, 2018, in which FDA advised that submission of a BTDR is premature given inadequate follow up to adequately assess the durability of response.

- Novartis submitted an updated Preliminary Breakthrough Therapy Designation (BTD) request on August 30, 2018, in follow-up to their previous Preliminary BTD tcon held on July 5, 2018. In the July 5, 2018 teleconference, FDA stated that a BTDR would be premature and recommended that Novartis re-submit a Preliminary BTD Request Advice meeting based on the results of in patients receiving first-line treatment for metasatic NSCLC (Cohort 5b) supported by the results in patients receiving second-line treatment (Cohort 4), given the apparent higher response rate in 5b as compared with 4. FDA further adviced that the request for preliminary BTD advice should be submitted when there is at least 6 months of follow up from the onset of response for all responders in Cohort 5b.

- On September 20, 2018, a Type C teleconference was held to discuss the overall clinical development strategy to support a potential NDA submission based on results from Study CINC280A2201. FDA stated that:

    - the proposed clinical package, comprising 69 patients with previously treated cMET mutation-positive NSCLC enrolled in Cohort 4 and 24 treatment-naïve patients with cMET mutation-positive NSCLC enrolled in Sub-cohort 5b, may be adequate to support filing of an NDA requesting accelerated approval if the observed ORR is large in magnitude and responses are durable.

    - the proposed NDA would need to include a description of the natural history of patients with cMET mutated NSCLC tumors (e.g., response to available therapy, prognosis).

- An application seeking accelerated approval would be expected to contain at least 12 months of follow up from the onset of response for all responders in order to allow adequate assessment of the durability of responses.

- On January 4, 2019, Novartis submitted a Preliminary Breakthrough Therapy Designation (BTD) advice request. FDA advised Novartis to submit a formal request for BTD.

- On February 22, 2019, Novartis submitted a request for BTD for capmatinib; the BTD was granted for the treatment of patients with metastatic NSCLC with an MET exon 14 skipping mutation who have disease progression on or after platinum-based chemotherapy as stated in the letter issued on April 18, 2019.

- On March 15, 2019, Novartis received Orphan Drug designation for capmatinib for the treatment of NSCLC with MET genomic tumor aberrations.

- On April 7, 2019, FDA issued an iPSP Agreement Letter for capmatinib for the treatment of patients who have received no prior systemic therapy for locally advanced or metastatic NSCLC and whose tumors are EGFR wild-type, ALK-rearrangement negative, and MET dysregulated (amplification or mutation), according to an FDA approved test.

- On April 19, 2019, FDA issued an iPSP Amended Agreement Letter, for capmatinib for the treatment of patients with metastatic NSCLC harboring a MET Exon 14 skipping mutation as detected by an FDA-approved test and who have received no more than two prior lines of systemic therapy for metastatic NSCLC.

- On May 29, 2019, Novartis requested a pre-NDA meeting to discuss the results from Study CINC280A2201 for patients with previously treated (Cohort 4) or treatment-naïve (Cohort 5b) locally advanced or metastatic NSCLC with a MET exon 14 skipping mutation and to discuss the proposed filing strategy for the proposed indication.

- On June 18, 2019, Novartis submitted a request for Breakthrough Therapy Designation for capmatinib for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with a MET exon 14 skipping mutation. This request is under review.

Chemistry, Manufacturing and Controls

Capmatinib is a small molecule drug formulated into film coated tablets. The tablets are manufactured using the capmatinib dihydrochloride monohydrate, which are available in 200 mg and 150 mg strengths according to the free base. The tablet core is composed of the drug substance and standard excipients (microcrystalline cellulose, mannitol, crospovidone, povidone, magnesium stearate, colloidal silicon dioxide, and sodium

lauryl sulfate.) The film coat is composed of excipients commonly used in solid oral formulations.

The discussion of the capmatinib drug product development occurred primarily under IND 124,033 and the cross-referenced IND 116,691. The most recent CMC updates have been reviewed under IND 116,691. The current drug substance synthetic manufacturing, drug product manufacturing processes, and their stability data have been evaluated. The commercial manufacturing sites are listed in the cross-referenced IND. The stability protocol and available stability data meet standard expectations for NDA submissions. There have been three meetings to discuss CMC issues regarding capmatinib development (July 9th, 2014, February 3, 2017, and September 9, 2018). In these meetings, drug substance starting materials were proposed and discussed, stability batches and stability protocols were presented, and minor changes to the film coating were discussed in regards to the comparability data that may be necessary. All typical CMC topics discussed in pre-NDA meetings have been raised with the sponsor and the sponsor declined to request a CMC-only meeting.

FDA notes that, although most topics referenced by FDA in the Guidance for Industry: IND Meetings for Human Drugs and Biologics, *Chemistry, Manufacturing, and Controls Information* have either been previously discussed or are contained in the CMC information filed under IND 116,691, items pertaining to CMC content and format of an NDA were not included in the meeting package.

Nonclinical

Capmatinib (INC280) is a tyrosine kinase inhibitor (TKI) with specificity for the receptor tyrosine kinase (RTK) cMET. Novartis has conducted several in vitro and in vivo pharmacology studies, a complete genotoxicity panel, an ototoxicity study, a phototoxicity study, safety pharmacology studies, and impurity qualification studies. Novartis has also conducted GLP-compliant repeat-dose toxicology studies of 7-day, 28-day, and 13-weeks durations in rats and cynomolgus monkeys, and GLP-compliant reproductive toxicology studies in rats and rabbits.

Clinical

Clinical Study CINC280A2201

Study CINC280A2201 is a multi-center, open-label, multi-cohort, single-arm, activity estimating study designed to evaluate the anti-tumor activity and safety of capmatinib in patients with EGFR wild-type (for exon 19 deletions and exon 21 L858R substitution mutations), ALK- rearrangement negative, metastatic NSCLC harboring cMET amplification (detected by FISH) and/or mutations (detected by RT-qPCR).

The protocol was amended multiple times. Following these amendments, Study CINC280A2201(Study A2201) comprised the following cohorts/sub-cohorts:

- Cohort 1: Previously-treated patients with cMET amplified NSCLC with gene copy number (GCN) ≥ 6, including
  Sub-cohort 1a: Patients with a cMET GCN ≥10 NSCLC
  Sub-cohort 1b: Patients with a cMET GCN ≥ 6 and < 10 NSCLC;
- Cohort 2: Previously-treated patients with cMET amplified NSCLC (GCN ≥ 4 and < 6);
- Cohort 3: Previously-treated patients with cMET amplified NSCLC (GCN < 4);
- Cohort 4: Previously-treated patients with cMET mutation-positive NSCLC regardless of cMET GCN;
- Cohort 5: Treatment-naïve patients with cMET dysregulated NSCLC, including:
  Sub-cohort 5a: Patients with a cMET amplified NSCLC (GCN ≥10)
  Sub-cohort 5b: Patients with cMET mutation-positive NSCLC, regardless of cMET
- Cohort 6: Pre-treated patients with either cMET GCN > 10 without c MET mutations or cMET mutations regardless of cMET GCN;
- Cohort 7: Patients with cMET mutations regardless of cMET GCN

Novartis states that based on a lack of response in patients with tumor cMET amplification < 10 GCN (Sub-cohorts 1b, 2, and 3), Novartis permanently closed enrollment in these cohorts. Cohort 6 will enroll 30 patients with similar eligibility criteria as cohort 4 and was added to the protocol to generate supportive safety and efficacy data in the 2nd line population. Cohort 7 will enroll 27 patients with similar eligibility criteria as cohort 5b and was added to the protocol to generate supportive safety and efficacy data in the 1st line population. As of April 15, 2019, enrollment to Cohorts 4 and 5b were complete. Enrollment status for the study is provided in Table 1.

