CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217513Orig1s000
217514Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 117898

MEETING MINUTES

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

Dear Dr.Zhu:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for dabrafenib (DRB4326).

We also refer to the teleconference between representatives of your firm and the FDA on March 16, 2022. The purpose of the meeting was to obtain FDA's feedback on whether the data from Study G2201 supports the use of dabrafenib in combination with trametinib for the treatment of pediatric patients 1 year of age and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy and to obtain feedback on the content and format of the proposed supplemental New Drug Application (sNDA) submission package and overall regulatory submission strategy.

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

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

If you have any questions, call me at 301-796-1273.

Sincerely,

{See appended electronic signature page}

Melanie Pierce
Director
Office of Regulatory Operations
Division of Regulatory Operations-Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Novartis Response Document

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-sNDA
Meeting Date and Time:	March 16, 2022, 2:00-3:00 p.m., EDT
Meeting Location:	Teleconference
Application Number:	117898
Product Name:	dabrafenib (DRB436) in combination with trametinib (TMT212)
Indication:	Treatment of patients 1 year of age and older with 1) BRAF V600E mutation-positive low-grade glioma (b) (4) [redacted]
Sponsor Name:	Novartis Pharmaceuticals Corporation
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair:	Diana Bradford, M.D.
Meeting Recorder:	Jana Highsmith

FDA ATTENDEES

Martha Donoghue, M.D.	Deputy Director, DO2
Diana Bradford, M.D.	Cross Discipline Team Lead, DO2
Elizabeth Duke, M.D.	Clinical Reviewer, DO2
Pallavi Mishra-Kalyani, Ph.D.	Biometrics Team Lead, DBV
Xiaoxue Li, Ph.D.	Biometrics Reviewer, DBV
Jeanne Fourie-Zirkelbach, Ph.D.	Clinical Pharmacology Team Lead, DCPII
Suryatheja Ananthula, Ph.D.	Clinical Pharmacology Reviewer, DCPII
Jana Highsmith	Regulatory Health Project Manager, DORO/OOD-DO2

SPONSOR ATTENDEES

Dushen Chetty	Global Program Head
Vanessa Passos	Global Program Clinical Head
Laura Huggins	Global Therapeutic Area Lead, Regulatory Affairs
Suman Redhu	Global Program Biostatistics Head
Lali Sandalic	Associate Director, Biostatistics, Trial Statistician
Mighael Roughton	Associate Director, Biostatistics, Trial Statistician
Mark Russo	Sr. Clinical Development Medical Director
Alexander Chesi	Global Program Regulatory Director
Maya Dajee	Global Biomarker Diagnostic Leader
Eugene Tan	Associate Director, PK Sciences

Maja Skataric	Senior Pharmacometrician
Andrew Bridge	Associate Director, Regulatory Affairs CMC
Alejandra Martin-Alos	Director, Regulatory Affairs CMC
Christoph Ziltener	Project Head TRD
Rohan Shah	US Medical Director
Carolyn Zhu	Global Program Regulatory Manager

BACKGROUND

On January 27, 2022, Novartis Pharmaceutical Corporation (Novartis) submitted a Type B pre-sNDA meeting request to review the results from Study CDRB436G2201 (Study G2201) in pediatric patients with gliomas and obtain agreement that the data and proposed key clinical submission content support filing of a supplemental New Drug Application (sNDA). The meeting request was granted on February 9, 2022, as a teleconference.

Regulatory

Dabrafenib and trametinib were developed by Novartis for multiple hematologic and solid tumor oncology indications. In 2013, dabrafenib and trametinib were both approved as monotherapy agents for adults with unresectable or metastatic melanoma with the BRAF V600E or V600K mutation. The combination therapy was subsequently approved for the following indications:

- Unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test
- Metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test
- Adjuvant treatment of melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection
- Locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and no satisfactory locoregional treatment options

An sNDA is currently under review in the Division of Oncology 3 (DO3) for the proposed indication of the treatment of adult and pediatric patients 6 years of age and older with (b) (4) or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment or have no satisfactory alternative treatment options (NDA 202806/S-022 and NDA 204114/S-024).

On March 7, 2013, the sponsor submitted IND 117898 to FDA.

On February 8, 2016, FDA granted orphan drug designation for dabrafenib for the treatment of malignant glioma with BRAF V600 mutation.

On March 1, 2016, FDA issued Written Requests for dabrafenib and trametinib. The clinical study submitted to support the proposed sNDA is included in the Written Request.

On July 26, 2021, FDA issued an Agreed Initial Pediatric Study Plan (iPSP) for dabrafenib in combination with trametinib for the treatment of patients with solid tumors with BRAF V600 mutation (IND 113557).

On January 31, 2022, the sponsor submitted a Breakthrough Therapy Designation (BTD) Request for the treatment of pediatric patients 1 year of age and older with low-grade glioma with a BRAF V600E mutation who require systemic therapy. The BTD review is ongoing.

Clinical Pharmacology

In the pre-sNDA meeting package, the sponsor proposes new liquid formulations of dabrafenib and trametinib. These formulations are currently administered in Study G2201 and the expanded access programs.

Dabrafenib 10 mg dispersible tablets (DT) are administered as an oral suspension to be consumed immediately after preparation. (b) (4)

Trametinib 4.7 mg powder for oral solution (PfOS) is a white or almost white powder to be reconstituted with 90 mL water prior to administration to achieve a concentration of 0.05 trametinib free base mg/mL. The patient individual dose is administered into the mouth of the patient using (b) (4) dosing syringes. (b) (4)

Sponsor stated that in Study G2201, dabrafenib was supplied as capsules (50 and 75 mg) which are equivalent to the commercial formulation (Tafinlar) and as a 10 mg DT for oral suspension and trametinib was supplied as tablets (0.5 or 2 mg) which are equivalent to the commercial formulation (Mekinist) and as a 4.7 mg powder for oral solution (PfOS).

Relative Bioavailability:
CDRB436G2101 and MEK115892 are relative bioavailability studies conducted in adults for dabrafenib and for trametinib, respectively, to investigate the relative bioavailability of the pediatric oral liquid formulations in comparison to their marketed oral solid formulations.

Study CDRB436G2101: Two variants (A and B) of the 10 mg dispersible tablet (DT) were tested and compared to the (b) (4) capsules ©.

Compared to the administration of the approved dabrafenib capsule ((b) (4) formulation, treatment with 10×10 mg dabrafenib DT resulted in a decrease in the geometric means of AUC_{inf}, AUC_{last} and C_{max} by 25.0%, 25.1% and 50.6%, respectively, for variant A and by 20.0%, 21.0% and 48.5%, respectively, for variant B. No new safety signals were observed with dabrafenib in this study and the Aes reported were consistent with the known safety profile of dabrafenib in healthy volunteers. Variant B was selected for further clinical development.

Study MEK115892: This study assessed the relative bioavailability of trametinib pediatric oral solution relative to the marketed tablet formulation after administration of a single 2 mg dose to adult patients with solid tumors under fasting conditions. After single dose oral solution of trametinib, AUC_{inf}, AUC_{last} and C_{max} were 12%, 10% and 71% higher compared to the marketed tablets.

Dosage optimization:
Novartis conducted a population pharmacokinetic (PopPK) analysis in support of the proposed pediatric dosage (reference - NDA 202806/S-022 and NDA 204114/S-024). Pediatric PK data collected with both solid and liquid dosage forms in the studies A2102 and X2101 (and ongoing pediatric study G2201) for PopPK analysis. Accordingly, body weight-based tiered dosing was proposed for pediatric patients as in the below table.

Body Weight	Recommended dabrafenib dose	Recommended trametinib dose
(b) (4)		

The PopPK analysis determined that the apparent clearance in pediatric patients aged 6 to 17 years old (14.77 L/h for dabrafenib and 5.02 L/h for trametinib) were comparable to the previously established clearance in adult patients (16.7 L/h for dabrafenib and 5.07 L/h for trametinib).

(b) (4)

Clinical

In the pre-sNDA meeting package, the sponsor proposes (b) (4) for dabrafenib and trametinib combination therapy:

- treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy

(b) (4)

The clinical data to support the sNDA is primarily from Study G2201, a multi-regional international dose-expansion trial in pediatric patients 1 to 18 years of age with glioma with a locally-assessed BRAF V600 mutation. As supportive evidence, the sponsor proposes to reference clinical data from Studies CDRB436A2102 and CTMT212X2101

(b) (4)

In Study G2201, patients received age- and weight-based dosing of dabrafenib in combination with trametinib. Dosing nomograms based on weight and age were used to determine each individual patient's dose. The total daily doses are as follows and did not exceed the adult recommended daily dosages of dabrafenib 300 mg (150 mg BID) or trametinib 2 mg:

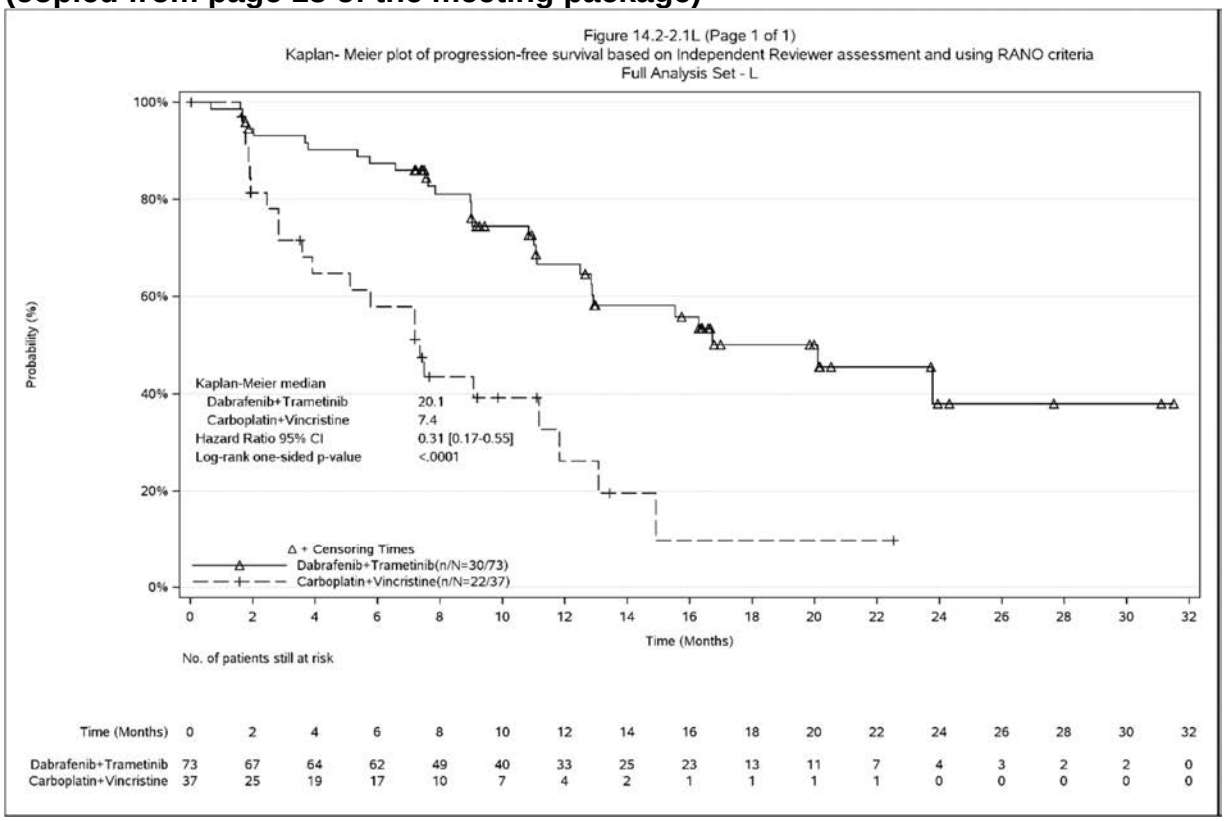
- Dabrafenib (capsule or dispersible tablet for oral suspension)
  - < 12 years old: 5.25 mg/kg/day, divided into two equal doses (BID dosing)
  - ≥ 12 years old: 4.5 mg/kg/day, divided into two equal doses (BID dosing)
- Trametinib (tablet or powder in bottle for oral solution)
  - < 6 years old: 0.032 mg/kg/day (once daily dosing)
  - ≥6 years old: 0.025 mg/kg/day (once daily dosing)

<u>Low Grade Glioma:</u>
The proposed indication for LGG is based on the cohort of 110 patients in Study G2201 with LGG with BRAF V600 mutation randomized 2:1 to dabrafenib and trametinib (n=73) or standard of care chemotherapy (carboplatin and vincristine; n=37). All patients were systemic therapy-naïve and had measurable disease. Patients either had prior surgery and subsequently progressed, or were non-surgical candidates and investigators determined the need to begin systemic treatment based on risk of neurological impairment with progression. Patients randomized to the standard of care arm were allowed to crossover after centrally confirmed disease progression.

The primary endpoint was overall response rate (ORR) as per Response Assessment in Neuro-Oncology (RANO) criteria as assessed by blinded independent central review (BICR). Secondary endpoints included duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Tumor assessments included brain MRI every 8 weeks during the first year and every 16 weeks thereafter until disease progression or patients were no longer receiving clinical benefit as determined by the investigator, death, or unacceptable toxicity.

Results of the primary analysis, performed with a data cut-off date of August 23, 2021, are provided in the meeting package. In the LGG cohort, demographics were generally similar between arms. Of the 73 patients in the experimental arm, 2 patients had complete responses and 32 had partial responses [confirmed ORR 46.6% (95% CI 34.8, 58.6)]. Of the 37 patients in the chemotherapy control arm, one patient had a complete response and 3 had partial responses [ORR 10.8% (95% CI 3.0, 25.4), p <0.001]. After a median duration of follow-up of 18.9 months, median duration of response was 20.3 months in the experimental arm (95% CI 12.0, NE) vs. not evaluable due to the low number of responders in the control arm (95% CI 6.6, NE). Median PFS was longer in the experimental arm (20.1 months) compared to the control arm (7.4 months) with HR 0.31 (95% CI 0.17, 0.53; p<0.001; Figure 1).

Figure 1: Kaplan-Meier plot of PFS as per RANO criteria and assessed by BICR (copied from page 13 of the meeting package)



(b) (4)

(b) (4)

Safety

The safety profile of dabrafenib and trametinib are well-characterized in the current product labeling. The sponsor states that there were no new safety signals identified in this population. The primary safety population includes 114 patients treated with dabrafenib and trametinib in Study G2201. The data cut-off is August 23, 2021, and the minimum study follow-up time is 7.9 months (from last patient randomization).

FDA sent Preliminary Comments to Novartis on March 11, 2022.

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

1. Does the Agency agree that the data from the Phase II registration Study G2201 supports (b) (4) the filing of the proposed LGG indication:

(b) (4)

BRAF V600E Mutation-Positive LGG
Dabrafenib in combination with trametinib is indicated for the treatment of pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

FDA Response: We agree that the summary level efficacy results of ORR and DOR, (b) (4) appear sufficient to support the filing of supplemental NDAs for the proposed LGG indication. (b) (4) Given the importance of the accuracy of confirmed response rate in the determination of efficacy for this study, additional information is needed to understand the nature of the blinded independent central review.

The heterogeneity of the patient populations, variable prior therapies, and interpretability of response rates in the context of prior treatment will be review issues.

a. We have the following comments regarding both cohorts in Study G2201 and recommend including the following information in the sNDA submission:

(i) Provide details regarding the conduct of the blinded independent central review, including the imaging charter(s).

(ii) Provide the current statistical analysis plan (SAP) for both cohorts.

(iii) Provide the number of patients with central confirmation of BRAF V600 status and provide rationale for discordant and missing results.

(iv) Provide justification for the inclusion of any patients without a BRAF V600E mutation in the primary efficacy population.

(v) Provide a patient-level listing of the tumor location and histological diagnosis for all patients and provide justification for the inclusion of WHO Grade 3 or 4 tumors in the LGG cohort, the inclusion of WHO Grade 1 or 2 tumors in the HGG cohort, and the inclusion of patients with missing histological tumor grade. In the patient-level listing, specify whether patients were confirmed responders or non-responders and any prior anti-cancer therapy(ies) they received.

(vi) Provide a detailed description of the reason for treatment discontinuation for each patient who discontinued treatment due to a reason other than progression of disease or completion of therapy per protocol.

(vii) Provide justification regarding the applicability of these data to the U.S. population, including the number and location of sites that enrolled patients, the race and ethnicity of enrolled patients, and a

comparison of the demographics of the enrolled population to the expected U.S. population.

(viii) Provide a summary of the preclinical and clinical data available to characterize the contribution of each component (dabrafenib monotherapy, trametinib monotherapy, and dabrafenib and trametinib combination therapy for the proposed indications).

Novartis Response Submitted 3/15/2022: Novartis acknowledges the Agency's comments regarding both cohorts in Study G2201 and the recommended information to be included in the sNDA submission, as well as the comments on the proposed indication for BRAF V600E mutation-positive LGG and the clinical pharmacology topics.

b. Regarding the proposed indication for BRAF V600E mutation-positive LGG, we have the following comments:

(i) We note that 11 responding patients had less than 6 months of follow-up from the time of initial response. In the sNDA submission, we recommend submitting updated data from a later data cut-off timepoint per blinded independent central review to better characterize durability of response in these additional patients.

Novartis Response Submitted 3/15/2022: Novartis acknowledges that at the time of the data cut-off date of August 23, 2021, 11 responding patients had less than 6 months of follow-up from the time of initial response. Note that the primary analysis was pre-planned per protocol to occur at 32 weeks after LPFV, resulting in a data cut-off in August 2021. Given that submission documents have been under preparation using the August 23, 2021 data cut-off date, in order to avoid delays to the submission, Novartis proposes to conduct independent RANO reviews per protocol to provide additional efficacy and safety data at the time of a 90/120-day safety update. These outputs will be submitted during the NDA review and will provide at least an additional 6 months of follow up to further evaluate the durability of response and longer-term safety in these pediatric patients. Additionally, the final CSR for Study G2201 is expected in October 2023 (timeline dependent on when all patients are moved to the rollover study) and can be provided as a post-marketing commitment.

Discussion During Meeting: FDA requested that the requested updated data be provided with the original NDA submission, or within 90 days of submission of the NDAs/supplemental NDAs.

(ii) We note that four patients randomized to the carboplatin and vincristine arm were not treated. Provide any additional information about the reason for not receiving treatment. Conduct a sensitivity analysis that excludes these patients to evaluate the effect on overall response rate.

(iii) Provide patient-level details, including narratives if available, regarding the investigator-determined neurologic signs and symptoms that prompted enrollment on the clinical trial.

Discussion During Meeting: There was no further discussion during the meeting for items ii and iii.

(iv) Provide any available Patient Report Outcome (PRO) data collected for patients in the LGG cohort, including analyses of completion rates and data missingness. In advance of the March 16, 2022, meeting, provide a high-level summary of the PRO data available to support the application.

Novartis Response Submitted 3/15/2022: The assessment of patient reported outcomes of dabrafenib in combination with trametinib versus carboplatin with vincristine is a secondary objective in Study G2201. The PROMIS Parent Proxy Global Health 7+2 was used to evaluate the QoL of subjects between the 2 treatment arms of the LGG cohort. The 7+2 item parent proxy pediatric global health measure includes one global health score plus a single score from pain and a score from fatigue interference item, which were scored independently. A higher score for global health indicates better overall well-being (i.e. physical, mental, social, and general health); a higher score for pain and fatigue indicates worsening pain and fatigue. Questionnaires were administered according to the visit evaluation schedule as defined in the Study G2201 protocol until disease progression per RANO criteria.

Among subjects taking the PROMIS parent proxy questionnaire, ≥ 89% of subjects in the targeted therapy (D+T) arm and ≥ 85% of subjects in the chemotherapy (C+V) arm fully completed the questionnaire at the scheduled time points.

There was a trend in improvement in global health scores and fatigue scores for the targeted therapy (D+T) arm compared to the chemotherapy (C+V) arm at the majority of the scheduled time points. The scores for pain did not show any difference in the D+T arm compared to the C+V arm.

The treatment difference in the overall least squares (LS) means of scores between the 2 treatment arms for global health and fatigue were in favor of the targeted therapy (D+T) arm compared to the chemotherapy (C+V) arm at all scheduled time points. For pain subscale, the treatment difference in the overall least squares (LS) means of scores between the 2 treatment arms showed no difference.

Discussion During Meeting: There was no further discussion during the meeting.

c. We have the following clinical pharmacology comments:

(i) Clinical trials designed to demonstrate efficacy and safety should evaluate appropriately justified dosages. Include the rationale for the selection of the dosages of dabrafenib and trametinib administered in Study G2201 and justification for dose optimization in the NDA submission (See response to Question 2).

