

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213411Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 119421
Request Receipt Date	10/18/2019
Product	Tucatinib
Indication	Locally advanced unresectable or metastatic HER2-positive breast cancer,
Drug Class/Mechanism of Action	Small molecule inhibitor of HER2
Sponsor	Seattle Genetics, Inc
ODE/Division	DO1
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	12/17/2019

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

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

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

Tucatinib, in combination with trastuzumab and capecitabine, is indicated for treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have been treated with trastuzumab, pertuzumab, and T-DM1.

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

YES NO

3. Was the BTDR submitted to a PIND?

YES NO

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

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

4. Consideration of Breakthrough Therapy Criteria:

- a. Is the condition serious/life-threatening¹?

YES NO

If 4a is checked "No," 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>

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- Undetermined
- NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

- i. Only animal/nonclinical data submitted as evidence
- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

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

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

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

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

Deny Breakthrough Therapy Designation

Reviewer Signature: { See appended electronic signature page }

Team Leader Signature: { See appended electronic signature page }

Division Director Signature: { See appended electronic signature page }

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

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

HER2+ breast cancer is a serious and life-threatening disease. Breast cancer is the most common form of cancer in women worldwide, and the fourth leading cause of cancer-related death in the United States (US).

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>

Approximately 20% of breast cancers overexpress HER2. HER2 is a transmembrane tyrosine kinase receptor that mediates cell growth, differentiation, and survival. Tumors that overexpress HER2 are more aggressive and historically have been associated with shorter survival compared to HER2 negative cancers.

Approximately 30% to 50% of patients with HER2+ metastatic breast cancer (MBC) will develop brain metastases. Median survival of HER2+ MBC patients with brain metastases is very poor and ranges from 1 to 3 years with treatment. Due to their poor prognosis and shortened life expectancy, patients with brain metastases have traditionally been excluded from participation in clinical trials.

The initial treatment for patients with HER2+ MBC is a combination of trastuzumab plus pertuzumab and a taxane. However, within 2 years, the majority of patients treated will have progression of disease. After progression of disease on trastuzumab, pertuzumab, and a taxane, standard of care treatment is T-DM1. Progression after T-DM1 remains a clinical challenge as there is no established standard of care. There are currently no approved therapies demonstrating a clinically meaningful improvement in PFS or OS for the treatment of patients with HER2+ MBC after progression of disease on T-DM1. Preferred regimens based on National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and European Society for Medical Oncology (ESMO) guidelines for these patients include trastuzumab or lapatinib in combination with chemotherapy.

Despite recent improvements in the treatment of HER2+ MBC overall, systemic therapies have not yet demonstrated a clinically meaningful impact on the prognosis of patients with brain metastases. No systemic agents are approved specifically for treatment of patients with HER2+ MBC with brain metastases, and generally these patients are treated outside of clinical trials with therapies not labeled for this indication. Treatment for brain metastases typically includes either surgical resection, radiosurgery, and/or whole brain radiotherapy in addition to continuation of systemic anti-HER2 therapy.

Tucatinib is a small molecule inhibitor of the receptor tyrosine kinase HER2. Tucatinib received fast track designation on June 24, 2016, and orphan designation for the treatment of breast cancer patients with brain metastases was granted on June 6, 2017 (#16-5707).

8. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The Sponsor is using results from the HER2CLIMB study to support this BTDR. The primary endpoint is progression free survival (PFS) per blinded independent central review (BICR); alpha-controlled secondary endpoints include overall survival (OS), PFS in subjects with brain metastases, and confirmed overall response rate (ORR).

- 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:

Clinical trial endpoints that have been used to support traditional approval of drugs used in patients with metastatic breast cancer include: ORR, TTP, PFS, and OS.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

There are no drugs specifically approved for patients with metastatic HER2+ breast cancer that have had progression of disease following pertuzumab+trastuzumab and T-DM1 therapy. In addition, no systemic agents are approved specifically for treatment of patients with HER2+ MBC with brain metastases.

The following table shows FDA-approved agents for metastatic HER2+ breast cancer.

Drug	Year Approved	ORR (%)	DOR (months)	PFS or TTP (months)	OS	Line of therapy
Trastuzumab+ paclitaxel	1998	38 vs 15 (paclitaxel)	8.3 vs 4.3	6.7 vs 2.5	22.1 vs 18.4	1
Lapatinib+ letrozole	2010	27.9 vs 14.8 (letrozole)	NR	8.3 vs 3.0		1
Pertuzumab+trastuzumab+ taxane	2012	80.2 vs 69.3 (trastuzumab+docetaxel)	20.2 vs 12.5	18.5 vs 12.4	56.6 vs 40.8	1
Lapatinib+ capecitabine	2007	23.7 vs 13.9 (capecitabine); 31.8 vs 17.4 (inv)	NR	6.3 vs 4.3; 5.6 vs 4.3 (inv)		2
Ado-trastuzumab Emantansine (T-DM1)	2013	43.6 vs 30.8 (capecitabine+lapatinib)	12.6 vs 6.5	9.6 vs 6.4	30.9 vs 25.1	2
-						
Trastuzumab	1998	14	NR	--	--	2+

DOR=duration of response; ORR=objective response rate; PFS=progression free survival; inv=investigator assessed; NR=not reported

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

Breakthrough therapy designation was granted for DS-8201a, an antibody drug conjugate consisting of a HER2-targeted antibody and a topoisomerase I inhibitor, in August 2017. The BTDR was granted for the following indication: for the treatment of patients with locally advanced or metastatic, HER2-positive breast cancer who have been treated with trastuzumab, pertuzumab, and have progressed after ado-trastuzumab emtansine (T-DM1). The BLA for DS-8201a is currently under review in DOI.