Table 1. Overall study enrollment (Briefing book, date 6/19/2019, page 22)

Table 3-1 CINC280A2201 study enrollment as of 15-Apr-2019

	Cohort 1a	Cohort 4	Cohort 5a	Cohort 5b	Cohort 6	Cohort 7
Enrolled	69	69	15	28	27	0
Targeted enrollment	69	69	27	27	30	27
*Approximately 456 planned to be enrolled across the cohorts Cohorts 1b, 2, 3 were stopped for futility						

Eligible patients are treated with capmatinib 400 mg (tablet) twice daily. The primary endpoint is overall response rate (ORR) by cohort/sub-cohort per RECIST v1.1 as assessed by blinded independent review committee (BIRC). Tumor assessments are performed every 6 weeks (i.e., every 2 cycles) from the first day of treatment with capmatinib until disease progression as determined by investigator and confirmed by BIRC. Secondary endpoints include duration of response (DOR) per RECIST 1.1 as assessed by BIRC by cohort/sub-cohort, ORR and DOR per RECIST 1.1 by investigator, time to response (TTR) per RECIST 1.1, disease control rate (DCR) per RECIST 1.1, progression free survival (PFS) per RECIST 1.1 by investigator and by BIRC, overall survival (OS).

An expected ORR of 35% with a lower limit of the exact 95% confidence interval (CI) excluding 25% for Cohort 4 and an expected ORR of 55% with a lower limit of the exact 95% confidence interval (CI) excluding 35% for Cohort 5b were pre-specified in the protocol's statistical analysis plan.

Preliminary Results
According to Novartis, the primary analysis was conducted when most of the responding patients from Cohort 4 and 5b had reached 12 months follow up from the onset of response. The data cut-off date for the proposed NDA submission is April 15, 2019. The confirmed ORR assessed by BIRC in treatment-naïve patients with NSCLC with a MET exon 14 skipping mutation (Cohort 5b, n=28) is 68% (95% CI 48, 84). Among the 19 responders in Cohort 5b, 68% have a confirmed DOR ≥6 months and 37% have a confirmed DOR≥12 months; two patients with ongoing responses have a follow up duration >6 months <12 months.

The confirmed ORR assessed by BIRC in the previously treated patients with NSCLC with a MET exon 14 skipping mutation (Cohort 4, n=69) is 41% (95% CI 29, 53). Among the 28 responders in Cohort 4, 64% have a confirmed DOR ≥6 months and 21% have a confirmed DOR ≥12 months; three patients with ongoing responses have a follow up duration >6 months but <12 months.

Real world data (RWD):
Novartis conducted a retrospective chart-review of 211 patients with MET dysregulated NSCLC (157 MET mutated and 54 MET amplified NSCLC) across five institutions in the US, three in Europe, two in Korea and one in Japan. Novartis indicated that none of these patients received capmatinib. The number of patients treated with a MET inhibitor was restricted to ensure no more than 50% of patients included in this chart review had prior exposure to a MET inhibitor. Novartis also presents OS data, provided in Table 2, in patients with MET-mutated NSCLC when treated with MET inhibitor from this study.

Table 2. Overall survival results from the RWD study (Briefing book, date 6/19/2019, page 15)

Table 2-4 Kaplan Meier estimates of overall survival, by selected treatment groups: All patients with MET mutation

	From first diagnosis of advanced/metastatic NSCLC		From start of first line treatment	
	Received METi (n=49)	Did not receive METi (n=108)	Received METi (n=49)	Did not receive METi (n=89)
N(%) of patients with event	27 (55.1)	72 (66.7)	27 (55.1)	57 (64.0)
Median OS, months (95% CI)	25.4 (18.8, 40.9)	10.7 (7.8, 14.4)	23.8 (14.7, 40.9)	9.9 (7.7, 15.9)
6-month OS rate	91.8%	65.4%	81.3%	69.1%
12-month OS rate	78.7%	46.4%	69.6%	43.1%

Novartis states that the safety database at the time of the planned NDA submission will comprise

- pooled safety data from all patients with NSCLC (N = 419) who received single-agent capmatinib at the proposed recommended dosage (400 mg twice daily for tablet or 600 mg twice daily for capsule) for each dosage form. This will include data from 334 patients with MET-mutated NSCLC enrolled across all the study cohorts who all received capmatinib tablets 400 mg twice daily
- pooled safety data from all patients with solid tumors (N = 541) who received single-agent capmatinib at the recommended dosage for that disease form. The safety data set from Study A2201 comprises.

In Study A2201, the most common adverse events were peripheral edema and nausea and the most common grade 3-4 adverse events were peripheral edema and dyspnea.

FDA sent Preliminary Comments to Novartis on July 18, 2019.

SPONSOR QUESTIONS and FDA RESPONSES

Clinical

1. Does the Agency agree that the proposed efficacy and safety package for capmatinib in MET exon 14 skipping mutated NSCLC comprising primarily of the registration Study CINC280A2201 and RWE providing natural history of such disease setting is adequate to substantiate the efficacy and safety of capmatinib and that the results support a filing for full approval for the treatment of patients with locally advanced or metastatic NSCLC with a MET exon 14 skipping mutation irrespective of line of treatment?

   FDA Response: The available efficacy and safety data from clinical trials of capmatinib appears adequate to support the filing of a marketing application for capmatinib for the treatment of patients with metastatic NSCLC with a MET exon 14 skipping mutation. A decision regarding the adequacy of the data to support accelerated or regular approval and the indicated population will be determined during review of the NDA. The duration of follow-up for responding patients and the limited number of patients who received capmatinib in the first-line setting may be inadequate to provide substantial evidence of effectiveness to support an approval in this population.

   While the information provided in the meeting package suggests that patients with metastatic NSCLC with MET exon 14 skipping mutation do not have a better prognosis when compared to an unselected population of patients with metastatic NSCLC, it provides no information regarding the expected response rate with available therapy in patients with metastatic NSCLC with MET exon 14

skipping mutation. Please see FDA's additional comment 6, requesting the protocol that describes the prospective criteria for patient selection in this retrospective chart review.

Novartis' July 19, 2019 Email Response: Novartis acknowledges that a decision regarding the adequacy of the data to support accelerated or regular approval and the indicated population will be determined during the review of the NDA.

With respect to Agency's comment regarding the absence of "expected response rate data with available therapy", please note that the RWE study report will be part of the NDA package and does include the expected response rate data with standard therapies in patients with metastatic NSCLC with MET exon 14 skipping mutation. The report will include the outcome on platinum doublet in 1st line, IO in 1st line, single agent chemotherapy in 2nd/3rd line and IO in 2nd/3rd line.

In regards to the activity of IO in this population of MET mutated NSCLC, the previously published retrospective data show limited efficacy of IO in this subset of patients irrespective of the line of therapy with ORR 6-20% and median PFS <2 months, and efficacy does not seem to be enriched in tumors with PD-L1 expression ≥50% nor high TMB (Awad 2017, Sabari 2017, Sabari 2018, Baba 2019).

Does the Agency have any additional comments on the interpretation on such data?

Furthermore, as requested in additional comment 6, Novartis will submit the study protocol for the retrospective medical chart review to the IND within 30 days of the date of this meeting.

Discussion during the July 22, 2019 meeting: The proposed approach to' provide the requested "real world" data characterizing the natural history of NSCLC with MET exon 14 skipping mutations is acceptable, as previously stated. However, whether the data will be fit for purpose, will be determined during the NDA review taking into account the adequacy and conduct of the protocol used to select the data, the summary data provided, and the supplemental literature review.

2. An Efficacy Update on all responding patients with 12 months follow up will be provided within 90 days after submission of the original NDA. In addition, the Safety Update will be submitted within 90 days after the date of the original submission, in the event priority review is granted. Does the Agency agree with the content and timing of the proposed efficacy update and safety update?