Discussion During Meeting: There was no further discussion during the meeting.

(ii) In the NDA submission, address the effect of food on the exposure of pediatric specific formulations containing dabrafenib or trametinib.

Discussion During Meeting: FDA stated that separate food effect studies with the pediatric formulations are required. FDA stated that the results of food effect studies should be provided during the NDA review cycle. The study could employ a low-fat meal and be conducted in healthy adult volunteers. Novartis stated that they had conducted a low-fat food effect study with the solid formulations and would submit the results and a proposed timeline for submission of the results of the planned food effects studies prior to the submission of the NDA.

(iii) In addition, in advance of the March 16, 2022, meeting, provide an assessment of the food effect with the pediatric formulations based on guidance provided, "*Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations*".

Novartis Response Submitted 3/15/2022: Novartis acknowledges that the cited guidance recommends that sponsors conduct a new FE study with the pediatric formulation in adults and

then extrapolate the results to the pediatric population. The currently marketed solid oral dosage forms of dabrafenib (capsules) and trametinib (tablets) are to be taken under fasting condition, at least 1 hour before or 2 hours after a meal. Reduced exposure was observed in food effect studies in the adult population: administration of dabrafenib capsules with a high fat and high-calorie meal reduced the bioavailability (C_{max} and AUCinf decreased by 51% and 31% respectively) and delayed the absorption, and administration of a single dose of trametinib tablets with a high-fat and high-calorie meal resulted in a 70% and 10% decrease in C_{max} and AUCinf, respectively, compared to fasted condition.

The proposed liquid oral dosage forms (dabrafenib DT and trametinib PfOS) were used under fasting condition in the phase I/II (Study A2102; Study X2101) and the pivotal (Study G2201) trials. Pediatric patients tolerated treatment well and showed efficacy. The effect of food on PK was not investigated for the dabrafenib and trametinib liquid formulations. Based on similar relative bioavailability for both formulations, the liquid formulation is expected to be similar to the immediate release solid formulation with respect to the food effect. The liquid formulations (dabrafenib DT and trametinib PfOS) are also proposed to be administered under fasted condition in the marketed setting, similar to what was done in the pivotal trial (Study G2201).

Discussion During Meeting: There was no further discussion during the meeting.

(iv) Given that the pivotal efficacy Study G2201 included pediatric patients treated with both solid and liquid oral dosage forms, provide a summary of the following as indicated below as a response to the March 16, 2022, meeting:

- Clarify how many patients in each age group (12 months to < 6 years, 6 to <12 years, 12 to < 18 years) received each of the solid or liquid oral dosage forms.

- Clarify whether PK sampling (dense and sparse) were collected within each of these age groups, and how many patients had dense and sparse PK sampling in each age group to provide support for the dosages in the pediatric patients.

Novartis Response Submitted 3/15/2022: A summary of the number of patients treated with solid and liquid dosage forms by age group in Study G2201 is provided for dabrafenib and trametinib

in Table 2-1 and Table 2-2 (see Novartis response document in attachment), respectively. Note that some patients switched formulations during treatment, and are accounted for in both formulation groups (solid and liquid). Patients who did not receive any dose of study drug are excluded from this summary.

A summary of how PK sampling (dense and sparse) were collected per age group, and how many patients had dense and sparse PK sampling in each age group, is provided for dabrafenib and trametinib in Table 2-3 and Table 2-4 (see Novartis response document in attachment), respectively.

- Samples below the lower limit of quantification (BLOQ) were excluded, and samples flagged as outliers were excluded
- Dense PK = At least 3 PK data points on Day 15 or Week 3 Day 1 for steady state PK profile with an assumption that Css,trough = steady state predose drug concentration.
- Sparse PK (number of patients) = (All PK – Dense PK)

Discussion During Meeting: There was no further discussion during the meeting.

2. Does the Agency agree with the content of the sNDA submission as outlined in the draft eCTD table of contents (TOC)?

FDA Response: No. Given the proposal for new liquid formulations of dabrafenib and trametinib, you should submit original new drug applications (NDAs) for both new formulations of dabrafenib and trametinib. In addition, you should submit separate supplemental NDAs for each proposed new or expanded indication for the existing formulations for both dabrafenib and trametinib.

In addition, Integrated Summaries of Efficacy and Safety should be included in Module 5 as per federal regulations for NDA submissions (21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)). The Integrated Summaries should include data relating to pediatric glioma from Studies G2201, A2102 and X2101, as applicable. Provide an integrated database that includes all pediatric patients with BRAF V600-mutated glioma in these studies, with links to the clinical study reports in other submissions as indicated.

Novartis Response Submitted 3/15/2022: Novartis acknowledges the Agency's request to submit original NDAs for both new formulations of dabrafenib and trametinib, as well as separate supplemental NDAs for each proposed new or expanded indication for the existing formulations for both dabrafenib and trametinib.

Novartis would like to clarify the expectation for the content of the original NDAs and supplemental NDAs. The proposed content is listed in Table 2-5 and Table 2-6 (see Novartis response document in the attachment) for Tafinlar and Mekinist, respectively.

Additionally, dabrafenib monotherapy is currently granted orphan designation for the treatment of malignant glioma with BRAF V600 mutation. (b) (4) would like to clarify whether an orphan designation granted for this indication would waive the NDA user fee requirement for both products.

Discussion During Meeting: FDA stated that original NDAs would be required for the two liquid formulations, and that a total of four supplemental NDAs would be needed for the tablet and capsule formulations of trametinib and dabrafenib, with separate sNDAs for addition of the pediatric LGG indication (b) (4)

FDA stated that older pediatric patients with LGG may prefer to take a tablet or capsule, and therefore supplemental NDAs for the tablet/capsule formulations would be needed. FDA stated that they would have further internal discussion to confirm the appropriate combination of NDAs and supplemental NDAs. FDA stated that if Orphan Designation is granted for the product/products and indications included in an application, the user fee would be waived.

For the summaries of clinical efficacy, Novartis stated that they would provide a pooled population of 171 patients who received the combination of dabrafenib and trametinib from studies G2201 and X2101. Safety data from monotherapy studies would be provided separately. (b) (4) FDA requested that this proposal be submitted in writing and proposed to provide feedback after the meeting.

3. Does the Agency agree with Novartis' proposal for the submission of electronic datasets and analysis programs?

FDA Response: We generally agree with the proposed approach and have the following comments:

a. In the datasets, include individual flags for patient-assigned cohort (LGG vs. HGG), BRAF V600 mutational status, and patients who received the recommended doses of dabrafenib and trametinib.

Novartis Response Submitted 3/15/2022: Novartis acknowledges the Agency's comments regarding the submission of electronic datasets and

analysis programs, and notes the request to "include individual flags for patients who received the recommended doses of dabrafenib and trametinib". Novartis is seeking additional clarification on how the "recommended doses of dabrafenib and trametinib" should be defined for purposes of flagging these patients.

Discussion During Meeting: FDA stated that the flags should indicate which patients received the recommended age/weight-based doses of each product.

b. In addition, include the dates of completion of all tumor-directed prior therapies (surgery, radiation, and systemic anti-cancer therapy), the date of determination of initial response (complete response or partial response) and the date of last follow-up (or progressive disease or death) in order to allow calculation of the duration of response follow-up time.

c. All analysis set programs should run on FDA computers without needing extensive modifications. These programs should not depend on macros that are not available in the submission.

d. The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format" (available at: https://www.fda.gov/media/74346/download). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance. Refer to Additional Comments #10 – 21 regarding the contents of the Summary of Clinical Pharmacology.

Discussion During Meeting: There was no further discussion during the meeting for items b-d.

4. Novartis proposes to submit a patient data report (PDR) and patient narratives for Study G2201. Does the Agency agree?

FDA Response: We agree with the proposed approach to include written patient narratives for deaths, serious adverse events, discontinuations due to adverse events, and other clinically significant events deemed to be of special interest. Include the narratives in a bookmarked PDF format separate from the clinical study report and include a tabular listing of the adverse events with hyperlinks to each narrative.

Ensure that narratives include the patient identifier, age and sex of patient, type and location of tumor, and prior cancer treatment (if applicable), as well as relevant details regarding the nature and intensity of the adverse event, the clinical course leading up to the event, timing of the adverse event relative to receipt of study treatment, relevant laboratory and imaging findings, action taken with the study drugs, countermeasures, the investigator's opinion on causality and sponsor's opinion on causality, etc.

Additional narratives may be requested during the review as needed. Regarding Studies X2101 and A2012, provide the relevant narratives for pediatric patients with glioma.

Novartis Response Submitted 3/15/2022: Novartis acknowledges the Agency's comments regarding the written patient narratives, including the request to provide relevant narratives for pediatric patients with glioma from Studies X2101 and A2102. Novartis notes the Agency's request to include the narratives in a bookmarked PDF format separate from the clinical study report and include a tabular listing of the adverse events with hyperlinks to each narrative, and would like to clarify whether FDA is requesting a tabular listing similar to the format shown in Figure 2-1 (see Novartis response document in attachment).

Discussion During Meeting: FDA stated that the proposed tabular listing of narratives appeared acceptable.

5. Novartis proposes to submit content for Modules 2 and 5 to NDA 202806 and incorporate these modules by cross-reference into NDA 204114. Module 1 and the respective Module 3 contents for each product will be submitted to both NDAs. Data and information regarding Study A2102 and Study X2101 will be incorporated by cross-reference to the previously submitted information in NDA 202806/S-022. Does the Agency agree with this approach?

FDA Response: Yes, for the proposed supplemental NDAs for the new indications, the proposed cross-referencing appears appropriate. As stated in Question 2, you should submit original NDAs for the new formulations of dabrafenib and trametinib, in addition to supplemental NDAs.

Novartis Response Submitted 3/15/2022: Novartis acknowledges the Agency's comments regarding the cross-referencing strategy. No further discussion is requested during the meeting.

6. Does the Agency agree that the established safety profile of dabrafenib in combination with trametinib is adequate, and that a waiver for a 90/120-day safety update as required per 21 CFR 314.50(d)(5)(vi)(b) may be granted?

FDA Response: Waiver of the 90/120-day safety update may be acceptable. However, clarify the data cut-off date for the safety population in the planned sNDA. Since six months have passed from the August 23, 2021, data cut-off date and the potential for long-term treatment for patients on this regimen, we strongly recommend an updated data cut-off for safety and efficacy as stated in Question 1.

In addition, if a new safety signal is identified, additional data may be required to further evaluate the risk. We may consider a post-marketing requirement to better evaluate and characterize long-term toxicities of dabrafenib and trametinib in this pediatric population.