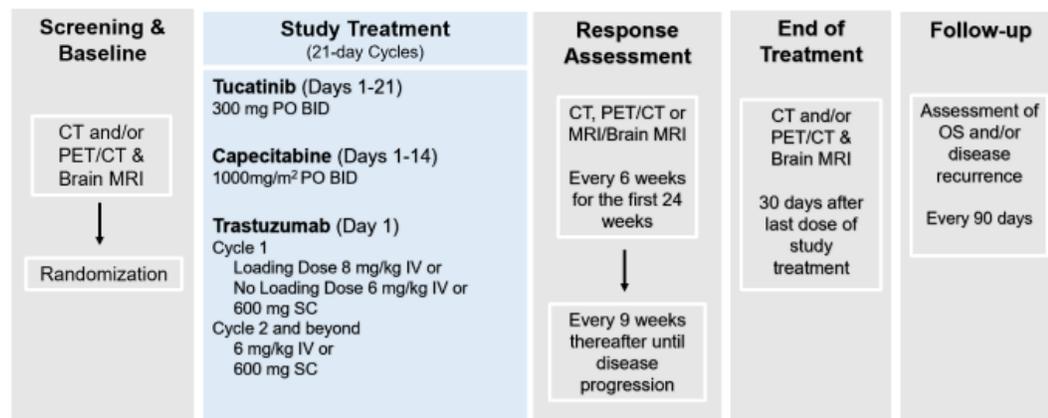
10. Information related to the preliminary clinical evidence:

There is a single phase 2 study (HER2CLIMB) to support this BTDR. HER2CLIMB is an ongoing randomized, double-blind, placebo-controlled, active comparator, global study designed to evaluate the efficacy and safety of tucatinib in combination with trastuzumab and capecitabine in subjects with HER2+ locally advanced unresectable or metastatic breast cancer who were previously treated with trastuzumab, pertuzumab, and T-DM1. Subjects were stratified by presence or history of treated or untreated brain metastases (yes/no), Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 vs 1), and region (US, Canada, rest of world). The trial population included a substantial proportion of subjects with

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

known brain metastases. The primary endpoint is PFS per blinded independent central review (BICR); alpha-controlled secondary endpoints include OS, PFS in subjects with brain metastases, and confirmed ORR.

The study design is shown below:



The trial enrollment period was February 23, 2016 to May 3, 2019. The study was conducted at 169 sites in 15 countries globally and randomized a total of 612 subjects in a 2:1 ratio to receive tucatinib or placebo in combination with trastuzumab and capecitabine. As of the September 4, 2019 data cutoff date, 145 subjects (24%) remained on treatment; 118 subjects (29%) on the tucatinib arm and 27 subjects (13%) on the control arm.

Subjects had received a median of 3 (range, 1 to 14) prior lines of therapy in the metastatic setting. Overall, 48% of patients had brain metastases or a history of brain metastases at the time of study entry.

Results for the final analysis of the primary endpoint (PFS) at final analysis and interim analysis of the secondary endpoints (OS, PFS in subjects with brain metastases, confirmed ORR) with a data cut-off date of September 4, 2019 are shown below. The median follow-up for the entire population was 14 months.

Summary of the PFS:

	Tuc+Cap+Tra (N=320)	Pbo+Cap+Tra (N=160)
Subjects with progression or death ^a , n (%)	178 (55.6)	97 (60.6)
Stratified Hazard Ratio ^{b, c} (95% C.I.)	0.544 (0.420, 0.705)	
Stratified Log-rank p-value ^{c, d}	<0.00001	
Median PFS (Months) (95% C.I.) ^e	7.8 (7.5, 9.6)	5.6 (4.2, 7.1)
25 th , 75 th percentile	4.3, 17.8	3.0, 9.7
Observed min, max ^f	0.0+, 34.6+	0.0+, 24.0+

Cap = capecitabine; Pbo = placebo; Tra = trastuzumab; Tuc = tucatinib

a. Death without either prior progression or more than two missed assessment visits.

b. Hazard ratio comparing Tuc+Cap+Tra to Pbo+Cap+Tra calculated from the Cox proportional hazards model. A hazard ratio <1.0 favors the Tuc+Cap+Tra arm.

c. Computed using stratification factors (Presence or history of brain metastases: Yes/No, ECOG performance status: 0/1, and Region of world: North America/Rest of World) at randomization.

d. Two-sided p-value based on rerandomization procedure (Rosenberger and Lachin, 2002).

e. Calculated using the complementary log-log transformation method (Collett, 1994).

f. '+' means the observed time is from censored subjects.

Summary of OS results:

	Tuc+Cap+Tra (N=410)	Pbo+Cap+Tra (N=202)
Number of deaths, n (%)	130 (31.7)	85 (42.1)
Stratified Hazard Ratio ^{a,b} (95% C.I.)	0.662 (0.501, 0.875)	
Stratified Log-rank p-value ^{b,c,d}	0.00480	
Median OS (Months) (95% C.I.) ^e	21.9 (18.3, 31.0)	17.4 (13.6, 19.9)
25 th , 75 th percentile	12.2, -	10.2, -
Observed min, max ^f	0.1+, 35.9+	0.1+, 33.9+

Cap= capecitabine; Pbo = placebo; Tra=trastuzumab; Tuc=tucatinib

Summary of PFS events in patients with brain metastases:

	Tuc+Cap+Tra (N=198)	Pbo+Cap+Tra (N=93)
Subjects with progression or death ^a , n (%)	106 (53.5)	51 (54.8)
Stratified Hazard Ratio ^{b,c} (95% C.I.)	0.483 (0.339, 0.689)	
Stratified Log-rank p-value ^{c,d,e}	<0.00001	
Median PFS (Months) (95% C.I.) ^f	7.6 (6.2, 9.5)	5.4 (4.1, 5.7)
25 th , 75 th percentile	4.2, 11.8	3.0, 7.5
Observed min, max ^g	0.0+, 34.6+	0.0+, 11.6

Cap= capecitabine; Pbo = placebo; Tra=trastuzumab; Tuc=tucatinib

Confirmed ORR results in patients with measurable disease:

	Tuc+Cap+Tra (N=340)	Pbo+Cap+Tra (N=171)
Best Overall Response ^a , n (%)		
Complete Response (CR)	3 (0.9)	2 (1.2)
Partial Response (PR)	135 (39.7)	37 (21.6)
Stable Disease (SD)	155 (45.6)	100 (58.5)
Progressive Disease (PD)	27 (7.9)	24 (14.0)
Not Evaluable (NE)	0	1 (0.6)
Not Available ^b	20 (5.9)	7 (4.1)
Subjects with Objective Response of Confirmed CR or PR, n	138	39
Objective response rate (ORR), %	40.6	22.8
95% CI ^c for ORR	(35.3, 46.0)	(16.7, 29.8)
Stratified CMH p-value for ORR ^d	0.00008	

Cap= capecitabine; Pbo = placebo; Tra=trastuzumab; Tuc=tucatinib

The most common treatment-emergent adverse events (TEAEs) with tucatinib treatment were diarrhea, palmar-plantar erythrodysesthesia syndrome (PPE) and elevations in liver function tests (LFTs). The events appear manageable with dose modifications.