FDA Response: FDA agrees with the content and timing of the proposed safety update. With regard to updated efficacy information, this should be limited to updated duration of response limited to the patients identified as responders with 12 months of follow-up in the original submission and should provide updated data through a cut-off date of 30 days prior to the submission of the efficacy update, in light of the limited number of responding patients (n=47) and limited information on durability of responses (11% of responding patients followed for less than 12 months). The updated DOR should be based on the independent review reader who was chosen at the time of the original CSR cutoff date, if adjudication was necessary (i.e., even if the independent review charter allows for change in reader at each data cutoff if adjudication is necessary, the assessment of response and resulting DOR should not be changed based on such re-adjudication).

Novartis' July 19, 2019 Email Response:

Efficacy update

Novartis would like to clarify the FDA's request. Note that the data cut-off for the planned NDA submission was calculated based on the discussion between Novartis and FDA at the 20-Sep-2018 Type C meeting in which "FDA stated that the request for 12-month follow-up from onset of response in all responding patients is based on the need to characterize the treatment effects observed in a first-line setting where alternative therapy offers the potential for improved survival. FDA stated that if follow-up is not available on all patients at the time of NDA submission, it would be acceptable to provide an efficacy update on all responding patients 90 days after submission of the original NDA; the efficacy update should provide a minimum of 12 months follow-up from onset of response in all responding patients."

Based on this statement, Novartis chose 15-Apr-2019 as the appropriate data cutoff for the original submission where all but 5 of the 47 responders (3 in Cohort 4 [2nd/3rd line setting] and 2 in Cohort 5b [1st line setting]) had less than 12 months follow-up since the onset of response. Since that data cut-off, 4/5 responders have reached their 12 months follow-up as of 11-Jul-2019. The last remaining responder (in Cohort 5b) will reach 12 months follow-up on 18-Sep-2019.

Novartis plans to update duration of response for all 47 responders, including the remaining 5 patients. Novartis had planned to include these ongoing responders in the efficacy update as they all will have at least 12 months of follow-up from onset of response at the data cut-off used for the efficacy update. Our understanding from the Type C meeting held on 20-Sep-2018 is that this approach would be acceptable for an efficacy update provided within 90 days of the original NDA submission.

For discussion at the meeting, can the Agency confirm a full SCE update is not expected? Specifically, no update on primary endpoint (ORR) and other

secondary endpoints (PFS, OS) will be provided. Based on the feedback provided by the Agency requesting only DOR update, we will therefore provide only an updated DOR table for both Cohort 4 and Cohort 5b as presented in Table 2-1. This will be submitted as an appendix to the current SCE part of the original NDA submission. Does the Agency agree?

Table Error! No text of specified style in document.-1 Proposed updated DOR table for responding patients (example for Cohort 4)

	Original submission: 15-Apr-2019 cut-off Cohort 4 (2nd/3rd line MET mutated) N = 28	Updated DOR: XX-Nov-2019 Cohort 4 (2nd/3rd line MET mutated) N = 28
No. of events, n(%)	20 (71.4)	XX (X)
No. of censored, n(%)	8 (28.6)	XX (X)
Event after ≥ 2 missing assessments	1 (3.6)	XX (X)
Ongoing without event	7 (25.0)	XX (X)
Percentiles [95% CI] (month)		
25th	4.22 [2.79, 7.16]	XX (X)
50th	9.72 [5.55, 12.98]	XX (X)
75th	13.80 [10.58, NE]	XX (X)
Kaplan-Meier estimates (%) DOR rate [95% CI] at:		
3 months	89.3 [70.4, 96.4]	XX (X)
6 months	64.3 [43.8, 78.9]	XX (X)
9 months	56.9 [36.8, 72.8]	XX (X)
12 months	31.8 [14.8, 50.3]	XX (X)
Descriptive summary of DOR-n (%)		
< 3 months	3 (10.7)	XX (X)
≥ 3 to < 6 months	7 (25.0)	XX (X)
≥ 6 to < 9 months	3 (10.7)	XX (X)
≥ 9 to < 12 months	9 (32.1)	XX (X)
≥ 12 to < 15 months	4 (14.3)	XX (X)
≥ 15 to < 18 months	1 (3.6)	XX (X)
≥ 18 to < 21 months	1 (3.6)	XX (X)
≥ 21 months	0	XX (X)

N: The total number of patients with confirmed CR or PR in FAS. It is the denominator for percentage (%) calculation.
n: Number of patients who are at the corresponding category.

Since the date of the original NDA submission is planned for 12-Sep-2019, the additional DOR update will be provided within 90 days of this date and therefore will be submitted on 11-Dec-2019.

In regards to the DOR update on the current responders using a data cut-off date of 30 days prior to this planned update submission, Novartis will move the cut-off date closer to the planned submission date. However, as the scheduled radiological assessment dates have limited flexibility (protocol allows a +/-4 days

windows) and are also related to the patient availability, would the Agency accept a cutoff date up to 45 days prior to the submission of the DOR update?
If a data cut-off up to 45 days prior to the submission of the DOR update is acceptable to the Agency, Novartis proposes an actual cut-off date between 01-Nov-2019 and 12-Nov-2019 (subject to radiological scheduled assessment dates and patient availability).

The independent radiology review charter allows for a change of previously accepted reader each time adjudication is necessary. Such change might also be triggered by reader substitution due to unavailability of the original reviewer at a specific time-point. However, every attempt will be made to use the same independent reader accepted for the data in the original CSR to avoid changes in previously assessed responses and DOR based on re-adjudication.

Safety update
Novartis would like to further clarify with the Agency the planned presentation of safety tables in the 120-day safety update report. Novartis plans to provide updated safety data from the pivotal study A2201. No updates on the pooled data are planned to be conducted because majority (n=334/541) of the pool is comprised of study A2201 and final data from all other studies in the pool were already included at the time of original submission, thus their data remains unchanged.

All updated safety data from study A2201 will be provided as side-by-side presentation (see example in Table 2-2 below). The two data cutoffs will then be 15-Apr-2019 and 18-Sep-2019.

Please note that the number of patients in the 120-day safety update will be slightly larger than the n=334 patients from the original submission since we will be including additional enrolled patients from cohort 6 and cohort 7 (since 15-Apr-2019 data cut-off date).

Does the Agency agree with this approach in the 120-day safety update report?

Table **Error! No text of specified style in document.**-2 Presentation of safety tables in 120-day safety update report

	Original submission: 15-Apr-2019 cut-off		**Safety update: 18-Sep-2019 cut-off**	
	Study A2201		**Study A2201**	
	N=334		**N=XXX**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Adverse events	**328 (98.2)**	**219 (65.6)**	**XX (X)**	**XX (X)**

	Original submission: 15-Apr-2019 cut-off		Safety update: 18-Sep-2019 cut-off	
	Study A2201		Study A2201	
	N=334		N=XXX	
	All grades	Grade 3/4	All grades	Grade 3/4
Category	n (%)	n (%)	n (%)	n (%)
Treatment-related	282 (84.4)	119 (35.6)	XX (X)	XX (X)
SAEs	169 (50.6)	139 (41.6)	XX (X)	XX (X)
Treatment-related	43 (12.9)	29 (8.7)	XX (X)	XX (X)
Fatal SAEs	11 (3.3)	11 (3.3)	XX (X)	XX (X)
Treatment-related	4 (1.2)	4 (1.2)	XX (X)	XX (X)
AEs leading to permanent discontinuation	54 (16.2)	33 (9.9)	XX (X)	XX (X)
Treatment-related	37 (11.1)	20 (6.0)	XX (X)	XX (X)
AEs leading to dose adjustment/interruption	198 (59.3)	132 (39.5)	XX (X)	XX (X)
AEs leading to dose adjustment	76 (22.8)	20 (6.0)	XX (X)	XX (X)
AEs leading to dose interruption	181 (54.2)	120 (35.9)	XX (X)	XX (X)
AEs requiring additional therapy	305 (91.3)	171 (51.2)	XX (X)	XX (X)

Numbers (n) represent counts of subjects.
A subject with multiple severity grades for an AE is only counted under the maximum grade.
MedDRA version 22.0, CTCAE version 4.03.