Novartis Response Submitted 3/15/2022: Novartis acknowledges the Agency's comments regarding waiver of the 90/120-day safety update and a potential post-marketing requirement to better evaluate and characterize the long-term toxicities of dabrafenib and trametinib in the pediatric population. Please refer to the Novartis response to Question 1 regarding the recommendation to use an updated data cut-off for safety and efficacy.

Discussion During Meeting: There was no further discussion during the meeting.

ADDITIONAL COMMENTS

Clinical

7. We recommend consideration of participation in Project Orbis for the submission of the proposed application for dabrafenib and trametinib, including the respective pediatric formulations. To participate in Project Orbis, you will need to submit a global submission plan for the proposed Project Orbis Countries. Current Project Orbis countries include Australia, Brazil, Canada, Israel, Singapore, Switzerland, and the United Kingdom. Please include your global submission plan in advance of the March 16, 2022, meeting.

Novartis Response Submitted 3/15/2022: The tentative global submission plan for this application under Project Orbis is provided in Appendix 1-(Project Orbis Global Submission Plan-see Novartis response document attachment). Planned participation in Project Orbis is currently expected to include Brazil, Israel, Singapore, and Switzerland, due to differences in local filing strategies for this application in other Project Orbis countries.

Discussion During Meeting: There was no further discussion during the meeting.

8. Provide an update regarding companion diagnostic development and plan for analytical evaluation of the device since BRAF V600E mutation status is essential for use of the therapy in the population.

Novartis Response Submitted 3/15/2022: (b) (4)

Discussion During Meeting: There was no further discussion during the meeting.

9. Provide an update regarding your plan for submission of the study reports to fulfill the Pediatric Written request for dabrafenib and trametinib issued on March 1, 2016, and most recently amended on February 16, 2022.

Novartis Response Submitted 3/15/2022: The final study reports for DRB436A2102 (Study 1 of the Tafinlar Written Request [WR]) and TMT212X2101 (Study 1 of the Mekinist WR) were submitted with proposed pediatric labeling on September 22, 2021 as part of (b) (4) sNDA (NDA 202806/S-022 and NDA 204114/S-024). The primary analysis study report for DRB436G2201 (Study 2 [HGG cohort] and Study 3 [LGG cohort] of the Tafinlar and Mekinist WRs) will be submitted with amended proposed pediatric labeling to include patients 1 year of age and older, along with the pediatric liquid formulations, as part of this NDA. The efficacy of dabrafenib and trametinib in adolescent patients (12 to less than 18 years of age) with unresectable or metastatic melanoma and adjuvant melanoma with BRAF V600E or V600K mutations will be supported by extrapolation utilizing PK data from Studies A2102, X2101, and G2201, (b) (4)

Discussion During Meeting: There was no further discussion during the meeting.

Address the following questions in the Summary of Clinical Pharmacology section of NDA and sNDA (See response to Question 2):

10. 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.

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

12. 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.

13. 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 NDA and sNDA submissions (See response to Question 2):

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

15. Provide 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.

16. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

    a. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

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

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

    a. Standard model diagnostic plots.

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

    c. Model parameter names and units in tables.

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

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

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

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

    b. A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets

    c. Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

19. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers, and safety) relationships in the targeted patient population. Refer to Guidance for Industry for population PK, exposure-response relationships, and pharmacometric data and models submission guidelines.

    Discussion During Meeting: FDA stated that this information could be submitted within 90 days of submission of the application.

20. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of

intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.

21. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.

Novartis Response Submitted 3/15/2022: Novartis acknowledges the Agency's comments regarding the information to be included in the Summary of Clinical Pharmacology and in the clinical pharmacology sections of the submission.

In regards to comment #19 requesting submission of a study report describing exploratory exposure-response (measures of effectiveness, biomarkers, and safety) relationships, Novartis believes the additional insights to be gained from such exploratory analyses to be limited for several reasons: (1) extensive safety and efficacy ER analyses have already been performed for large studies in adult BRAF V600 mutation positive patients exposed to wider dose ranges; and (2) the exposure range in the pivotal G2201 study (which used body weight adjusted dosing to achieve a comparable exposure to adult patients) was narrow, with AUCtau CV of 45-54% for dabrafenib and 22-23% for trametinib, which limits the scope for exposure-related analyses of safety and efficacy data. Limited dose-response data are available for the dose escalation cohorts of the phase I clinical studies CDRB436A2102 and CTMT212X2101; no additional pediatric specific exposure response analyses were planned in this relatively small sample set of BRAF V600 positive glioma patients.

Additional Comment Discussed During Meeting: FDA referred to correspondence from the Division of Medical Error Prevention and Analysis and noted that the Human Factors Validation Study requested should be included in the original filing of the application. Novartis will reassess their timelines based on this and other requirements discussed during the meeting, and communicate with FDA regarding the anticipated timeline for NDA submission.

Post-Meeting Addendum:

1. Regarding the proposed approach for the original NDA and supplemental NDA submissions:

    a. We recommend that you submit two original NDAs for the proposed liquid formulation (dabrafenib dispersible tablet and trametinib powder for oral solution).

b. Regarding the solid formulations of dabrafenib and trametinib, (b) (4) [redacted] Therefore, we recommend that you submit two efficacy supplemental NDAs (one for dabrafenib solid formulation and one for trametinib solid formulation) for the first-line pediatric LGG indication. The clinical data for this indication may be submitted to the original NDAs and cross-referenced in the sNDAs.

c. We acknowledge your plan to submit (b) (4) [redacted] we recommend that you submit these data as soon as possible given the unmet medical need in this population.

d. In addition, please clarify whether you intend to seek indications for the currently approved indications of dabrafenib and trametinib for the new liquid formulations of dabrafenib and trametinib. Adult patients who have difficulty swallowing, either due to the location of their disease (e.g., patients with anaplastic thyroid cancer) or treatment complications, may benefit from liquid formulations of dabrafenib and trametinib.

2. Regarding the proposed food effect studies for dabrafenib and trametinib:

   We acknowledge your response submitted on March 29, 2022. We agree with your approach to submit the results of a dedicated food effect study for the liquid formulations as a post-marketing commitment should dabrafenib and trametinib be approved for the proposed indication.

3. We have the following comments regarding your proposed Project Orbis timeline.

   a. (b) (4) [redacted]

   b. For your awareness, per current regulations, Brazil has 60 days to take action for review of new supplemental indications.

   c. We recommend that you submit a CMC assessment aid to facilitate review of FDA applications as well as sharing with the Orbis partners.

4. To facilitate review of your application, we recommend the following programs developed by the Oncology Center for Excellence (OCE):

   a. Real-Time Oncology Review (RTOR) 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. We strongly recommend that you consider participating. Please see the following link to the FDA website describing this program: https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review.

   b. The Assessment Aid (AA) is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). The document is based on the FDA Multidisciplinary Review template with most sections divided into two parts, clearly delineated to emphasize ownership of each position as either the Applicant's position or the FDA's position. The applicant fills in their positions in the relevant sections. If you choose to participate, FDA would expect receipt of the completed AA as part of the complete NDA package or within 30 days of submission. The AA instructions and template are included as an addendum to these meeting minutes. In general, the AA should be concise and only include critical information. Please see the following link to the FDA website describing this program: https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid.

PREA REQUIREMENTS

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

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

progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the 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 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.

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

Meeting requests should be sent to the appropriate review division with the cover letter clearly stating, "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package to be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- 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

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

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.

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

ONCOLOGY PILOT PROJECTS

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

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

- Assessment Aid[10]

ATTACHMENTS:

Novartis Response Document submitted March 15, 2022.

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

[8] https://www.fda.gov/media/85061/download
[9] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[10] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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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/

MELANIE B PIERCE
04/13/2022 12:29:48 AM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	117898
Request Receipt Date	January 31, 2022
Product	Dabrafenib and Trametinib
Indication	Dabrafenib in combination with trametinib for the treatment of pediatric patients one year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy
Drug Class/Mechanism of Action	Dabrafenib (BRAF inhibitor) Trametinib (MEK1/2 inhibitor)
Sponsor	Novartis Pharmaceuticals Corporation
ODE/Division	CDER/OND/DO2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	April 1, 2022

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

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

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**
   Dabrafenib in combination with trametinib is intended for the treatment of pediatric patients one year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy.

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

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

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

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

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

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

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

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

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

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

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

[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

Disease Background

Low-grade glioma (LGG) is the most common pediatric brain tumor. Approximately 1500 children per year are diagnosed with LGG, which is defined histologically as a WHO Grade 1 or 2 tumor of glial origin.[1] While ten-year overall survival is 85-95%, many patients have disease progression and recurrence, particularly those who do not have a gross total surgical resection.[2] Neurological morbidity is high and deficits are secondary to the anatomic location of the tumor. Patients may experience visual loss, cranial neuropathies, motor and sensory deficits, and endocrine abnormalities. There are no approved therapies for pediatric LGG. Standard of care treatment includes surgical resection, when possible, followed by observation or cytotoxic chemotherapy for residual or recurrent disease. Studies of carboplatin and vincristine combination chemotherapy have shown response rates ranging from 10% to 35% for molecularly unselected pediatric LGG.[3] Radiation is avoided due to negative neurodevelopmental and other long-term side effects. In a study published in 2020, BRAF V600E point mutations were identified in 17% of a population-based cohort of nearly 500 pediatric LGGs diagnosed between 2000 through 2017.[4] Patients with BRAF V600E mutations tend to have worse prognosis overall and lower objective response rates to chemotherapy.[5] There is a clear unmet need for pediatric patients with BRAF V600E-mutant LGG.

Relevant Regulatory History

Dabrafenib and trametinib were developed by Novartis Pharmaceuticals Corporation (Novartis) for multiple hematologic and solid tumor oncology indications. In 2013, dabrafenib and trametinib were both approved as monotherapy agents for adults with unresectable or metastatic melanoma with the BRAF V600E or V600K mutation.[6] The combination therapy was subsequently approved for unresectable or metastatic melanoma with BRAF V600E or V600K mutations, adjuvant treatment of melanoma with BRAF V600E or V600K mutations and involvement of lymph node(s), following complete resection, metastatic NSCLC with BRAF V600E mutation, and locally advanced or metastatic anaplastic thyroid cancer (ATC) with BRAF V600E mutation and no satisfactory locoregional treatment option.

An sNDA is currently under review in the Division of Oncology 3 (DO3) for the proposed indication of the treatment of adult and pediatric patients 6 years of age and older with (b) (4) or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment or have no satisfactory alternative treatment options (NDA 202806/S-022 and NDA 204114/S-024).