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

GRANT:

Provide brief summary of rationale for granting:

HER2-positive MBC is an incurable disease with currently available therapies and represents an ongoing medical need. Tucatinib is a small molecule inhibitor of HER2 exhibiting activity in a patient population previously treated with trastuzumab, pertuzumab and T-DM1. Tucatinib offers an

additional treatment option for patients with HER2-positive MBC that have progression of disease after current first and second line standard of care options. The addition of tucatinib to trastuzumab and capecitabine resulted in statistically significant improvements in PFS, OS, PFS in subjects with brain metastases, and confirmed objective response rate (ORR). The tucatinib arm demonstrated the following compared to the control arm:

- *46% reduction in the risk of disease progression or death (hazard ratio [HR] 0.54 [95% confidence interval [CI]: 0.42, 0.71], $p < 0.00001$)*
- *34% reduction in the risk of death (HR 0.66 [95% CI: 0.50, 0.88], $p = 0.0048$)*
- *52% reduction in the risk of progression or death (HR 0.48 [95% CI: 0.34, 0.69], $p < 0.00001$) in subjects with brain metastases*
- *Significantly higher confirmed ORR (41% vs 23%, $p = 0.00008$)*

These results demonstrate a substantial improvement over existing therapy on clinically significant endpoints.

DENY:

Provide brief summary of rationale for denial:

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

Based on results from the HER2CLIMB study, the sponsor has started submission of an NDA application under the real time oncology review (RTOR) pilot program. We will facilitate and expedite review of this application as much as possible.

14. List references, if any:

American Cancer Society: Breast Cancer Facts and Figures 2019. <https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf>

Baselga J, Cortés J, Kim S-B, Im S-A, Hegg R, Im Y-H, Roman L, Pedrini JL, Pienkowski T, Knott A, Clark E, Benyunes MC, Ross G, Swain SM (2012). Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer. *New England Journal of Medicine* 366(2): 109-119.

Dieras V, Miles D, Verma S, Pegram M, Welslau M, Baselga J, Krop IE, Blackwell K, Hoersch S, Xu J, Green M, Gianni L (2017). Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol* 18(6): 732-42.

Giordano SH, Temin S, Chandarlapaty S, Crews JR, Esteva FJ, Kirshner JJ, Krop IE, Levinson J, Lin NU, Modi S, Patt DA, Perlmutter J, Ramakrishna N, Winer EP, Davidson NE (2018). Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: ASCO Clinical Practice Guideline update. *J Clin Oncol* 36(26): 2736-40.

Giordano SH, Temin S, Kirshner JJ, Chandarlapaty S, Crews JR, Davidson NE, Esteva FJ, Gonzalez-Angulo AM, Krop I, Levinson J, Lin NU, Modi S, Patt DA, Perez EA, Perlmutter J, Ramakrishna N, Winer EP, American Society of Clinical Oncology (ASCO) (2014). Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 32(19): 2078-99.

Mounsey LA, Deal AM, Keith KC, Benbow JM, Shachar SS, Zagar T, Dees EC, Carey LA, Ewend MG, Anders CK (2018b). Changing Natural History of HER2-Positive Breast Cancer Metastatic to the Brain in the Era of New Targeted Therapies. Clinical Breast Cancer 18(1): 29-37.

NCCN Clinical Practice Guidelines in Oncology: Breast Cancer (Version 2.2019- July 2, 2019).

https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

Swain SM, Kim S-B, Cortés J, Ro J, Semiglazov V, Campone M, Ciruelos E, Ferrero J-M, Schneeweiss A, Knott A, Clark E, Ross G, Benyunes MC, Baselga J (2013). Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, doubleblind, placebo-controlled, phase 3 study. The Lancet Oncology 14(6): 461-471.

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

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

Grant Breakthrough Therapy Designation
Deny Breakthrough Therapy Designation

Reviewer Signature: { See appended electronic signature page }

Team Leader Signature: { See appended electronic signature page }

Division Director Signature: { See appended electronic signature page }

Revised 3/18/19/M. Raggio

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

/s/

SUPARNA B WEDAM
12/09/2019 10:03:51 PM

JULIA A BEAVER
12/10/2019 06:24:51 AM



IND 119421

MEETING PRELIMINARY COMMENTS

Seattle Genetics, Inc.
Attention: Tina Kim-Hafken
Director, Regulatory Affairs
21823 30th Drive Southeast
Bothell, WA 98021

Dear Ms. Kim-Hafken:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tucatinib (ONT-380).

We also refer to your January 30, 2019, correspondence, requesting a meeting to discuss your

(b) (4)

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, call Jeannette Dinin, Regulatory Project Manager (240) 402-4978.

Sincerely,

{See appended electronic signature page}

Jeannette Dinin
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Sincerely,

{See appended electronic signature page}

Jennifer Gao, MD
Acting Clinical Team Lead
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: End of Phase 2

Application Number: IND 119421
Product Name: tucatinib (ONT-380)

Indication:



Sponsor/Applicant Name: Seattle Genetics, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for April 8, 2019, from 3:00 – 4:00 pm, between Seattle Genetics and the Division of Oncology Products 1. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On January 30, 2019, Seattle Genetics requested a Type B End-of-Phase 2 meeting with the FDA to obtain feedback on their  ^{(b) (4)}

Tucatinib is an orally available, reversible HER2 small molecule tyrosine kinase inhibitor.

Fast Track status was designated for the investigation of tucatinib for the treatment of advanced HER2+ MBC on June 24, 2016. Orphan drug designation for the treatment of breast cancer patients with brain metastases was granted June 5, 2017. Tucatinib, in combination with capecitabine and trastuzumab, is currently in development for the treatment of patients with locally advanced or metastatic HER2+ breast cancer who have received at least 2 prior HER2 targeted regimens (ONT-380-206). An NDA is planned for submission in Q3 2019, primarily supported by data from this trial.

ONT-380-004 Study Design and Results:

This was a Phase 1b, open-label, dose-escalation trial in subjects with HER2+ mBC to assess safety and tolerability and identify the MTD of tucatinib in combination with the approved dose of T-DM1. Fifty-seven (57) T-DM1-naïve subjects were enrolled and treated at 11 sites in the United States and Canada. Fifty subjects were treated at tucatinib 300 mg BID + T-DM1 (8 during initial dose escalation cohort of tucatinib 300 mg BID, 23 in the MTD expansion cohort, and 19 in the CNS expansion cohort). During the dose finding phase of the trial, one dose limiting toxicity (DLT) of AST increased was reported in the first 8 subjects treated with tucatinib 300 mg BID + T-DM1, and a cohort was opened with tucatinib 350 mg BID + T-DM1 with an additional 7 subjects treated at this dose level. Three of 7 subjects (43%) reported DLTs of vomiting, fatigue, and drug hypersensitivity, leading to the tucatinib 350 mg BID dose in combination with T-DM1 being declared not tolerable and the tucatinib MTD in combination with T-DM1 was determined to be 300 mg PO BID.