Discussion during the July 22, 2019 meeting: FDA stated that the proposal, as further clarified during the meeting, to submit updated efficacy information for all 47 responding patients for duration of response (DOR) from the original data cut-off date of April 15, 2019, through October 28, 2019, and submission of an addendum to the SCE, an addendum to the CSR for Study A2201, updated patient level datasets for efficacy and revised labeling in the efficacy update planned for December 11, 2019, is acceptable. FDA stated, and Novartis agreed, that the original primary IRC reader's assessment of response will be maintained in providing the updated efficacy data despite the IRC charter, which allows for change in the primary IRC reader when data is updated.

FDA clarified the data to be included in the tabular format for presentation of DOR [i.e., provide the observed proportion of responding patients that were durable for ≥6, ≥12, and ≥18 months; do not provide KM-estimated DOR] and stated that the information suggested for inclusion by Novartis in Table 2-1 above is too granular and confusing.

FDA stated, and Novartis agreed, that the safety update will contain an updated pooled safety dataset for all 541 patients plus any additional patients enrolled in Study A2201 through the data cutoff date of September 18, 2019.

3. Novartis believes that the results of Study CINC280A2201 are clinically compelling in addressing a population with an unmet need. Novartis is planning to submit a priority review request at the time of NDA submission. Does the Agency agree that the NDA application could qualify for priority review?

   FDA Response: FDA does not object to Novartis including a request for priority review designation, with justification for such a request, in the proposed NDA. A determination regarding priority review status will be made during initial review of the NDA submission.

   Novartis' July 19, 2019 Email Response: Novartis acknowledges the Agency's comments. No further discussion is needed.

   Discussion during the July 22, 2019 meeting: FDA inquired regarding the timing for the planned submission of the marketing application for the companion diagnostic test. Novartis stated that the pre-market application (PMA) for the companion diagnostic will be submitted in time for planned approval of the PMA to be concurrent with approval of the NDA for capmatinib.

4. Novartis believes the NDA qualifies for a user fee waiver based on the orphan drug designation received. Does the Agency agree?

   FDA Response: FDA agrees. Under section 736(a)(1)(F) of the FD&C Act, a human drug application for a product that has been designated as a drug for a rare disease or condition (referred to as an orphan drug) under section 526 of the FD&C Act is not subject to an application fee unless the human drug application includes an indication for other than a rare disease or condition.

   Novartis' July 19, 2019 Email Response:
   Novartis acknowledges the Agency's comments. No further discussion is needed

   Discussion during the July 22, 2019 meeting: There was no discussion during the meeting.

5. Novartis believes the application qualifies for a disease-specific waiver from conducting pediatric studies in the proposed indication. Does the Agency agree?

   FDA Response: FDA refers to the April 7, 2019, iPSP Agreement letter for capmatinib *for the treatment of patients who have received no prior systemic therapy for locally advanced or metastatic non-small cell lung cancer (NSCLC) and whose tumors are EGFR wild-type, ALK-rearrangement negative, and MET dysregulated (amplification or mutation), according to an FDA approved test.* FDA also refers to the April 19, 2019, iPSP Amended Agreement letter, for capmatinib *for the treatment of patients with metastatic non-small cell lung*

cancer (NSCLC) harboring a MET Exon 14 skipping mutation as detected by an FDA-approved test and who have received no more than two prior lines of systemic therapy for metastatic NSCLC. Based on these agreements to Novartis' plan to seek a waiver from the requirements of PREA for all age groups, Novartis has completed its requirements for this stage of drug development and should submit a copy of the iPSP Amended Agreement letter in the planned NDA.

FDA further notes that Novartis received Orphan Drug Designation for capmatinib on March 17, 2019 for the indication *for the treatment of non-small cell lung cancer with MET genomic tumor aberrations.* A copy of this letter should also be submitted in the NDA. If the application is submitted prior to August 18, 2020, when the requirements of FDARA will be fully implemented, Novartis is exempt from PREA requirements. Please see the section on PREA Requirements below on implementation of FDARA.

Novartis' July 19, 2019 Email Response:
Novartis acknowledges the Agency's comments. No further discussion is needed

Discussion during the July 22, 2019 meeting: There was no discussion during the meeting.

ADDITIONAL COMMENTS

Clinical

6. Please submit the study protocol for the retrospective medical chart review to the IND within 30 days of the date of this meeting

   Novartis' July 19, 2019 Email Response:
   Novartis acknowledges the Agency's request and will submit the study protocol to the IND within 30 days of the date of this meeting. No further discussion is needed.

   Discussion during the July 22, 2019 meeting: There was no discussion during the meeting.

Clinical Pharmacology

7. FDA requests that Novartis submit their plan for assessing the in vivo drug-drug interaction (DDI) potential of capmatinib when coadministered with CYP2C8 substrates as well as with MATE substrates.

   FDA recommends the content and format of information found in the Clinical Pharmacology section (Section 12) of the labeling submitted to support this application be consistent with FDA Guidance for Industry, "Clinical Pharmacology

Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at https://go.usa.gov/xn4qB). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Address the following questions in the Summary of Clinical Pharmacology:

a. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.

b. What are the exposure-response relationships for efficacy, safety and biomarkers?

c. What is the effect of capmatinib on the QT/QTc interval?

d. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?

e. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.

f. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Novartis' July 19, 2019 Email Response to items 7a-7f: Novartis acknowledges the Agency's request.

The DDI potential of capmatinib on the PK of CYP2C8 substrate was evaluated using a verified PBPK model. As agreed during the pre-IND meeting on 12-Dec-2014, Novartis will include Simcyp model files and specific excels files in the submission. Novartis will address Agency's question on the adequacy of the modeling and the need for clinical DDI study, if any, during the NDA review.

The potential inhibition of capmatinib on renal transporters (MATE in this case) was evaluated using renal biomarker Cystatin C in comparison to creatinine in serum in healthy subjects. The rationale and data will be discussed in study CSR and Summary of Clinical Pharmacology. Novartis will address Agency's question on the need for clinical DDI study for MATE during the NDA review.

In addition, Novartis acknowledges the Agency's advice in additional comments 8-14. No further discussion is needed.

Discussion during the July 22, 2019 meeting: There was no discussion during the meeting.

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

8. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

9. Provide a final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.

10. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
    - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

11. Submit the following for the population pharmacokinetic analysis reports:
    - Standard model diagnostic plots
    - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
    - Model parameter names and units in tables.
    - Summary of the report describing the clinical application of modeling results.

    Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

12. Submit the following information and data to support the population pharmacokinetic analysis:
    - SAS transport files (*.xpt) for all datasets used for model development and validation.

- A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

13. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.

14. Include the following items when you submit your QT study report:
    a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed.
    b. Electronic copy of the study report.
    c. Electronic or hard copy of the clinical protocol.
    d. Electronic or hard copy of the Investigator's Brochure.
    e. Annotated CRF.
    f. A data definition file which describes the contents of the electronic data sets.
    g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses.
    h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable).
    i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point.
    j. Narrative summaries and case report forms for any:
        i. Deaths
        ii. Serious adverse events
        iii. Episodes of ventricular tachycardia or fibrillation
        iv. Episodes of syncope
        v. Episodes of seizure

vi. Adverse events resulting in the subject discontinuing from the study

k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com).
l. A completed Highlights of Clinical Pharmacology Table.

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

Discussion during the July 22, 2019 meeting: There was no discussion during the meeting for Additional Comments 8-14.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 14, 2019, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. However, agreement cannot be reached because the meeting package did not provide information on the planned content and format of the planned NDA.