Dabrafenib is a selective RAF inhibitor and trametinib is a selective MEK1/2 inhibitor. Blockade of the two sequential kinases in the RAS/RAF/MEK/ERK pathway in resulted in greater growth inhibition of BRAF V600 mutation-positive tumor cell lines in vitro and prolonged inhibition of tumor growth in BRAF V600 mutation positive tumor xenografts compared with either drug alone.[7]

IND 117898 was submitted to the Division of Oncology 2 (DO2) on March 7, 2013. (b) (4)

Orphan drug designation was granted for dabrafenib for the treatment of malignant glioma with BRAF V600 mutation on February 8, 2016. Trametinb does not have orphan drug designation.

FDA issued Pediatric Written Requests for dabrafenib and trametinib on March 1, 2016. The results submitted to support the BTDR are derived from Study CDRB436G2201, which is one of the studies included in the Written Request.

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.

Study CDRB436G2201 was a multi-center, open-label, randomized trial of dabrafenib and trametinib vs. standard of care chemotherapy (carboplatin and vincristine) in 110 pediatric patients 1 to 18 years of age with LGG with *BRAF* V600 mutation. The primary endpoint was overall response rate (ORR) as per Response Assessment in Neuro-Oncology (RANO) criteria as assessed by blinded independent central review (BICR). Secondary endpoints included duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

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.*

DO2 agrees that demonstration of a clinically meaningful and statistically significant improvement in confirmed overall response rate according to RANO as assessed by BICR, supported by durability of responses and prolonged progression-free survival, in an adequately powered randomized study, may provide evidence of clinical benefit which could be used to support an application for traditional approval. Overall survival is not likely to be a feasible endpoint for pediatric LGG because many patients survive for decades.

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

None.

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

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

Current standard of care treatment for pediatric LGG consists of maximal safe surgical resection. If the tumor is unresectable or progresses after resection, most patients receive systemic chemotherapy due to the risk of neurological impairment with progression. FDA approved treatments for low-grade glioma are shown in Table 1. The safety and effectiveness of these therapies in children have not been established. The most commonly used chemotherapy regimen is carboplatin and vincristine; alternative options include a combination of thioguanine, procarbazine, CCNU and vincristine (TPCV) or vinblastine alone.[2] Historical response rates to systemic chemotherapy range from 10-35%.[3] Patients with BRAF V600E mutations have lower 10-year progression-free survival compared to patients without these molecular alterations (approximately 30% vs. 60%, respectively).[4,5]

Table 1: Available Therapies for the Treatment of Low-Grade Glioma*

Treatment	Mechanism of Action	Population	Approval?	Endpoint	Year
Lomustine (CCNU)	Alkylating chemotherapy (oral)	Primary and metastatic brain tumors	Yes	ORR	1976
Carmustine (BCNU)	Alkylating chemotherapy (intravenous)	Primary and metastatic brain tumors	Yes	ORR	1977

*These agents are approved for adults; the safety and effectiveness in pediatric patients have not been established.

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

Table 2: Breakthrough Therapy Designation Requests for Low Grade Gliomas

IND	Product	Indication	Granted/Denied
[redacted]	[redacted]	[redacted]	(b) (4)
[redacted]	[redacted]	[redacted]	(b) (4)

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.

[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.

Study ID (n)	Study Design	Endpoints	Results
Study CDRB436G2201 (n=110)	Multi-center, open-label, randomized trial of dabrafenib and trametinib (D + T; n=73) vs. standard of care chemotherapy (carboplatin and vincristine; n=37) in chemotherapy-naïve pediatric patients with low-grade glioma with BRAF V600 mutation	Primary endpoint: Confirmed ORR as per RANO criteria as assessed by blinded independent central review Secondary endpoints: DOR, PFS, OS	ORR: p-value <0.001 • D + T: 47% (95% CI 35, 59) • Chemo: 11% (95% CI 3, 25) Median DOR: • D + T: 20.3 months (95% CI 12.0, NE) • Chemo: NE (95% CI 6.6, NE) Median PFS: HR 0.31 (95% CI 0.17, 0.53), p value <0.001 • D + T: 20.1 months • Chemo: 7.4 months

Study CDRB436G2201 was an international, open-label, randomized (2:1) trial of dabrafenib and trametinib combination therapy vs. standard of care chemotherapy (carboplatin and vincristine) in 110 pediatric patients with low-grade glioma with BRAF V600 mutation. All patients were chemotherapy-naïve and had measurable disease. Patients either had prior surgery and subsequently progressed, or were non-surgical candidates and investigators determined they needed to begin systemic treatment because of risk of neurological impairment with progression. Eligibility was based on locally-assessed histology and BRAF V600 mutational status; however, all patients were required to have available tumor samples for central confirmation of BRAF V600 mutation.

Patients randomized to the experimental arm received age- and weight-based dosing of dabrafenib in combination with trametinib (n=73); patients on the standard of care chemotherapy arm received carboplatin and vincristine with standard dosing (n=37). Patients randomized to the standard of care arm were allowed to crossover after centrally confirmed disease progression. Tumor assessments included brain MRI every 8 weeks during the first year and every 16 weeks thereafter until disease progression or patients were no longer receiving clinical benefit as determined by the investigator, death or unacceptable toxicity.

In the LGG cohort, demographics were generally similar between arms; 95% had BRAF V600E mutations. Of the 73 patients in the experimental arm, there were 2 complete responses and 32 partial responses [ORR 47% (95% CI 35, 59), p-value <0.001 (computed from chi-square test [Mantel-Haenszel] at a one-sided 2.5% level of significance)]. Of the 37 patients in the control arm, there was 1 complete response and 3 partial responses [ORR 11% (95% CI 3, 25)]. After a median duration of follow-up of 18.9 months, median DOR was 20.3 months in the experimental arm (95% CI 12.0, NE) and was not evaluable in the control arm due to the low number of responders (95% CI 6.6, NE). Median PFS was longer in the experimental arm (20.1 months) compared to the control arm (7.4 months) with HR 0.31 (95% CI 0.17, 0.53), p-value <0.001 (computed from log-rank test at an overall one-sided 2.5% level of significance).

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

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

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

The Division concludes that the data provided represent preliminary clinical evidence of a substantial improvement over available therapies.

The safety data appears consistent with current product labeling which includes clinical trial data from over 1000 patients who received the combination therapy of dabrafenib and trametinib. The sponsor did not identify any new safety signals in this population of patients with pediatric low grade glioma.

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

☒ GRANT:

Provide brief summary of rationale for granting:

The data provided indicate that pediatric patients with low-grade glioma with BRAF V600E mutation have durable objective responses to dabrafenib and trametinib with prolonged progression-free survival when compared to patients treated with standard of care chemotherapy. Pediatric patients with low grade glioma have no approved treatment options. The current standard of care consists of surgery and cytotoxic chemotherapy; chemotherapeutic regimens are associated with variable response rates in this disease and can be associated with substantial toxicities, which are a particular concern in the setting of young patients with relatively long survival.

In the context of a plausible biologic rationale and relevant mechanism of action, the observed statistically robust improvement in ORR compared to standard cytotoxic chemotherapy supported by durability of responses and improved PFS represents a substantial improvement in a clinically significant endpoint over available therapies.

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

☐ DENY:

Provide brief summary of rationale for denial: N/A

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):

DO2 is committed to working closely with the sponsor on the as development progresses. A pre-sNDA meeting to discuss a planned sNDA for the indication proposed for Breakthrough Designation will be held on March 16, 2022. Ongoing discussions will include issues related to dose optimization and companion diagnostic development.

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:

N/A

14. List references, if any: See Endnotes

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

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

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

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

Revised 10/13/20 /M. Raggio

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[1] Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012-2016. Neuro Oncol. 2019 Nov 1;21(Suppl 5):v1-v100. doi: 10.1093/neuonc/noz150.

[2] de Blank P, Bandopadhayay P, Haas-Kogan D, Fouladi M, Fangusaro J. Management of pediatric low-grade glioma. Curr Opin Pediatr. 2019 Feb;31(1):21-27. doi: 10.1097/MOP.0000000000000717.

[3] Jones DTW, Kieran MW, Bouffet E, Alexandrescu S, Bandopadhayay P, Bornhorst M, Ellison D, Fangusaro J, Fisher MJ, Foreman N, Fouladi M, Hargrave D, Hawkins C, Jabado N, Massimino M, Mueller S, Perilongo G, Schouten van Meeteren AYN, Tabori U, Warren K, Waanders AJ, Walker D, Weiss W, Witt O, Wright K, Zhu Y, Bowers DC, Pfister SM, Packer RJ. Pediatric low-grade gliomas: next biologically driven steps. Neuro Oncol. 2018 Jan 22;20(2):160-173. doi: 10.1093/neuonc/nox141. Erratum in: Neuro Oncol. 2018 Jan 22;20(2):293.

[4] Ryall S, Zapotocky M, Fukuoka K, Nobre L, Guerreiro Stucklin A, Bennett J, Siddaway R, Li C, Pajovic S, Arnoldo A, Kowalski PE, Johnson M, Sheth J, Lassaletta A, Tatevossian RG, Orisme W, Qaddoumi I, Surrey LF, Li MM, Waanders AJ, Gilheeney S, Rosenblum M, Bale T, Tsang DS, Laperriere N, Kulkarni A, Ibrahim GM, Drake J, Dirks P, Taylor MD, Rutka JT, Laughlin S, Shroff M, Shago M, Hazrati LN, D'Arcy C, Ramaswamy V, Bartels U, Huang A, Bouffet E, Karajannis MA, Santi M, Ellison DW, Tabori U, Hawkins C. Integrated Molecular and Clinical Analysis of 1,000 Pediatric Low-Grade Gliomas. Cancer Cell. 2020 Apr 13;37(4):569-583.e5. doi: 10.1016/j.ccell.2020.03.011.