ONT-380-004 dose levels: starting dose tucatinib with T-DM1 was 300 mg PO BID (tablet formulation). (b) (4)

ONT-380-004 patient population: The median age in the tucatinib 300 mg BID + T-DM1 cohort was 51 years (range 30-72), all female, predominantly white (74%), 3 median prior systemic regimens (range 1 to 12), 62% with advanced stage disease, 98% had distant metastases, and 60% (30 subjects) had brain metastases.

ONT-380-004 adverse events (AEs):

- Treatment emergent adverse events (TEAEs): TEAEs occurring $\geq 40\%$ in order of decreasing frequency were nausea, diarrhea, fatigue, vomiting, thrombocytopenia, epistaxis, headache, aspartate aminotransferase (AST) increased, constipation, decreased appetite, and hypokalemia.
- Serious AEs: 24 (42%) subjects total, with very few subjects reporting >1 SAE; 9 (16%) subjects experienced treatment-related SAEs. The treatment-related SAEs included cardiac failure and fatigue in 2 (4%) subjects each and acute respiratory distress syndrome, constipation, drug hypersensitivity, hypokalemia, pneumococcal sepsis, pneumonia, pyrexia, respiratory distress, and vomiting in 1 (2%) subject each.
- Deaths: 3 died within 30 days after their last dose of study drug (2 due to disease progression and 1 due to accidental drowning)

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3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines 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. 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 conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the 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 Pedsdrugs@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 (cdcr-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 after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start 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 on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the 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>.

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 <https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf>.

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>.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: <https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf>) and for more information.

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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JEANNETTE L DININ
04/01/2019 01:41:52 PM

JENNIFER J GAO
04/01/2019 01:45:32 PM



IND 119421

MEETING MINUTES

Seattle Genetics, Inc.
Attention: Tina Kim-Hafken
Director, Regulatory Affairs
21823 30th Drive Southeast
Bothell, WA 98021

Dear Ms. Kim-Hafken:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tucatinib (ONT-380).

We also refer to the meeting between representatives of your firm and the FDA on February 25, 2019. The purpose of the meeting was to discuss your upcoming NDA submission for patients with HER2+ metastatic breast cancer.

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, contact Jeannette Dinin, Regulatory Project Manager, at (240) 402-4978 or email: Jeannette.Dinin@fda.hhs.gov.

Sincerely,

Sincerely,

{See appended electronic signature page}

{See appended electronic signature page}

Jeannette Dinin
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Jennifer Gao, MD
Acting Clinical Team Lead
Division of Oncology Products 1
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: Pre-NDA

Meeting Date and Time: February 25, 2019; 4:00 – 5:00 pm
Meeting Location: FDA White Oak Building 22, Conference Room: 1311

Application Number: IND 119421
Product Name: Tucatinib
Proposed Indication: Tucatinib, in combination with capecitabine and trastuzumab, is indicated for the treatment of patients with locally advanced or metastatic HER2+ breast cancer who have received at least 2 prior HER2 targeted regimens.

Sponsor/Applicant Name: Seattle Genetics, Inc.

Meeting Chair: Jennifer Gao, MD
Meeting Recorder: Jeannette Dinin

FDA ATTENDEES

Laleh Amiri-Kordestani, MD, Supervisory Associate Director, DOP1
Jennifer Gao, MD, Acting Clinical Team Leader, DOP1
Suparna Wedam, MD, Clinical Reviewer, DOP1
Joyce Cheng, PhD, Biometrics Reviewer, DBV
Anamitro Banerjee, PhD, Branch Chief, ONDP
Xiao H. Chen, PhD, Pharmaceutical Assessment Lead, ONDP
Feiyan Jin, PhD, Chemist, OPQ/OPF/DPAIII/PABVII
Banu Zolnik, PhD, Biopharmaceuticals Team Leader, ONDP
Manheng Wimolnut, PhD, Pharmacology/Toxicology Reviewer, DHOT
Gang Chen, PhD, Fellow, OCE
Joyce Weaver, PharmD, Risk Management Analyst, DRISK, OCE
Jeannette Dinin, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES

Roger Dansey, MD, Chief Medical Officer, Seattle Genetics
Nancy Whiting, PharmD, Senior VP Clinical Development, Seattle Genetics
Luke Walker, MD, VP Clinical Development, Seattle Genetics
Mukesh Verma, MD, Executive Director – Drug Safety, Seattle Genetics
Jiang Qi, PhD, VP of Biometrics, Seattle Genetics
Feng Wentao, PhD, Director of Biometrics, Seattle Genetics

Christopher Endres, PhD, Director of Clinical Pharmacology, Seattle Genetics
Marissa Braff, PhD, Executive Director of Regulatory Affairs, Seattle Genetics
Tina Kim-Hafken, MS, Director of Regulatory Affairs, Seattle Genetics
Amrit (Amy) Walia, MBA, Associate Director of Regulatory Affairs CMC, Seattle Genetics
Natalie Rossignol, MBA, Executive Director Global Product Lead, Seattle Genetics
Daniel Watson, PhD, Director CMC, Seattle Genetics
Sree Nadkarni, PhD, Sr. Director of Small Molecule Manufacturing, Seattle Genetics
Karen Walker, BS, VP of Quality, Seattle Genetics
Corinna Palanca-Wessels, MD, PhD, Medical Director Clinical Development, Seattle Genetics

1.0 BACKGROUND

On December 21, 2018, Seattle Genetics requested a Type B pre-NDA meeting with the FDA to discuss the content and format of a planned New Drug Application (NDA) under the 505(b)(1) pathway for tucatinib (planned Q3 2019). The planned NDA submission is primarily based on data from protocol ONT-380-206 (HER2CLIMB), an ongoing Phase 2, randomized (2:1) double-blinded, placebo-controlled study of tucatinib/placebo in combination with capecitabine and trastuzumab in patients with pretreated unresectable locally advanced or metastatic HER2+ breast cancer. The sponsor's proposed indication is: *Tucatinib, in combination with capecitabine and trastuzumab, is indicated for the treatment of patients with locally advanced or metastatic HER2+ breast cancer who have received at least 2 prior HER2 targeted regimens.*

Tucatinib (ONT-380; ARRY-380) is a selective, adenosine triphosphate (ATP)-competitive small molecule inhibitor of the receptor tyrosine kinase human epidermal growth factor receptor-2 (ErbB2/HER2). Fast Track status was designated for the investigation of tucatinib for the treatment of advanced HER2+ MBC on June 24, 2016. Orphan drug designation for the treatment of breast cancer patients with brain metastases was granted June 5, 2017.