Discussion during the July 22, 2019 meeting: Novartis acknowledged there are no agreements on the content and format of the planned NDA. FDA reminded Novartis that the application must therefore be complete at the time of submission. Novartis inquired about whether an application orientation meeting (AOM) would be helpful to the FDA review team for the NDA. FDA stated that an AOM may not be needed, but Novartis may request one.

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.

We refer to the April 7, 2019, iPSP Agreement letter for capmatinib *for the treatment of patients who have received no prior systemic therapy for locally advanced or metastatic non-small cell lung cancer (NSCLC) and whose tumors are EGFR wild-type, ALK-*

rearrangement negative, and MET dysregulated (amplification or mutation), according to an FDA approved test. We also refer to the April 19, 2019, iPSP Amended Agreement letter, for capmatinib *for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) harboring a MET Exon 14 skipping mutation as detected by an FDA-approved test and who have received no more than two prior lines of systemic therapy for metastatic NSCLC.* Based on these agreements your plan to seek a waiver from the requirements of PREA for all age groups, you have completed your requirements for this stage of drug development and should submit a copy of the iPSP Amended Agreement letter in the planned NDA.

We also note that you received Orphan Drug Designation for capmatinib on March 17, 2019 for the indication *for the treatment of non-small cell lung cancer with MET genomic tumor aberrations.* A copy of this letter should also be submitted in the NDA. If the NDA for capmatinib is submitted prior to August 18, 2020, when the requirements of FDARA will be fully implemented, you will be exempt from PREA requirements. However, if the NDA is submitted after August 18, 2020, you will be required to address the provisions of FDARA as discussed below and may need to further amend the April 19, 2019, Amended Agreed iPSP.

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.

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

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

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA." These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants
[2] 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

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2 https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm5 44641.htm

[2] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*

3 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

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 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

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4 http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08 4159.htm

5 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09 3307.htm

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.

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)				

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* (February 2018) and the associated *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.[6]

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[7]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid[8]

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6 https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRe quirements/UCM332468.pdf

7 https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm61292 7.htm

8 https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm61292 3.htm

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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/

NORMA S GRIFFIN
07/26/2019 02:47:02 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 124033

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Andrea M. Wagner, Pharm.D.
Associate Director, Regulatory Affairs, Oncology
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Wagner:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for capmatinib.

We also refer to the meeting between representatives of your firm and the FDA on March 1, 2017. The purpose of the meeting was to obtain FDA feedback on the clinical data intended to support a planned NDA seeking accelerated approval of capmatinib for the following proposed indication: "Capmatinib (INC280) is indicated for the treatment of (b) (4)

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

If you have any questions, call me at (240) 402-3656.

Sincerely,

{See appended electronic signature page}

Susan Truitt, R.N., M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	March 1, 2017, 3:00 – 4:00 p.m. ET
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1311 Silver Spring, Maryland 20903
Application Number:	IND 124033
Product Name:	Capmatinib
Indication:	Treatment of (b) (4)
Sponsor/Applicant Name:	Novartis Pharmaceuticals Corporation
Meeting Chair:	Patricia Keegan, M.D.
Meeting Recorder:	Susan Truitt, R.N., M.S.

FDA ATTENDEES

Patricia Keegan, M.D., Director
Erin Larkins, M.D., Clinical Team Leader
Luckson Mathieu, M.D., Clinical Reviewer
Susan Truitt, R.N., M.S., Regulatory Health Project Manager
Shubhangi (Gina) Mehta, Pharm.D., Regulatory Health Project Manager
Whitney Helms, Ph.D., Nonclinical Team Leader
Jeanne Fourie Zirkelbach, Ph.D., Clinical Pharmacology Team Leader
Brian Furmanski, Ph.D., Clinical Pharmacology Reviewer
Rosane Charlab Orbach, Ph.D., Genomics Team Leader
Kun He, Ph.D., Statistics Team Leader
Thomas Ly, Ph.D. Statistics Reviewer
Eunice Lee, Ph.D., CDRH Team Leader
Timothy Schaefer, Ph.D., CDRH Reviewer

FDA Observer Participants:
Abena Agyeman, M.D., Clinical Reviewer
Ashley Ward, M.D., Clinical Reviewer
Kelly Norsworthy, M.D., Clinical Reviewer
Julie Schneider, Ph.D., Regulatory Scientist

SPONSOR ATTENDEES

Margaret Dugan, M.D., Global Program Head, Oncology Clinical Development
Mikhail Akimov, M.D., Global Clinical Leader, Oncology Clinical Development
Shanthi Ganeshan, Ph.D., Vice President, North American Region Head, Oncology Regulatory Affairs
Beth DiDomenico, Ph.D., Global Program Regulatory Director, Oncology Regulatory Affairs
Andrea Wagner, Pharm.D., Global Program Regulatory Manager, Oncology Regulatory Affairs
Monica Giovannini, M.D., Sr. Global Clinical Leader, Oncology Clinical Development
Alaknanda Joshi, Ph.D., Executive Director, Biostatistics, Oncology Global Development
Stephane Wong, Ph.D., Global Head, Oncology Precision Medicine
Aastha Kohli, M.S., Associate Director, Companion Diagnostics Regulatory
Xiaoming Cui, Ph.D., Director Principal Fellow, Clinical Pharmacology, Oncology Clinical Development
Kevin Wu, M.D., Medical Director, Clinical Development and Medical Affairs

BACKGROUND

Proposed Indication

"Capmatinib (INC280) is indicated for the treatment of patients (b) (4)
(b) (4)

Regulatory

Novartis requested a pre-IND meeting in 2014 with FDA's Division of Oncology Products 2 (DOP2) to discuss the design of study CINC280A2201, an activity estimating study in patients with advanced NSCLC. FDA sent Preliminary Comments to Novartis on December 11, 2014, and on December 12, 2014, Novartis requested cancellation of the scheduled December 12, 2014, meeting because FDA's responses were clear and addressed Novartis' questions. Novartis submitted new IND 124033 on January 29, 2015, and FDA issued a Study May Proceed letter on February 27, 2015.

Novartis submitted a Type B, End-of-Phase 2 meeting request on December 21, 2016, to obtain FDA feedback on the clinical data intended to support a planned NDA seeking accelerated approval of capmatinib for the proposed indication cited above. Novartis submitted the meeting package on January 27, 2017. FDA sent Preliminary Comments to Novartis on February 13, 2017.

Chemistry, Manufacturing and Controls

The drug substance capmatinib (b) (4) has the chemical name 2-fluoro-*N*-methyl-4-(7-(quinolin-6-ylmethyl)imidazo[1,2-b][1,2,4]triazin-2-yl)benzamide dihydrochloride monohydrate. The molecular formula is $C_{23}H_{17}FN_6O \cdot 2HCl \cdot H_2O$, and the molecular weight is 503.3 (b) (4) g/mol. The drug substance is a light yellow to yellow powder that has (b) (4) solubility in acidic media and low solubility in neutral and basic media. The drug product film-coated tablets have been manufactured in 100 mg and 200 mg dose strengths, and the 150 mg dose strength has recently been developed for clinical use. The composition of the 150 mg film-coated tablet is proportional to the 100 mg and 200 mg tablets. The drug product tablets contain drug substance and the following excipients: mannitol, microcrystalline cellulose, crospovidone, povidone, magnesium stearate, colloidal silicon dioxide, sodium lauryl sulfate, and film coating. The proposed drug product film-coated tablets are packaged in HDPE bottles with desiccant, aluminum induction seal, (b) (4) and stored at room temperature.

Clinical

Clinical Study CINC280A2201

CINC280A2201 is a multi-center, open-label, multi-cohort activity estimating study designed to evaluate the anti-tumor activity and safety of single agent capmatinib in patients with EGFR wild-type (for exon 19 deletions and exon 21 L858R substitution mutations), ALK-rearrangement negative, metastatic NSCLC harboring cMET amplification (detected by FISH) and/or mutations (detected by RT-qPCR).