[5] Lassaletta A, Zapotocky M, Mistry M, Ramaswamy V, Honnorat M, Krishnatry R, Guerreiro Stucklin A, Zhukova N, Arnoldo A, Ryall S, Ling C, McKeown T, Loukides J, Cruz O, de Torres C, Ho CY, Packer RJ, Tatevossian R, Qaddoumi I, Harreld JH, Dalton JD, Mulcahy-Levy J, Foreman N, Karajannis MA, Wang S, Snuderl M, Nageswara Rao A, Giannini C, Kieran M, Ligon KL, Garre ML, Nozza P, Mascelli S, Raso A, Mueller S, Nicolaides T, Silva K, Perbet R, Vasiljevic A, Faure Conter C, Frappaz D, Leary S, Crane C, Chan A, Ng HK, Shi ZF, Mao Y, Finch E, Eisenstat D, Wilson B, Carret AS, Hauser P, Sumerauer D, Krskova L, Larouche V, Fleming A, Zelcer S, Jabado N, Rutka JT, Dirks P, Taylor MD, Chen S, Bartels U, Huang A, Ellison DW, Bouffet E, Hawkins C, Tabori U. Therapeutic and Prognostic Implications of BRAF V600E in Pediatric Low-Grade Gliomas. J Clin Oncol. 2017 Sep 1;35(25):2934-2941. doi: 10.1200/JCO.2016.71.8726.

[6] U.S. Food and Drug Administration, Drugs@FDA [database on the internet]. Dabrafenib USPI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202806s000lbl.pdf.

[7] U.S. Food and Drug Administration, Drugs@FDA [database on the internet]. Dabrafenib USPI. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/202806s019lbl.pdf.

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/

ELIZABETH S DUKE
03/28/2022 09:44:54 AM

DIANA L BRADFORD
03/28/2022 09:48:18 AM

MARTHA B DONOGHUE
03/28/2022 02:15:30 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117898

MEETING MINUTES

GlaxoSmithKline, LLC
Attention: Amita Chaudhari, M.Sc.
Manager, Global Regulatory Affairs
1250 South Collegeville Road, UP4400
Collegeville, PA, 19426

Dear Ms. Chaudhari:

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

We also refer to the meeting between representatives of your firm and the FDA on February 27, 2015. The purpose of the meeting was to discuss the clinical development program for dabrafenib, specifically, (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 (301) 796-1721.

Sincerely,

{See appended electronic signature page}

Meredith Libeg
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:	EOP2
Meeting Date and Time:	Friday, February 27, 2015; 11:00 to 12:00 PM (ET)
Meeting Location:	White Oak Building 22, Conference Room: 1309
Application Number:	IND 117898
Product Name:	Dabrafenib
Indication:	(b) (4)
Sponsor/Applicant Name:	GlaxoSmithKline, LLC (GSK)
Meeting Chair:	Suzanne Demko PA-C
Meeting Recorder:	Meredith Libeg, B.S.

FDA ATTENDEES

Patricia Keegan, M.D.	Division Director, DOP2
Suzanne Demko PA-C	Clinical Team Leader, DOP2
Denise Casey, M.D.	Medical Officer, DOP2
Vivian Yuan, Ph.D.	Biometrics Reviewer, OBV
Donna Roscoe, Ph.D.	Branch Chief, CDRH/OIR/DMGP/MGB
Reena Philip, Ph.D.	Director, CDRH/OIR/DMGP
Latonia Ford	Senior Program Management, OSE
Meredith Libeg, B.S.	Senior Regulatory Health Project Manager, DOP2
Leah Her, M.S.	Regulatory Health Project Manager, DOP2
Claire Myers, Ph.D	Regulatory Health Project Manager, DOP2

SPONSOR ATTENDEES

In-Person:

Jeff Legos, Ph.D., M.B.A.	V.P., Medicine Development Leader
Bijoyesh Mookerjee, M.D.	Director, Clinical Development
Fatima Rangwala, M.D.	Director, Clinical Development
Mark Russo, MD, PhD	Clinical Development
Allison Florance, M.S.	Senior Director, Clinical Statistics

Noelia Nebot, Ph.D.	Manager, Clinical Pharmacology
Amita Chaudhari, M.Sc.	Manager, Global Regulatory Affairs
Angela Windt, Pharm. D.	Director, Global Regulatory Affairs

Via Telephone:

Anne-Marie Martin, Ph.D.	Head of Precision Medicines and Diagnostics
Sulabha Ranganathan	Clinical Development
Yuan Liu, Ph.D.	Oncology Biomarkers
Michelle DeSilvio	Statistics
Ben Stockham	Regulatory Affairs
Susannah Lyon	Regulatory Affairs

1.0 BACKGROUND

Dabrafenib mesylate is a small molecule, RAF kinase inhibitor; based on in vitro data, dabrafenib inhibits wild type BRAF, BRAF V600E, BRAF V600K, and BRAF V600D protein kinase activity at clinically relevant concentrations. Dabrafenib has demonstrated suppression of a downstream pharmacodynamic biomarker (phosphorylated extracellular signal-related kinase [pERK]) in tumor cell lines, demonstrated anti-proliferative activity against multiple BRAF mutation-positive tumor cell lines, achieved proximal biomarker suppression and tumor regression in BRAF mutant xenograft models, and has demonstrated significant anti-tumor efficacy in BRAF V600-mutation positive tumors, including melanoma, (b) (4) thyroid cancer, and non-small cell lung cancer.

The formulations currently available for oral administration in clinical studies are a (b) (4) capsules in strengths of (b) (4) 50, and 75 mg; however, a dispersible tablet is also being developed. The dispersible tablet is intended to be dispersed with water to make a suspension which can then be administered to the patient. At the current stage of development, excipient compatibility and formulation manufacturability are being evaluated (b) (4) The selected formulation will be evaluated in a relative bioavailability study where it will be compared to the commercial capsule formulation.

Regulatory History:

- GSK initiated development of dabrafenib under IND 105032 in 2009.
- On January 12, 2011, dabrafenib was granted orphan designation for the treatment of patients with BRAF V600 mutation positive Stage IIb through IV melanoma.
- On September 27, 2012, GSK submitted a proposed pediatric study request (PPSR) under IND 105032 for dabrafenib (b) (4)
- On January 23, 2013, FDA issued an inadequate PPSR letter to GSK.

- On February 20, 2013, FDA issued a memorandum agreeing that, based on justification and additional information provided following the January 23, 2013, letter, Study BRF116013 could be safely initiated prior to completion of the relative bioavailability study comparing the oral suspension formulation to the capsule formulation of dabrafenib.
- On March 7, 2013, GSK submitted a new IND 117898 for the investigation of dabrafenib in pediatric patients with BRAF V600 mutation-positive tumors. On March 23, 2013, FDA issued waiver from the 30-day review period for IND 117898.
- On May 29, 2013, dabrafenib received approval for the treatment of adult patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.
- (b) (4) this request was withdrawn by GSK on April 17, 2014.

(b) (4)

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

(b) (4)

[redacted]

PREA REQUIREMENTS

20. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. 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.

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.

GSK's emailed response of 2/26/15: GSK acknowledged FDA's response. There was no discussion during the meeting.

PRESCRIBING INFORMATION

21. 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. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

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

GSK's emailed response of 2/26/15: GSK acknowledged FDA's response. There was no discussion during the meeting.

DATA STANDARDS FOR STUDIES

22. CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

GSK's emailed response of 2/26/15: GSK acknowledged FDA's response. There was no discussion during the meeting.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

23. 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 CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

GSK's emailed response of 2/26/15: GSK acknowledged FDA's response. There was no discussion during the meeting.

3.0 ATTACHMENTS AND HANDOUTS

- OHOP's End-of-Phase 2 General Advice for Planned Marketing Applications
- Additional DOP2 CDISC Guidance

OHOP's End-of-Phase 2
General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

FDA's methodology and submission structure for regulatory applications supports research study design, as indicated in the *Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* and the *Study Data Specifications*. Our methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits. The sponsor/applicant should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See *SEND*, *SDTM* and *ADaM* as referenced in *Study Data Specifications*). Study analyses datasets should be traceable to the tabulations datasets.

The *PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017* guidance provides specific requirements for electronic submissions and standardization of electronic drug application data. Sponsors/Applicants should design and implement data standardization in all research protocols to be included in regulatory submissions, as required, based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. The sponsor/applicant should use the Clinical Data Interchange Standards Consortium (CDISC) Technical Road Map to design end-to-end harmonized data standardization, including the Clinical Data Acquisition Standards Harmonization (*CDASH*) standard for design and implementation of data collection instruments.

The *Study Data Specifications* provide the current specifications for submissions. The specifications provide the most conducive data content definition and structure for the review team. The review team assigned to the submission determines the acceptability. Therefore, you are encouraged to follow this best practice noted in the *Study Data Specifications*, "prior to submission, sponsors should discuss with the review division the datasets that should be provided, the data elements that should be included in each dataset and the organization of the data within the file".

In addition, please reference the *CDER Common Data Standards Issues Document* for further information on data standardization in submissions. The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration.

Additional Links:

Electronic Regulatory Submissions and Review Helpful Links
Electronic Common Technical Document (eCTD)

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application.

These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application, we encourage you to provide justification and discuss it with us.

GENERAL

Special Protocol Assessment (SPA) Requests

1) It is strongly recommended that you discuss protocols for SPA request at an EOP2 meeting. The SPA protocol should be limited to one indication. Discussions of other indications may warrant another meeting. In addition, the Agency may agree that a specific finding (e.g., a particular p-value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision. However, final determinations are made after a complete review of a marketing application and are based on the entire data in the application.

SPA Requests for a Single Trial Intended to Support Marketing Approval

Note: You may also apply these concepts to a trial for which you are not seeking SPA agreement.

2) If the protocol for your SPA request is intended to be used as the sole registration trial to support marketing approval, this single trial should be optimally designed and the development program optimally planned. Therefore, you should address the following in your SPA request, and you may also briefly describe these items in your EOP2 meeting briefing document:
   - Justification of why a single trial and not multiple trials are appropriate or not possible for drug development and marketing approval for an NME or substantially different indication (e.g., a study is designed to show a clinically meaningful effect on mortality, irreversible morbidity, or prevention of disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. *See 'Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products'*).
   - A description of your drug development plan, including each indication that is being (or has been) studied and a timetable for submission of the planned studies. You should also include information on where the drug/biologic is marketed outside of the U.S. or indicate if an application for the drug/biologic has been submitted to foreign regulators.

Additional Content for SPA Request Submission

Note: You may also apply some of the concepts below to trials for which you are not seeking SPA agreement.