Protocol ONT-380-206 was originally submitted to the IND on August 13, 2015 and has been subsequently amended 7 times. On October 24, 2018, the FDA agreed with the sponsor's most recent proposal to increase the overall sample size to 600 patients with plans to perform the analysis of the primary endpoint of progression free survival (PFS) per independent radiologic review when ~288 PFS events are observed among the first 480 patients. Key secondary endpoints of PFS in patients with brain metastases and overall survival (OS) would be performed using all patients enrolled. Patients must have locally advanced or metastatic HER2+ breast cancer and prior treatment with a taxane, trastuzumab, pertuzumab, and T-DM1. Stratification factors used in the dynamic hierarchical randomization include presence or history of treated or untreated brain metastases (yes/no), Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 vs. 1), and region of world (US vs Canada vs rest of world).

The sponsor plans to further amend the protocol and statistical analysis plan for ONT-380-206 due to an acceleration in patient enrollment. Enrollment of all planned 600 patients is anticipated May 2019 (previously projected July 2019) and the sponsor proposes to analyze PFS on the first 480 patients once all 600 have been enrolled and at least 288 PFS events have been observed in the first 480 patients. At the same time, the sponsor plans to conduct an interim analysis of key secondary endpoints of PFS in patients with brain metastases and OS on all 600 patients.

Analyzing PFS once enrollment of 600 patients is complete will result in ~312 events in the first 480 patients.

The safety dataset for the NDA will include safety data from approximately 800 subjects treated with tucatinib (of which approximately 250 are healthy volunteers). Additionally, approximately 200 subjects treated with placebo plus capecitabine and trastuzumab in ONT-380-206 will be included.

Tucatinib clinical trials planned for inclusion in NDA are:

Trial Identifier	Description	Treatment Regimen	Number of Subjects	Current Status	Inclusion in NDA			
					CSR	SCP (m2.7.2)	SCE (m2.7.3)	SCS (m2.7.4)
ONT-380-206	Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib vs. Placebo in Combination with Capecitabine and Trastuzumab in Patients with Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma	Tucatinib (tablet) 300 mg or placebo PO BID every 21-day cycle plus capecitabine 1000 mg/m ² PO BID for 14 days of every 21-day cycle plus trastuzumab 8 mg/kg IV loading dose Day 1 Cycle 1, followed by 6 mg/kg IV Day 1 of all subsequent cycles.	N=600	Recruiting	Primary analysis	Yes	Yes	Yes
ONT-380-005	A phase 1b, Open-label Study to Assess the Safety and Tolerability of ONT-380 Combined with Capecitabine and Trastuzumab, Alone and in Combination in HER2+ Metastatic Breast Cancer	Tucatinib (tablet) 300 mg or 350 mg PO BID of every 21-day cycle and either capecitabine 1000 mg/m ² PO BID for 14 days of every 21-day cycle (Combination 1); trastuzumab 8 mg/kg IV loading dose Day 1 Cycle 1, followed by 6 mg/kg IV Day 1 of all subsequent cycles (Combination 2); or capecitabine 1000 mg/m ² PO BID for 14 days of every 21-day cycle + trastuzumab 8 mg/kg IV loading dose Day 1 Cycle 1, followed by 6 mg/kg IV Day 1 of all subsequent cycles (Combination 3)	N=60	Enrollment complete	Primary analysis ^a	Yes	Yes	Yes
ONT-380-004	A phase 1b, Open-label Study to Assess the Safety and Tolerability of ONT-380 Combined with Ado-trastuzumab emtansine (Trastuzumab Emtansine; T-DM1) in Patients with HER2+ Breast Cancer	Dose-escalation: tucatinib (tablet) 300 mg or 350 mg PO BID and T-DM1 3.6 mg/kg IV on Day 1 of each 21 day cycle Expansion (at MTD): tucatinib (tablet) 300 mg BID and T-DM1 3.6 mg/kg IV on Day 1 of each 21 day cycle	N=57	Enrollment Complete	Primary analysis ^a	No	No	Yes

Trial Identifier	Description	Treatment Regimen	Number of Subjects	Current Status	Inclusion in NDA			
					CSR	SCP (m2.7.2)	SCE (m2.7.3)	SCS (m2.7.4)
ARRAY-380-101	A phase 1, Open-label, Multiple Dose Study to Assess the Safety, Tolerability, and Pharmacokinetics of ARRY-380 Given on a Daily Oral Regimen in Subjects with Advanced Cancer	Dose-escalation: 25 to 800 mg PO BID, 28-day cycles, PIC Expansion (at MTD): 600 mg PO BID, 28-day cycles, PIC	N=50	Complete	Final	Yes	No	Yes
ARRAY-380-102	An Exploratory, Open-label, Single dose, Four-Period Study Evaluating the Pharmacokinetics, Relative Bioavailability, and Safety of Four Oral ARRY-380 Formulations in Healthy Subjects	Single 300 mg PO dose of tucatinib as each of the 4 treatment formulations, fasted: tucatinib capsules (PIC formulation), tucatinib micronized PIC, tucatinib aqueous suspension, tucatinib 20% Captisol®/apple juice solution	N=14	Complete	Final	No	No	Yes
ARRAY-380-103	An Open-label, Single-dose Four-period Study Evaluating the Relative Bioavailability, Potential Food Effect, and Omeprazole Drug Interaction of Oral ARRY-380 Capsules and Tablets in Healthy Subjects	Single 300 mg PO dose in each of the four treatment periods: tucatinib capsules (PIC, fasted) tucatinib tablets (fasted) tucatinib tablets (fed) tucatinib tablets (fasted) following omeprazole (40 mg) for 5 days	N=12	Complete	Final	Yes	No	Yes
ONT-380-008	Phase 1, Open-label Study of the Absorption, Metabolism, and Excretion of [14C]-Tucatinib Following a Single Oral Dose in Healthy Male and Female Subjects	Single dose of 300 mg of [14C]-tucatinib administered as an oral solution	N=8	Complete	Final	Yes	No	Yes
ONT-380-009	An open-label, nonrandomized, single-dose, parallel-group, safety, tolerability, and pharmacokinetic study of tucatinib administered at 300 mg in fasted, hepatically-impaired male and female subjects and fasted matched-control healthy subjects	Single dose of 300 mg of tucatinib	N=48	Ongoing	Final	Yes	No	Yes