The study design for CINC280A2201 at the time of initiation of IND 124033 included three cohorts of patients categorized based on the level of cMET amplication:

- **Cohort 1:** Pre-treated patients with cMET gene copy number (GCN) ≥ 6;
- **Cohort 2:** Pre-treated patients with cMET GCN ≥ 4 and < 6;
- **Cohort 3:** Pre-treated patients with cMET GCN < 4.

As stated in the protocol, "pre-treatment" is defined as one or two prior lines of systemic therapy for advanced/metastatic NSCLC. Planned enrollment is 69 patients per cohort or subcohort. Characterization of cMET gene amplification for the purpose of eligibility and assignment to treatment cohorts was to be performed at Novartis-designated central laboratories using the Abbott Molecular Vysis MET CDx fluorescence in situ hybridization (FISH) kit.

The following significant amendments occurred between September 2015 and November 2016.

1. Protocol Version 02 (dated September 11, 2015). To assess the activity of INC280 in cMET mutated NSCLC, a new cohort (Cohort 4) was implemented to enroll patients with cMET exon 14 deletions as detected by the MET Exon 14 Deletion Test irrespective of cMET amplification status. The MET Exon 14 Deletion Test detects in-frame deletion of the entire exon 14 in total RNA; specific DNA mutations are not identified.

2. Protocol version 03 (dated July 28, 2016). To ensure adequate representation of NSCLC patients with very high amplified disease, two sub-cohorts were implemented within Cohort 1:
   - Sub-cohort 1a: Patients with a cMET GCN ≥10;
   - Sub-cohort 1b: Patients with a cMET GCN ≥ 6 and < 10.

   The protocol states that this change was made based on emerging data from the ongoing phase 1 clinical trial of capmatinib, Study CINC280X2102. Cohort 1 of Study CINC280A2201 was divided into these two sub-cohorts to explore the hypothesis that patients with NSCLC with higher GCN may derive greater benefit from cMET inhibition with a higher chance of response to treatment. At the time of this amendment, 148 patients had been enrolled to the study; information on enrollment per cohort was not provided.

3. Protocol Version 04 (dated November 17, 2016). To investigate the safety and antitumor activity of INC280 in treatment-naïve NSCLC patients, a new cohort (Cohort 5) was implemented to enroll treatment-naïve patients with cMET dysregulation:
   - Sub-cohort 5a: Patients with a cMET GCN > 10 (without cMET mutations);
   - Sub-cohort 5b: Patients with cMET mutations regardless of cMET GCN.

Following these amendments, Study CINC280A2201 comprised the following cohorts/sub-cohorts:

- **Cohort 1:** Previously-treated patients with cMET amplified NSCLC with gene copy number (GCN) ≥ 6, divided into
  - Sub-cohort 1a: Patients with a cMET GCN ≥10 NSCLC, or
  - Sub-cohort 1b: Patients with a cMET GCN ≥ 6 and < 10 NSCLC;
- **Cohort 2:** Previously-treated patients with cMET amplified NSCLC (GCN ≥ 4 and < 6);
- **Cohort 3:** Previously-treated patients with cMET amplified NSCLC (GCN < 4);
- **Cohort 4:** Previously-treated patients with cMET mutation-positive NSCLC regardless of cMET GCN;
- **Cohort 5:** Treatment-naïve patients with cMET dysregulated NSCLC, including:
  - Sub-cohort 5a: Patients with a cMET amplified NSCLC (GCN ≥10), or
  - Sub-cohort 5b: Patients with cMET mutation-positive NSCLC, regardless of cMET GCN.

Planned enrollment for Sub-cohorts 1a and 1b and Cohort 4 was 69 patients each, while planned enrollment for Sub-cohorts 5a and 5b was 27 patients each. The primary endpoint is overall response rate (ORR) by cohort/sub-cohort per RECIST v1.1 as assessed by blinded independent review committee (BIRC) every 6 weeks (i.e., every 2 cycles) from the first day of treatment with INC280 until disease progression as determined by investigator and confirmed by BIRC. Duration of response (DOR) as determined by BIRC is a secondary endpoint. For Sub-cohorts 1a and 1b and Cohorts 2-4, assuming ORR = 25% under H_0, a test size of α=0.025, and a sample size of 69 patients per cohort, each sub-cohort/cohort was designed to detect an ORR of 35% based on a one-sided binomial exact test. For Sub-cohorts 5a and 5b, assuming ORR = 35%

under H_0, a test size of α=0.025, and a sample size of 27 patients per cohort, each sub-cohort was designed to detect an ORR of 55% based on a one-sided binomial exact test.

One interim analysis per sub-cohort/cohort for futility based on Bayesian predictive probabilities was planned for Sub-cohorts 1a and 1b and Cohorts 2-4. The current version of the protocol states that interim analyses for each cohort/sub-cohort are planned when at least 28 patients in of Sub-cohorts 1a and 1b, Cohort 2, and Cohort 4 and 20 patients in Cohort 3 have completed at least 6 cycles of treatment (18 weeks) or have discontinued treatment earlier. Cohorts will be stopped for futility at the interim analysis if the probability of success is <10%. No interim analyses are planned for Sub-cohorts 5a and 5b. The protocol states that the primary analysis for any cohort that was stopped for futility may be combined with the primary analyses for other cohorts that were not stopped for futility.

Novartis reports that data from interim analyses for Study CINC280A2201 have demonstrated a lack of drug response in patients with a level of cMET amplification < 10 GCN (Sub-cohorts 1b, 2, and 3). As a result, Novartis has permanently closed enrollment in these cohorts.

In the meeting package, Novartis provides a summary of an unplanned interim analysis of ORR among the first 19 of the planned 69 patients to be enrolled Sub-cohort 1a (patients with cMET GCN ≥ 10) based on a data cut-off date of August 12, 2016. The confirmed ORR assessed by BIRC was 52.6% (95% CI 29, 76) based on 10 patients with responses among 19 patients. Novartis stated that the confirmed durations of response range from 1.4+ months to 8.3+ months.

Novartis states the safety database at the time of the planned NDA submission will consist of ≥ 500 patients with safety information, where more than 400 of these patients treated at the recommend phase 2 dose of either 400 mg tablets orally, twice daily [BID], or 600 mg capsules orally BID.

SPONSOR QUESTIONS AND FDA RESPONSES

Clinical/Statistical

1. Novartis Question 1: Data from Interim Analyses for Phase 2 study CINC280A2201 has demonstrated a lack of drug response in patients with a level of cMET amplification < 10 GCN (Sub-cohort 1b [GCN ≥ 6 and < 10], and Cohorts 2 [GCN ≥ 4 and < 6] and 3 [GCN < 4]). As a result, Novartis has permanently closed enrollment in these cohorts, however, the enrollment for patients with cMET amplification is continuing for those patients whose tumors harbor cMET amplification defined as GCN ≥ 10 (Sub-cohort 1a). *Does the Agency agree?*

   FDA Response: FDA does not object to Novartis permanently closing enrollment to Cohorts 1b, 2, and 3 due to a demonstrated lack of drug response. FDA does not object to Novartis continuing enrollment in Sub-cohort 1a according to a prospectively defined analysis plan for assessment of anti-tumor activity.

Novartis February 17, 2017, Email Response: Novartis acknowledged FDA's response and stated that no further discussion is needed.