3) Please submit/address the items below in your SPA request.
   - The protocol must be complete, including a FINAL detailed statistical analysis plan for the evaluation of primary and secondary clinical trial endpoints that potential claims will be sought. The cover letter should identify the need for an expert statistical review if the planned trial includes (1) adaptive design, (2) enrichment design, (3) non-inferiority hypotheses, or (4) novel, new or composite endpoints.
   - If study is blinded, discuss toxicities of agents (or regimens) that may unmask blinding.
   - If radiologic, you should discuss whether an external radiological review will be performed of primary endpoint
   - If your trial uses an *in vitro* diagnostic test to identify the treatment population, you should meet with CDRH to discuss the plans for co-development of the diagnostic test prior to the SPA request. Also, you should provide your plans for a commercially available test at the time of proposed approval. The testing procedure used in your clinical trial should be identical (or "bridged") to your proposal for a commercial kit.
   - If registration trial is to be primarily completed outside of the U.S., the following issues need to be addressed:

- How assessment of safety and efficacy of U.S. minorities will be examined (e.g., will another study be conducted?)
- Applicability of comparator treatment or of disease characteristics to U.S. population

- Any single arm submission should be accompanied by an adequate explanation of the reasons a randomized trial cannot be performed. Please refer to the transcripts for the February 8, 2011 ODAC on Accelerated Approval for Committee recommendations on single arm trials: (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf).

Accelerated or Regular Approval:

4) You should include a statement of whether you are seeking approval under 21 CFR 314 Subpart H/21 CFR 601 Subpart E (accelerated approval) or regular approval in your meeting briefing document, SPA request and NDA/BLA submission. If seeking accelerated approval, there should be a description of all protocols for confirmatory trials (including a timetable for expected trial initiation(s), completion of the planned trial(s), submission of final clinical study report(s)) in your SPA request and NDA/BLA submission. Under §314.510 and 601.41, confirmatory trials would usually be underway at the time of accelerated approval. Please refer to the transcripts for the February 8, 2011 ODAC on Accelerated Approval for Committee recommendations on the timing and number of confirmatory trials: (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM245644.pdf).
   - If surrogate endpoint is being used for accelerated approval, you should justify (i.e., from the literature) why the proposed effect on this surrogate is reasonably likely to predict clinical benefit.

NDA/BLA content and format

CLINICAL

1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.

2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.

3) Investigator instructions that may have been produced in addition to the protocol and investigator brochure

4) All randomization lists and, if used, IVRS datasets (in SAS transport format)

5) All datasets used to track adjudications (in SAS transport format)

6) A Reviewers Guide to the data submission that includes, but is not limited to the following:
   a) description of files and documentation
   b) description of selected analysis datasets
   c) key variables of interest, including efficacy and safety variables
   d) SAS codes for sub-setting and combining datasets
   e) coding dictionary used
   f) methods of handling missing data
   g) list of variable contained in every dataset
   h) listing of raw data definitions
   i) analysis data definitions
   j) annotated CRF (the annotated CRF should contain links connecting to the document that defines

the variable name and lists the data sets that contain the specific item)

k) documentation of programs

7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf).

8) Pediatric Studies:

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the FDA Pediatric Team at Pedsdrugs@fda.hhs.gov. You may also refer to the following FDA website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

9) Quantitative Safety Analysis Plan (QSAP):

The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components:

a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).

b) Safety endpoints for Adverse Events of Special Interest (AERI)

c) Definition of Treatment Emergent Adverse Event (TEAE)

d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter))

e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)

f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.

10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:

a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf)

b) Cancer Drug and Biological Products-Clinical Data in Marketing Applications (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf)

11) Perform the following Standard MedDRA Queries (SMQs) on the ISS adverse event data and include the results in your ISS report. Also, provide any additional SMQ that may be useful based on your assessment of the safety database. Be sure the version of the SMQ that is used corresponds

to the same version of MedDRA used for the ISS adverse event data.
12) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application
13) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.
14) References: There should be active links from lists of references to the referenced article.
Studies, Data And Analyses
15) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).
16) Provide a table with the following columns for each of the completed Phase 3 clinical trials: a) Site number b) Principle investigator c) Location: City State, Country d) Number of subjects screened e) Number of subjects randomized f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection) g) Number of protocol violations (Major, minor, including definition)
17) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).
18) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components: a) subject age and gender b) signs and symptoms related to the adverse event being discussed c) an assessment of the relationship of exposure duration to the development of the adverse event d) pertinent medical history e) concomitant medications with start dates relative to the adverse event f) pertinent physical exam findings g) pertinent test results (for example: lab data, ECG data, biopsy data) h) discussion of the diagnosis as supported by available clinical data i) a list of the differential diagnoses, for events without a definitive diagnosis j) treatment provided k) re-challenge and de-challenge results (if performed) l) outcomes and follow-up information m) an informed discussion of the case, allowing a better understanding of what the subject

experienced.

19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.

20) Provide reports for any autopsies conducted on study.

21) For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

22) Regulations require that the safety and effectiveness data be presented for subgroups including "by gender, age, and racial subgroups". Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis

23) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
b) Exposure-Response Relationships – important exposure-response assessments.
c) Less common adverse events (between 0.1% and 1%).
d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
f) Marked outliers and dropouts for laboratory abnormalities.
g) Analysis of vital signs focused on measures of central tendencies.
h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
i) Marked outliers for vital signs and dropouts for vital sign abnormalities.
j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
l) Standard analyses and explorations of ECG data.
m) Overdose experience.
n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify

for each patient the toxicities that result in study discontinuation or dose reduction.

o) Explorations for:
   i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
   ii) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
   iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
   iv) Drug-demographic interactions
   v) Drug-disease interactions

p) Drug-drug interactions
   i) Dosing considerations for important drug-drug interactions.
   ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

24) Marketing applications must include the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Provide all appropriate data as well as a clinical study report for any study performed to evaluate QT/QTc prolongation.

Financial Disclosure Information

25) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm).

Physician's Labeling Rule

Highlights

1) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]

2) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

3) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]

4) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]

5) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for

complete boxed warning." Refer to 21 CFR 201.57(a) (4) and to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).
6) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).
7) The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights: (a) "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."
8) Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
9) Refer to 21 CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
10) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a) (11)].
11) Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights
12) The Patient Counseling Information statement must appear in Highlights and must read "See 17 for PATIENT COUNSELING INFORMATION." [See 21 CFR 201.57(a)(14)]
13) A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a) (15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
14) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]
Table of Contents
15) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
16) The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
17) Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
18) Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
19) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d) (1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows: 8.1 Pregnancy 8.3 Nursing Mothers *(not 8.2)*

8.4 Pediatric Use *(not 8.3)* 8.5 Geriatric Use *(not 8.4)*
20) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed."
Full Prescribing Information (FPI)
22) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23) Other than the required bolding [See 21 CFR 201.57(d) (1), (d) (5), and (d) (10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
24) Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format" (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf).
25) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf]
26) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
28) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
29) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
30) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31) If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry:

Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
32) Refer to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format.
33) Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

Additional DOP2 CDISC Guidance

The following two tables identify variables and domains that the division uses in conducting standardized analyses on data for marketing or licensing applications. Following the tables is a description of the Tumor Identification (TU), Tumor Results (TR), Response (RS), domains and variables therein. These are provided because DOP2 uses these domains and variables in analysis tools developed by FDA. These domains and variables will be added to the CDISC implementation guide in the near future, however, we request that you implement the use of this STDM format with all your upcoming submissions.

Please use the draft CDISC *Oncology Disease-Specific Therapeutic Area Supplement to the SDTM Implementation Guide* (http://www.cdisc.org/sdtm) for submitting tumor identification, results, and response data to DOP2 as soon as they become available.

Please follow the guidance as provided in the CDER Data Standards Issues Document that can be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

Table 1: Variables that DOP2 requires for analyses of OS, PFS, RR, Disposition, and Adverse Reactions

Domain	Variable Name	Variable Label	Required Variable Values	Currently Available	CDISC Core	CDISC Data Type	CDISC Code List
ADSL	STRATA<N>	Based on definition of strata variable	0,1	No		Num	0,1
AE	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
AE	AEBODSYS	Body System or Organ Class	--	Yes	Exp	Char	
AE	AEDECOD	Dictionary-Derived Term	--	Yes	Req	Char	
AE	AETOXGR	Standard Toxicity Grade	--	Yes	Perm	Char	
AE	AESTDTC	Start Date/Time of Adverse Event	--	Yes	Exp	Char	ISO 8601
CM	CMCAT	Category for Medication	ANTI-CANCER	Yes	Perm	Char	--
CM	CMDECOD	Standardized Disposition Term	--	Yes	Perm	Char	NCOMPLT (Completion/Reason for Non-Completion)

CM	CMENDTC	End Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDY	Study Day of Start of Medication	--	Yes	Perm	Num	--
CM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DM	AGE	Age	--	Yes	Req	Num	--
DM	AGEU	Age Units	--	Yes	Exp	Char	AGEU
DM	ARM	Description of Planned Arm	--	Yes	Req	Char	--
DM	ACTARM		--	New			--
DM	ARMCD	Planned Arm Code	--	Yes	Req	Char	--
DM	COUNTRY	Country	--	Yes	Req	Char	ISO 3166 3- char. code
DM	DTHDTC	Date of Death	--	New		Char	ISO 8601
DM	DTHFL	Subject Death Flag	Y	New		Char	--
DM	ETHNIC	Ethnicity	--	Yes	Perm	Char	--
DM	RACE	Race	--	Yes	Exp	Char	--
DM	RFPENDTC	Date/Time of End of Participation	--	New		Char	ISO 8601
DM	SEX	Sex	--	Yes	Req	Char	M, F, U
DM	SITEID	Study Site Identifier	--	Yes	Req	Char	--
DM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DS	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
DS	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE,ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	NCOMPLT (Completion/Reason for Non-Completion)
DS	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601

DS	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
DS	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
DS	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
DS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	EXSTDTC	Start Date/Time of Treatment	--	Yes	Exp	Char	ISO 8601
EX	EXENDTC	End Date/Time of Treatment	--	Yes	Perm	Char	ISO 8601
LB	LBBLFL	Baseline Flag	Y	Yes	Exp	Char	NY
LB	LBNRIND	Reference Range Indicator	HIGH, LOW	Yes	Exp	Char	--
LB	LBTEST	Lab Test or Examination Name	--	Yes	Req	Char	--
LB	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
MH	MHDECOD	Dictionary-Derived Term	--	Yes	Perm	Char	--
MH	MHENDTC	End Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	MHSTDTC	Start Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	RSACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
RS	RSDTC	Date/Time of Response Assessment	--	Yes	Exp	Char	ISO 8601