Trial Identifier	Description	Treatment Regimen	Number of Subjects	Current Status	Inclusion in NDA			
					CSR	SCP (m2.7.2)	SCE (m2.7.3)	SCS (m2.7.4)
ONT-380-011	A phase 1, Randomized, Partially Double blind, Placebo and Positive controlled Study to Evaluate the Effect of Tucatinib on Cardiac Repolarization in Healthy Subjects	Treatment A: tucatinib 300 mg Treatment B: tucatinib matching placebo Treatment C: moxifloxacin 400 mg	N=60	Ongoing	Final	Yes	No	Yes
ONT-380-012	A phase 1, open-label, fixed-sequence, 5-part, drug-drug interaction study of tucatinib to evaluate the effects of CYP3A4 and CYP2C8 inhibition and induction on the pharmacokinetics of tucatinib and to evaluate the effects of tucatinib on the pharmacokinetics of substrates of CYP3A4, CYP2C8, CYP2C9, and P-glycoprotein in healthy male and female Subjects	Part A-E: tucatinib 300 mg Part A: itraconazole 200 mg Part B: rifampin 600 mg Part C: gemfibrozil 600 mg Part D: repaglinide 0.5 mg, tolbutamide 500 mg, midazolam 2 mg Part E: digoxin 0.5 mg	N=117	Ongoing	Final	Yes	No	Yes
SGNTUC-020	Phase 1, single center, open-label, fixed sequence drug-drug interaction study in healthy subjects evaluating the effects of tucatinib on the PK of a substrate probe of the MATE1/2-K transporters	Single dose of 300 mg of tucatinib Metformin (850 mg for oral administration) Iohexol (1500 mg for IV administration)	N=18	Planned Feb 2019	Final	Yes	No	Yes

Abbreviations: BID = twice daily; CNS = central nervous system, CSR = clinical study report, HER2 = human epidermal growth factor receptor-2; ISS = Integrated Summary of Safety, IV= intravenous; MATE = multidrug and toxin extrusion, MTD = maximum tolerated dose; PIC = powder-in-capsule; PK = pharmacokinetic(s); PO = oral, SCE = Summary of Clinical Efficacy, SCP = Summary of Clinical Pharmacology, SCS = Summary of Clinical Safety

a Although the primary analysis for the ONT-380-004 and ONT-380-005 trials has been conducted, these trials are ongoing with subjects receiving treatment in a long-term follow-up portion where only SAEs and EOs are being collected.

FDA sent Preliminary Comments to Seattle Genetics on February 20, 2019.

2.0 QUESTIONS/RESPONSES

Question 1: The proposed strategy for the manufacture of process validation (process performance qualification [PPQ]) batches of tucatinib tablets is provided in Section 15.2.1, Table 6., of the background package. (b) (4)

(b) (4)

FDA Response: The FDA does not approve (b) (4)

Meeting Discussion: None.

Question 2: Tucatinib drug product primary stability batches will be placed on stability in the configurations provided in Table 9 as per the protocol provided in Table 8.

The sponsor proposes to provide the following data in the initial NDA submission:

- Six months (1, 2, 3 and 6 month time points) of data for 3 primary stability batches for the 50 mg strength (b) (4) at long term ($25^{\circ}\text{C} \pm 2 / 60 \pm 5\% \text{ RH}$) and accelerated conditions ($40^{\circ}\text{C} \pm 2 / 75 \pm 5\% \text{ RH}$)
- Six months (1, 2, 3 and 6 month time points) of data for 3 primary stability batches for the 150 mg strength at long term ($25^{\circ}\text{C} \pm 2 / 60 \pm 5\% \text{ RH}$) and accelerated conditions ($40^{\circ}\text{C} \pm 2 / 75 \pm 5\% \text{ RH}$).

The sponsor proposes to provide the following data in an amendment to be submitted during the review period after the initial NDA submission to support the proposed shelf-life:

- Nine and twelve-month time points data for 3 primary stability batches for the 50 mg strength (b) (4) at long term ($25^{\circ}\text{C} \pm 2 / 60 \pm 5\% \text{ RH}$) and accelerated conditions ($40^{\circ}\text{C} \pm 2 / 75 \pm 5\% \text{ RH}$)
- Nine and twelve-month time points data for 3 primary stability batches for the 150 mg strength at long term ($25^{\circ}\text{C} \pm 2 / 60 \pm 5\% \text{ RH}$) and accelerated conditions ($40^{\circ}\text{C} \pm 2 / 75 \pm 5\% \text{ RH}$).

The data for both nine and twelve-month time points will be available in January 2020.

Does the Agency agree with the proposal for submission of drug product stability data?

FDA Response: Your approach appears reasonable. It appears that the updated stability data will be submitted after 30 days from the initial NDA submission. Information

submitted after 30 days of initial submission may or may not be reviewed depending on the agency's resources and internal timelines. The expiration dating period for the drug product will be assigned based on the totality of data available at the time of the NDA review. Primary stability batches are the drug product batches manufactured with different drug substance lots using the proposed commercial process and packaged in the proposed commercial packaging system and in the same configuration.

Refer also to the FDA responses in the cross-referenced IND 078304 Type C CMC meeting (dated October 25, 2017, Questions 3 and 4). In addition, see Additional Comments below with regard to the dissolution method development and validation report as a QC test and for stability testing for the final proposed drug product.

Sponsor Response [submitted February 22, 2019]: The sponsor would like to clarify the totality of DP stability data available at the time of NDA submission. The totality of data include 11 batches of both strengths that are designated clinical and primary stability batches (table below). The totality of stability data are from batches produced at the intended commercial manufacturing site and are representative of the intended commercial process and equipment.

Lot	Strength (mg)	Last Time Point for NDA (Months)	Use
KH16/0046	50	24	Clinical
KH16/0045	150	24	Clinical
KH17/0064	150	24	Clinical
KH17/0071	150	12	Clinical
KH18/0207	50	6	Clinical
KH18/0224	50	6	Primary Stability
KH18/0225	50	6	Primary Stability
KH18/0226	50	6	Primary Stability
KH18/0227	150	6	Primary Stability
KH18/0228	150	6	Primary Stability
KH18/0229	150	6	Primary Stability

Could the Agency confirm these data will be considered to assign expiry dating?

Meeting Discussion: FDA stated that the stability data obtained from the clinical batches will be considered as supportive stability batch data and will be used to help assign the expiration dating period. The FDA also stated that the sponsor should provide the differences between the primary stability batch and the clinical batches (i.e., manufacturing process, scale, site, packaging system, and drug substance batch information). The sponsor may submit updated stability data as they become available during the NDA review. The 9 month stability data and the 12 month stability data can be submitted separately.

Question 3: Data from pivotal trial ONT-380-206 will serve as the primary efficacy data to support the NDA for tucatinib. Supportive data from the 27 subjects treated with the triplet combination of tucatinib, capecitabine and trastuzumab from trial ONT-380-005 will be summarized side-by-side with the ONT-380-206 data as part of the Summary of Clinical Efficacy (Module 2.7.3; Comparison and analyses of results across studies). A detailed description of the efficacy analyses for the planned NDA is provided in the draft statistical analysis plan (SAP) for ONT-380-206 (Appendix 3).