2. Novartis Question 2: Given that Sub-cohort 1b, and Cohorts 2 and 3 were declared inefficacious and stopped for futility, Novartis intends to proceed with Sub-cohort 1a (cMET amplification ≥ 10 GCN; N=69) and Cohort 4 (cMET mutated NSCLC; N=69), either separately or together, to support filing(s) under Subpart H regulations for single agent capmatinib in previously-treated patients who have advanced EGFR wild-type, ALK-negative rearrangement NSCLC with cMET dysregulation (as determined by FDA approved tests). *Is this approach acceptable?*

FDA Response: A proposed NDA supported by the results of 69 patients enrolled in Cohort 1a or 69 patients enrolled in each of Cohorts 1a and 4, analyzed separately, where the effect on ORR is large in magnitude and durable, as discussed in FDA's response to Question 3, may support filing an NDA requesting accelerated approval. The proposed NDA would need to include a description of the natural history of patients with cMET amplified/mutated NSCLC tumors (e.g., response to available therapy, prognosis). The evaluation of the clinical significance of the ORR and the adequacy of the data to support accelerated approval would consider the magnitude and duration of the responses in a risk-benefit analysis during NDA review. For additional information regarding accelerated approval see the FDA Guidance for Industry entitled "*Expedited Programs for Serious Conditions – Drugs and Biologics*," found at http://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf.

Novartis February 17, 2017, Email Response: Novartis acknowledges the Agency's recommendation to provide a description of the natural history of patients with cMET amplified/mutated NSCLC at the time of NDA submission and intends to collect it, to the extent possible. However, collecting such information from real life evidence presents challenges due to a number of factors:

- cMET amplification and mutation have only recent been identified as druggable targets in NSCLC, therefore molecular pre-screening is still not conducted on a routine basis.
- cMET amplification (with a GCN ≥ 10) and cMET mutation regardless of amplification is exceedingly rare.
- Assays for cMET mutation and cMET amplification are based on different methodologies and therefore the use of local molecular screening results in a certain level of heterogeneity.
- cMET amplification introduces added complexity because:
    1. Various criteria for detection can be used (i.e. GCN vs. GCN ratio), and
    2. If GCN is used, the cut-off selected to define "amplification" may be different across local sites.

Taking into consideration all these factors, during the meeting, Novartis would like to discuss an appropriate data collection plan and analyses in order to provide the requested

description of natural history of the disease. Specifically we would like to discuss the following proposals:

- Sample size
  We will aim to collect approximately 100 patients with cMET dysregulated NSCLC to include cMET amplification and cMET mutation
- Pre-selection molecular assays
  We will include patients who have cMET dysregulation using assays such as:
  1. amplification by FISH (GCN ≥ 5 and/or GCN ratio > 2.2), NGS
  2. over-expression by IHC (≥2+)
  3. over-expression by RNA
  4. cMET mutation detection by DNA or RNA using PCR or NGS
- Response parameters
  For each line of therapy in the advanced setting, we will collect best overall response and time to progression by investigators.
- Additional information for collection
  In addition we will collect demography, disease characteristics, and type of therapies administered in the advanced setting.

Discussion During the Meeting: Novartis clarified that patients to be included in the characterization of the natural history of cMET dysregulated NSCLC would be identified from clinical sites that pre-screen patients to identify a cMET dysregulation in tumor tissue. FDA stated that since different assays may have been used to identify the patients within and across clinical sites, information on the assays used to identify patients in the natural history assessment should also be provided in the report submitted to the NDA. Novartis confirmed that if more than one test was performed on tumor tissue for an individual patient, that all results related to cMET dysregulation in that patient would be provided in the report.

FDA further stated that the general approach appeared to be acceptable.

3. Novartis Question 3: *Does the Agency agree that the proposed statistical analysis plan for the primary and secondary endpoints, methodology for analysis, and statistical assumptions for study CINC280A2201 are adequate to demonstrate the clinical benefit and safety of single agent capmatinib in this patient population of cMET dysregulated advanced NSCLC patients (as defined in Sub-cohort 1a and Cohort 4)?*

   FDA Response: In a single arm trial, FDA will not use any inferential procedures to evaluate the trial results. Instead, the efficacy decision will be based on whether the lower limit of the 95% confidence interval of the response rate exceeds a clinically irrelevant response rate and whether the duration of response is sufficient, together with the observed response rate, to be reasonably likely to predict clinical benefit and demonstrates a substantial improvement over available therapy which includes pemetrexed, docetaxel (alone or in combination with ramucirumab), nivolumab, pembrolizumab, and atezolizumab. FDA recommends that the sample size calculation for

Cohorts 1a and 4 consider the expected ORR and the lower limit of the 95% confidence interval necessary to exclude ORR observed with these available therapies. Also note that any time-to-event endpoints are uninterpretable in a single arm trial.

Novartis February 17, 2017, Email Response: Targeted efficacy for INC280 in study CINC280A2201 will be determined according to the following parameters for Sub-cohort 1a and Cohort 4, as assessed by BIRC:

- ORR $\geq$ 35%
- Lower limit of the 95% CI of the ORR > 25%

Novartis acknowledges that the efficacy decision for INC280 will be based on whether the lower limit of the 95% CI of ORR exceeds a clinically relevant ORR and, along with duration of response, is reasonably likely to predict clinical benefit and a substantial improvement over available therapy.

A review of response rates for currently available therapies is summarized in Table 2-1. Note that the CINC280A2201 study is designed to detect a clinically meaningful ORR with lower bound of the 95% CI of ORR of 25% which is higher than the ORR in each of the referenced studies below.

Novartis believes, therefore, that the statistical analysis plan adequately reflects the Agency's request. *Does the Agency agree?*

Table -1 Response rates for currently available 2nd line treatments for advanced NSCLC (as per randomized phase III trials)

Author	Treatment arms (Sample size, N)	Biomarker for pre-selection	Efficacy by BIRC	Both SCC and nonSCC	ORR% (95% CI)
Hanna 2004	Pemetrexed (N=265) vs. Docetaxel (N=276)	No	No	Yes	9.1 vs. 8.8 (NA)
Garon 2014	Docetaxel+ramucirumab (N=627) vs. Docetaxel (N=618)	No	No	Yes	23.0 (20-26) vs. 14.0 (11-17)
Herbst 2016	Pembrolizumab 10 mg/kg (N=346) vs. Docetaxel (N=343)	Yes (PD-L1 > 1%)	Yes	Yes	18.0 (14-23) vs. 9.0 (7-13)
Rittmeyer 2017	Atezolizumab (N=425) vs. Docetaxel (N=425)	No	No	Yes	14.0 vs. 13.0 (NA)
Borghaei 2015	Nivolumab (N=292) vs. Docetaxel (N=290)	No	No	nonSCC only	19.0 (15-24) vs. 12.0 (9-17)
Brahmer 2015	Nivolumab (N=135) vs. Docetaxel (N=137)	No	No	SCC only	20.0 (14-28) vs. 9.0 (5-14)

Abbreviations: BIRC = blind independent radiology committee; CI = confidence interval; NA = not available; nonSCC = non-squamous; ORR = objective response rate; SCC = squamous

Discussion During the Meeting: FDA stated that the proposed analysis plan (excluding an ORR of 25% based on the lower limit of the 95% CI around the observed treatment effect) would allow for detection of a treatment effect that exceeds the ORR achieved with available therapy as described in the table immediately above. FDA noted that the assessment of the treatment effect would be considered descriptive only and evaluated in the context of available therapy at the time of submission of the NDA.

4. Novartis Question 4: The Sponsor considers the size of the expected safety database at the time of NDA submission to be adequate to support registration in the proposed indication. *Does the Agency agree?*

   FDA Response: A safety database consisting of ≥ 500 patients treated with single agent capmatinib with ≥ 400 patients treated with the recommended phase 2 dose (RP2D) of either 400 mg tablets BID or 600mg capsules BID would likely be adequate to support the assessment of safety for the proposed NDA.

   Novartis February 17, 2017, Email Response: Novartis acknowledged FDA's response and stated that no further discussion is needed.

5. Novartis Question 5: Assuming positive results from CINC280A2201 Sub-cohorts 5a and 5b, Novartis proposes to use these results to:

   a. Serve as confirmatory data and conversion to full approval for the pre-treated setting (as per Subpart H requirements), and
   b. File a supplement for cMET dysregulated NSCLC patients who are treatment-naïve.

   Is this approach acceptable?

   FDA Response: This discussion is premature as there is insufficient information regarding the magnitude of the treatment effect on ORR or its durability.

   Novartis February 17, 2017, Email Response: Novartis thanks the FDA for its comment. Given the FDA's response to Question 2, and Novartis's intention to generate data on natural history of cMET mutant/amplified NSCLC, we would like to understand the opportunity to use this data, in conjunction with positive data from study CINC280A2201 (Sub-cohort 1a and Cohort 4), for consideration of full approval in the pre-treated setting.

   Furthermore, in light of the expected efficacy readout at the next interim analysis for Sub-cohort 1a and Cohort 4 (estimated Q4-2017), and given the challenges in conducting a randomized study, Novartis would like to explore during the upcoming meeting development opportunities in the treatment-naïve setting to support a first-line registration.

   Discussion During the Meeting: FDA stated that a response rate that is large in magnitude with prolonged duration can support regular approval and cited the example of the

supplemental approval of crizotinib for treatment of patients with ROS-1 positive NSCLC. If the initial approval is an accelerated approval, FDA stated that they would be open to options other than a randomized controlled trial to verify and characterize the clinical benefit.

Additional Discussion During the Meeting: Novartis stated that, based on the most recent data cut of 21 patients with GCN greater than 10, the ORR was 52% as assessed by IRC and the median duration of response was approximately 6 months. FDA stated that submission of a preliminary breakthrough therapy request should contain a minimum of 6 months follow up from the onset of response for all IRC-assessed patients with confirmed responses among these 21 patients. In the preliminary request, Novartis should also provide available data on the natural history of cMET dysregulated NSCLC.

ADDITIONAL COMMENTS

Co-Diagnostics

6. With regard to the companion diagnostic test (Vysis MET CDx FISH Kit) used to determine eligibility for enrollment in Cohorts 1a and 5a, there is insufficient information regarding validation for the cut-point chosen for GCN ≥ 10. Since the currently approved IDE has a cut-point of cMET GCN ≥ 6, the potential exists for enrollment of patients who do not meet the revised eligibility criterion. In order to ensure that the trial can meet its stated objectives, it is essential that the companion diagnostic test be analytically validated, particularly with regard to the higher cut-point (GCN 10). Submit an IDE supplement to CDRH with the appropriate validation study results and the revised study protocol. Also submit a supplement to the IDE for the MET Exon 14 Deletion Test with the revised study protocol, since Cohort 5b was not previously included in the approved IDE.

   Novartis February 17, 2017, Email Response: For the Vysis MET CDx FISH Kit (IDE (b) (4)), Abbott Molecular (AM) will submit an IDE supplement to CDRH by April 14, 2017 with the revised study protocol (Novartis protocol CINC280A2201 and corresponding AM protocol V560-02-14C11-01) and a summary of the analytical performance plan and data to support use of the Vysis MET CDx FISH Kit around the cut-point for GCN ≥ 10. Data from updated "Precision Study" and "Analytical Cutoff Study" (Abbott Molecular studies currently in IDE (b) (4)) will demonstrate that the companion diagnostic test is analytically validated to ensure that the Novartis trial can meet its stated objectives.

   The Vysis MET CDx FISH assay enables detection of MET gene amplification through determination of copy number of the MET gene region in non–small cell lung cancer (NSCLC) formalin-fixed, paraffin-embedded (FFPE) tissue specimens. The assay is being used to characterize MET gene amplification in subjects to confirm eligibility for main screening and enrollment by Novartis in the clinical study CINC280A2201. Primary justification for the higher cut-point chosen (GCN ≥ 10) is contained in Novartis clinical study protocol (CINC280A2201, Version 4, 17-Nov-2016). Clinical validation study

results for the Vysis MET CDx FISH assay using the clinical cutoff (GCN ≥ 10) are an expected outcome of this ongoing clinical trial (CINC280A2201).

AM and Novartis intend to request a meeting with CDRH (e.g., Pre-Submission supplement) in order to address the open AM/CDRH interaction in the Vysis MET CDx FISH Kit Pre-Submission (Q151509, AM Question 1.I. General Comments and AM Question 3.1). The meeting request is planned to occur following the Novartis March 1, 2017 Type B meeting and the Vysis MET CDx FISH Kit IDE supplement described above.

For the MET Exon 14 Deletion Test (IDE G150211), Novartis will submit IDE supplement to CDRH by March 15, 2017 with the revised study protocol for CINC280A2201 (Version 4, 17-Nov-2016).

ISSUES REQUIRING FURTHER DISCUSSION
N/A

ACTION ITEMS
N/A

ATTACHMENTS AND HANDOUTS
N/A

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (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, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) **within 60 days of this End of Phase 2 (EOP2) meeting**. The PSP must contain an outline of the pediatric study or studies 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 PSP 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 PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at

301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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 (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), 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 will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page 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.

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 start 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 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 Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

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 and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors 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), sponsors 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 draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

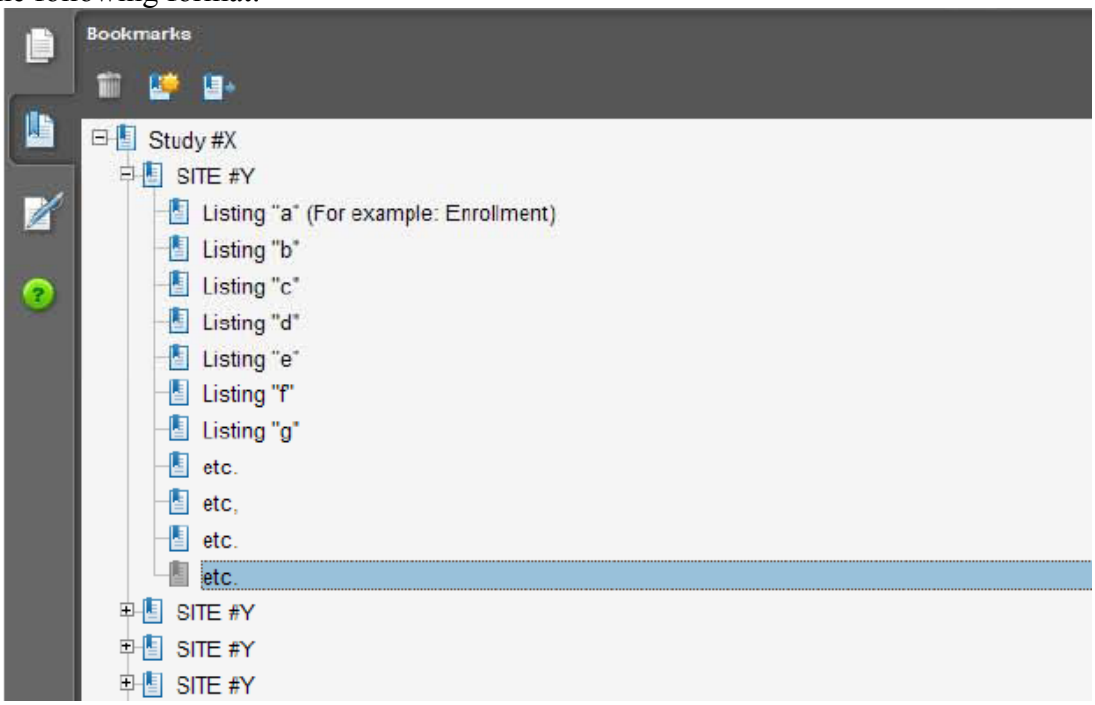
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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 Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

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.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN B TRUITT
03/06/2017