Given that ONT-380-206 will provide the primary evidence to support the proposed indication, the sponsor considers that efficacy can be sufficiently detailed in the Summary of Clinical Efficacy; therefore, the sponsor does not plan to include an Integrated Summary of Efficacy (ISE). A document will reside in Module 5.3.5.3 (Reports of analyses of data from more than one study) that will include a statement of cross reference to Module 2.7.3 in the NDA.

Does the Agency agree with the proposed efficacy data analyses and presentation within the electronic common technical document (eCTD)?

FDA Response: Yes.

Meeting Discussion: None.

Question 4: As previously agreed, the sponsor plans to analyze the primary endpoint of PFS from the pivotal trial (ONT-380-206) when at least 288 PFS events have been observed in the first 480 randomized subjects (24 October 2018 Meeting Comments, Reference ID 4339701). We would like to further clarify the timing of this analysis. Based on a recently observed acceleration in enrollment, we anticipate completing enrollment of the trial (n=600) in May 2019 (previously projected to be July 2019). Therefore, we plan to analyze the primary endpoint of PFS on the first 480 subjects once all 600 subjects have been enrolled and at least 288 PFS events have been observed in the first 480 subjects. At this same time, the interim secondary endpoint analyses of PFS in subjects with brain metastases (PFSBM) and OS will also be performed on all 600 subjects. Based on our current projections using blinded investigator-reported PFS, we estimate that occurrence of 288 events and full enrollment with 600 subjects will occur within weeks of each other. Therefore, the most efficient approach would be to perform the primary analysis once both ≥ 288 events have occurred plus all 600 subjects have been enrolled. This also enables the interim analyses of the secondary endpoints (PFSBM and OS) to be performed after all subjects have been enrolled. Analyzing the primary endpoint once enrollment is complete will result in approximately 312 events in the first 480 subjects (~10% more PFS events than the minimum threshold of 288 events required in the protocol).

The sponsor plans to update the ONT-380-206 protocol and SAP to clarify the timing of the primary endpoint analysis and the interim secondary endpoint analyses. Proposed revisions to the protocol are provided in Appendix 2 and the SAP is provided in Appendix 3.

Does the Agency agree with the proposed timing of the PFS primary endpoint analysis to support the planned NDA in relation to the interim analysis of alpha-controlled secondary endpoints?

FDA Response: Yes, this is acceptable.

Meeting Discussion: None.

Question 5: In order to preserve the integrity of the ongoing pivotal trial (ONT-380-206), an independent data monitoring committee (IDMC) using an external statistical group will initially conduct the analyses of the primary endpoint of PFS in the intent-to-treat (ITT) population, the pre-specified interim analyses of the key secondary endpoints (PFS_{BM} and OS) and relevant safety assessments. For efficacy endpoints, the IDMC will only disclose the results of the primary endpoint and key secondary endpoint(s) [REDACTED] (b) (4) to an executive team at Seattle Genetics including the Chief Medical Officer, Head of Regulatory Affairs, and Head of Biometrics.

The sponsor proposes to provide results of the primary endpoint analysis in the planned NDA. Results from the interim analysis of PFS_{BM} and OS will only be included in the NDA [REDACTED] (b) (4). Sponsor personnel responsible for the ongoing trial will remain blinded to treatment assignments. A separate unblinded submission team within the company will support preparation of the NDA. Further description is provided in Section 15.4.3.

Does the Agency agree with the proposed approach for analyzing and presenting the results of the primary and key secondary endpoints and for maintaining trial integrity to support the planned NDA?

FDA Response: No. In the planned NDA submission, you should include results from the interim analysis of OS [REDACTED] (b) (4).

Sponsor Response [submitted February 22, 2019]: We agree to include results from the interim analysis of OS in the NDA [REDACTED] (b) (4); therefore, we assume that the OS interim results will be publicly disclosed in the label and NDA review documents. Could the Agency confirm?

For PFS_{BM}, the sponsor is reevaluating the proposed data integrity plan for the pivotal trial. As a reminder, this is a double-blind, placebo-controlled trial that uses blinded independent central review for the PFS endpoints. If we choose to have knowledge of and publicly disclose the PFS_{BM} interim results, regardless of statistical significance, would the Agency have concerns with data integrity for the ongoing trial? Under this scenario, we would no longer utilize an IDMC and external statistical group. Seattle Genetics would analyze the results and a small unblinded team would have access to patient level data and would no longer be involved in trial conduct.

Meeting Discussion: FDA stated the results from the interim OS analysis would be included in the FDA review documents. The label will include interim OS information if the results are statistically significant. The label will state the results are immature if the results of the interim OS analysis are not statistically significant.

FDA stated that the data integrity plan, presented by the sponsor on February 25, 2019, for the PFS_{BM} interim analysis is acceptable. FDA may provide additional comments regarding the interim analysis of PFS_{BM} in the label.

Post-Meeting FDA Comment: The inclusion of PFS-BM results in labeling will be a review issue.

Question 6: The safety dataset for the NDA will include safety data from approximately 800 subjects treated with tucatinib (of which approximately 250 are healthy volunteers). In addition, approximately 200 subjects treated with placebo in ONT-380-206 will be included.

The sponsor proposes to pool safety data from subjects who received tucatinib with capecitabine and/or trastuzumab in ONT-380-206 and ONT-380-005 as described in Section 15.4.4.

Clinical trials planned to be displayed in a side by side manner include ONT-380-206, ONT-380-005, and ARRAY-380-101. Subjects who received tucatinib doses at or above the MTD/recommended phase 2 dose (RP2D) (600 mg PO BID powder in capsule [PIC] or 300 mg PO BID tablet) will be included. These populations are described in Section 15.4.4.

A draft SAP for the Integrated Summary of Safety (ISS), which details the proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled populations, and planned analytic strategies to manage differences in trial design, is provided in Appendix 4.

Given the number and size of the clinical studies included in the submission, the sponsor proposes to provide the narrative text of the ISS in Module 2.7.4 (Summary of clinical safety [SCS]). Datasets, programming files, and appendices for supporting tables and figures will be placed in Module 5.3.5.3 (Reports of analyses of data from more than one study). A document will reside in Module 5.3.5.3 which includes a statement of cross reference to Module 2.7.4 for the ISS text. The SCS will also include line listings for safety reports from any additional ongoing trials.

Does the Agency agree with the proposed safety data analyses and presentation within the eCTD?

FDA Response: Yes.

Meeting Discussion: None.

Question 7: In accordance with 21CFR§314.50(5)(vi)(b), the sponsor plans to submit a safety update report 90 days after the NDA submission date. The report is planned to include an updated SCS and integrated safety tables in the same format and with the same content as the NDA submission for all ongoing trials during NDA review. New and updated subject narratives will be provided, as described in Question 8. In addition, proposed US prescribing information (USPI) will be revised and submitted if impacted by the safety update report.

Does the Agency agree with the proposed timing of the safety update report?

FDA Response: Yes.

Meeting Discussion: None.

Question 8: The sponsor proposes to provide case report forms (CRFs) for subjects in the safety population who experienced a qualifying event as listed below, regardless of relationship to tucatinib, as well as subject narratives comprising the subject's demographic data, event data, and a brief description of the event.

- Deaths that occur up through 30 days after the last dose of any study drug(s)
- Treatment-emergent serious adverse events (SAEs)
- Adverse events (AEs) leading to discontinuation of study drug
- Events considered dose-limiting toxicities (DLTs) in applicable studies
- Hepatic events of interest (EOIs), and
- Pregnancy

Does the Agency agree with the proposed CRF and subject narrative approach for the planned NDA?

FDA Response: Yes. In addition, provide narratives for all adverse events of special interest (including but not limited to potential drug induced liver injury, cerebral edema, asymptomatic left ventricular systolic dysfunction, etc.).

Meeting Discussion: None.

Question 9: The sponsor proposes to submit the following datasets as part of the NDA:

Studies primarily supporting efficacy and safety (ONT-380-004, ONT-380-005, ONT-380-206):

- Clinical Data Interchange Standards Consortium (CDISC) Standard Data Tabulation Model (SDTM) compliant (following SDTM IG 3.2) data packages including data sets (.xpt files), define.xml, annotated CRFs, and Reviewer's guides
- CDISC analysis data model (ADaM) compliant (following ADaM IG 1.1) data packages including data sets (.xpt files), define.xml and Reviewer's guides
- Statistical analysis software (SAS) programs (in .txt format) that produce ADaM data sets
- SAS programs (in .txt format) that produce key efficacy and safety tables

Studies for pooled safety analyses (ONT-380-005 and ONT-380-206):

- Data package for integrated ADaM data that includes data sets (.xpt files), define.xml and Reviewer's guide
- SAS Programs (in .txt format) that produce integrated ADaM datasets
- SAS programs (in .txt format) that produce key integrated analyses

Clinical pharmacology studies (ONT-380-008, ONT-380-009, ONT-380-011, ONT-380-012, SGNTUC-020):

- CDISC SDTM compliant data sets (.xpt files)

- CDISC ADaM compliant data sets (.xpt files)

For ARRAY-380-101, ARRAY-380-102 and ARRAY-380-103:

- ARRAY-380-101 (completed in 2013): PK and safety data sets (.xpt files) in non-CDISC format
- ARRAY-380-102 (completed in 2010): safety data sets (.xpt files) in non-CDISC format
- ARRAY-380-103 (completed in 2010): PK and safety data sets (.xpt files) in non-CDISC format

Does the Agency agree with the proposed datasets to be included in the planned NDA for tucatinib?

FDA Response: Yes.

Meeting Discussion: None.

Question 10: Per the request of the Office of Scientific Investigations (OSI), the sponsor plans to provide general trial related information, comprehensive clinical investigator information, and subject level data listings by site to facilitate development of clinical investigator, sponsor, monitor, and/or contract research organization (CRO) inspection assignments. Also in compliance with 21CFR§54, the sponsor plans to provide financial information on all clinical investigators participating in ONT-380-206. ONT-380-206 is the primary efficacy and safety trial supporting the planned tucatinib NDA. Therefore, the sponsor proposes to include bioresearch monitoring (BIMO) information and financial disclosure information from investigators from this trial only.

Does the Agency agree with the proposal for providing BIMO information and financial disclosure information from ONT-380-206 investigators for the planned NDA?

FDA Response: Yes.

Meeting Discussion: None.

CMC Additional Comments:

We have the following comments regarding the dissolution information that should be provided in your NDA.

- 1. Dissolution Test: Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:**
 - a. Solubility data for the drug substance covering the pH range;**

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA review. However, the acceptability of the proposed dissolution acceptance criterion for your product will be made during the NDA review based on the totality of the dissolution data provided.

Meeting Discussion: None.

Clinical Pharmacology Additional Comments:

- 1. You should evaluate the potential for tucatinib metabolite to act as a substrate, inhibitor, or inducer of drug metabolizing enzymes and transporter.**

Sponsor Response [submitted February 22, 2019]:

At steady state there are no circulating metabolites that exceed 10% of total drug-related exposure. The primary circulating metabolite (ONT-993) has a potency corrected exposure of 9% of tucatinib. Per 2017 FDA Guidance, this is below the threshold for in vitro characterization as a substrate, inhibitor, or inducer of drug metabolizing enzymes and transporters. Studies that have been performed with ONT-993 to characterize the in vitro potential to inhibit CYP enzymes (TR-00036) or inhibit transporters (OPT-2017-063, OPT-2017-081, OPT-2018-241) are listed in Table 21 of the briefing document and planned to be included in the NDA.

Does the Agency agree that full in vitro characterization of the DDI potential of ONT-993 is not required?

Meeting Discussion: FDA stated the sponsor's proposal is acceptable.

- 2. We recommend the content and format of information found in the Clinical Pharmacology section (Section 12) of 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:

- 3. 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.**
- 4. What are the exposure-response relationships for efficacy, safety and biomarkers?**
- 5. What is the effect of tucatinib on the QT/QTc interval?**

6. **What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?**
7. **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.**
8. **How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?**

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

9. **Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.**
10. **Provide a final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with minimum and maximum values as appropriate.**
11. **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.**
12. **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>.**

13. 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. Submit these files as ASCII text files with *.txt extension (e.g.,: myfile_ctl.txt, myfile_out.txt)**

14. 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.

15. Include the purpose of the simulations, assumptions, detailed process of PBPK model building and verification, summary of model input parameters, version of software, simulation results, and conclusions in the study report. Provide the study reports as PDF files (screenshots can be incorporated if required). Include the model files used to generate the final PBPK simulations. These files should be executable by FDA reviewers using the specified software. Include appropriate supporting documentations such as any special instructions and file definitions.

16. Include the following items when you submit your QT study report:

- 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**
- m. 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/>**

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our January 11, 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. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at:

<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric

cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For the latest version of the molecular target list, please refer to:

<https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm>

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* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>.

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:

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

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) 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*

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

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:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

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: <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612927.htm>. In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid:<https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612923.htm>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

See attached slides.

9 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

JEANNETTE L DININ
03/04/2019 12:31:53 PM

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