RS	RSEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
RS	RSSTAT	Response Assessment Status	NOT DONE	Yes	Perm	Char	ND
RS	RSSTRESC	Response Assessment Result in Std Format	CR or COMPLETE RESPONSE, PR or PARTIAL RESPONSE, SD or STABLE DISEASE, PD or PROGRESSIVE DISEASE, NE or NOT EVALUABLE	Yes	Exp	Char	--
RS	RSTESTCD	Response Assessment Short Name	OVRLRESP, looks for TGRESP, NTGRESP & BESTRESP	Yes	Req	Char	--
RS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	VISIT	Visit name	Must contain "UNSCH" for unscheduled	Yes	Perm	Char	
SV	SVSTDTC	Start Date/Time of Visit	--	Yes	Exp	Char	ISO 8601
SV	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TA	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
TA	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
TA	TGTPRD	Length of assessment schedule		NEW		Char	ISO 8601 Duration
TR	TRACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TR	TRDTC	Date/Time of Tumor Measurement	--	Yes	Exp	Char	ISO 8601
TR	TREVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL

TR	TRLINKID	Link ID	--	Yes	Exp	Char	--
TR	TRLNKGRP		--	NEW		Char	--
TR	TRSTAT	Tumor Assessment Status	NOT DONE	Yes	Perm	Char	ND
TR	TRSTRESC	Character Result/Finding in Std. Format	If TRTESTCD equals "TUMSTATE" Looks for PRESENT, ABSENT, UNEQUIVOCAL PROGRESSION	Yes	Exp	Char	--
TR	TRSTRESN	Numeric Result/Finding in Std. Format	--	Yes	Exp	Num	--
TR	TRTESTCD	Tumor Assessment Short Name	LDIAM, TUMSTATE, Looks for SUMLDIAM	Yes	Exp	Char	--
TR	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TS	DCUTDTC	Data cut off date	--	New		Char	ISO 8601
TS	TSPARMCD	Trial Summary Parameter Short Name	PSSDDUR, PSCDUR	New	Req	Char	--
TS	TSVAL	Parameter Value	ISO Duration	New	Req	Char	--
TU	TUACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TU	TUDTC	Date/Time of Tumor Identification	--	Yes	Exp	Char	ISO 8601
TU	TUEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TU	TULINKID	Link ID	--	Yes	Exp	Char	--

TU	TULOC	Location of Tumor	--	Yes	Exp	Char	LOC
TU	TUMETHOD	Method of Identification	--	Yes	Exp	Char	
TU	TUSTRESC	Tumor Identification Result Std. Format	NEW	Yes	Exp	Char	
TU	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

Please ensure that the following domains and variables are included in your CDISC data submissions. Although the CDISC Implementation guide lists many variables as permissible, in order for DOP2 to conduct efficient and timely reviews of the clinical trial data, most permissible variables should be considered as required variables. Please consult with the division on any permissible variables that you intend not to include in your data files so we can determine the impact this will have on the review process and the acceptability of the omission.

Table 2: Additional variables in SDTM and ADaM that are necessary for efficient review

DOMAIN	VARAIBLE	DATA TYPE
ADaM		
ADSL	STUDYID	C
ADSL	USUBJID	C
ADSL	TRT01A	C
ADSL	TRT01P	C
ADSL	ARM	C
ADSL	AGE	N
ADSL	AGEGR1	C
ADSL	SEX	C
ADSL	RACE	C
ADSL	TRTEDT	N
ADSL	TRTEDTM	N
ADSL	TRTSDT	N
ADSL	TRTSDTM	N
ADSL	DEATHDSC	C
SDTM		
AE	STUDYID	C
AE	USUBJID	C
AE	AEDECOD	C
AE	AEBODSYS	C
AE	AEREL	C
AE	AESEV	C
AE	AETOXGR	C

AE	AESTDTC	C
AE	AEENDTC	C
AE	AESTDY	N
AE	AEENDY	N
AE	AEDUR	C
CM	STUDYID	C
CM	USUBJID	C
CM	CMDECOD	C
CM	CMSTDTC	C
CM	CMENDTC	C
CM	CMENDY	N
CM	CMSTDY	N
CM	CMDUR	C
DM	STUDYID	C
DM	USUBJID	C
DM	AGE	N
DM	SEX	C
DM	RACE	C
DM	ARM	C
DM	RFENDTC	C
DM	RFSTDTC	C
DS	STUDYID	C
DS	USUBJID	C
DS	DSDECOD	C
DS	DSCAT	C
DS	DSSTDTC	C
DS	DSSTDY	N
EX	STUDYID	C
EX	USUBJID	C
EX	EXTRT	C
EX	EXDOSE	N
EX	EXSTDTC	C
EX	EXENDTC	C
EX	EXSTDY	N
EX	EXENDY	N
EX	EXDUR	C
LB	STUDYID	C
LB	USUBJID	C
LB	LBTEST	C
LB	LBSTRESN	N
LB	LBSTNRHI	N
LB	LBSTNRLO	N
LB	LBDTC	C
LB	LBDY	N
MH	STUDYID	C
MH	USUBJID	C
MH	MHDECOD	C
MH	MHBODSYS	C

VS	STUDYID	C
VS	USUBJID	C
VS	VSTEST	C
VS	VSSTRESN	N
VS	VSDTC	C
VS	VSDY	N

CDISC Oncology Domains

Introduction

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials[1]. RECIST (Response Evaluation Criteria in Solid Tumors)[2] has been widely adopted in solid tumor clinical trials where the primary endpoints are objective response or progression and is accepted by regulatory authorities as an appropriate guideline for these assessments. The SDTM domains presented here were developed with RECIST Criteria in mind. However, the domains are intended to represent data collected in clinical trials where tumors are identified and then repeatedly measured/assessed at subsequent timepoints and used in an evaluation of response(s). As such these domains would be equally applicable for criteria other than RECIST e.g. Chesson classification[3] in the assessment lymphomas, or, MacDonald Response[4] in the assessment of malignant gliomas.

The tumor assessment package consists of three SDTM domains based on the SDTM Findings Observation Class. The three domains are related but each domain has a distinct purpose:

TU (Tumor Identification): The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

TR (Tumor Results): The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement record because this would be a duplication of information already represented in TU. This duplication of data was a deciding factor in multi-domain approach to representing this data.

RS (Response): The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

New variables:
--LINKID – The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). Therefore a new ID variable --LINKID is being proposed in order to support the linking requirements. The --LINKID variable is specifically designed to support a relrec dataset to dataset relationship. Values of LINKID could concatenate values of other variables when more than one variable are needed to do join data rows.

--ACPTFL – The Acceptance Flag identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

--EVALID – The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The --EVALID variable is not subject to Controlled Terminology. When --EVALID is populated --EVAL must also be populated.

References:

(1) E.A. Eisenhauera,*, P. Therasseb, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) *EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247*
(2) RECIST Criteria - http://www.eortc.be/recist/
(3) Bruce D. Cheson, Beate Pfistner, et al. Revised Response Criteria for Malignant Lymphoma *Journal of Clinical Oncology. Vol 25 Number 5 Feb 10 2007*
(4) DR Macdonald, TL Cascino, et al. Response criteria for phase II studies of supratentorial malignant glioma *Journal of Clinical Oncology, Vol 8, 1277-1280*

1. Oncology Domains:

1.1. TUMOR IDENTIFICATION - TU

tu.xpt, Tumor Identification - Findings, Version 3. *x.x* …….. One record per identified tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example:	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the assessment results over the course of the study.	Exp	
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TUMIDENT, NEWTUMOR. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion identification. The value in TUTEST cannot be longer than 40 characters. Examples: Tumor Identification, New Tumor Identified. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	Result of the Tumor identification. Examples: When TUTESTCD=TUMIDENT (Tumor Identification), values of TUORRES might be: TARGET or NON-TARGET. When TUTESTCD=NEWTUMOR the value of TUORRES might be: Y When TUTESTCD=BENIGNAB the value of TUORRES might be: BENIGN RENAL LESIONS	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	Contains the result value for all findings copied from TUORRES.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor Identification.	Perm	SDTM 2.2.3
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	Used to specify the anatomical location of the identified tumor. Example: Gastrointestinal Tract. Note: When anatomical location is broken down and collected as distinct pieces of data that when combined provide the overall location information (e.g. organ / laterality /location / sub-location) then the additional information should added as supplemental qualifiers. See Assumption 3	Exp	SDTMIG 2.2.3
TUMETHOD	Method of Identification		*	Record Qualifier	Method used to identify the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TUEVAL to provide an additional level of detail. When multiple assessors play the role identified in TUEVAL, values of TUEVALID will attribute a row of data to a particular assessor. TUEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2.. The TUEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5.	Perm	
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

TU Definition: The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor.

2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categorized at screening or that the Tumor is identified as New (has appeared since the Screening assessment).

   Proposed TUTESTCD / TUTEST values for this domain:

TUTESTCD	TUTEST
TUMIDENT	Tumor Identification
NEWTUMOR	New Tumor Identified
BENIGNAB	Benign Abnormality
TUSPLIT	Tumor Split or Divided
TUMERGE	Tumor Merged or Coalesced

   During the course of a trial when a new Tumor (or lesion) is identified information about that new tumor may be collected to different levels of detail. The following three scenarios represent the most commonly seen data collection methods employed when a new Tumor (or lesion) is identified. The scenarios set out below are not intended to be exhaustive. The sponsor must decide the appropriate collection method based on their analysis needs or internal processes and it is possible that a sponsor's chosen method is not reflected in the scenarios presented below.

   a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease progression and no further details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y".

   b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces of information. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TULOC variable would be populated with the anatomical location information (the additional location variables may be populated depending on the level of detail collected).

   c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In this case the occurrence of the new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measurement/assessment of the New Tumor would be recorded in the TR domain.

3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally not be needed and so the variables are not included in the accompanying examples.

4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these cases the text string is captured in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variables (that might possibly be subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplemental Qualifiers:

QNAM	QLABEL	Definition
TUSUBLOC	Sub-location of the Tumor	Anatomical location information with more specificity than a gross location
TULOCDET	Detailed Location Information	Detailed anatomical location information that would include details such as: direction (Superior, Posterior); relative direction (Proximal, Distal); axes (Dorsoventral, Mediolateral); planes (Sagittal, Coronal); and any other divisions or sub-anatomy information.
TUORGAN	Organ Affected	Actual Body Organ location of the tumor. This is more specific than Body Organ Class
TULAT	Tumor Location Laterality	Lateral location used to distinguish Right & Left sides. For example if a Tumor was located in the "Right Lung" then the TULOC and QNAM.TULAT values would be TULOC=LUNG; QNAM.TULAT=RIGHT.

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALID="RADIOLOGIST 1". The TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.

7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tumor when that information is known:

QNAM	QLABEL	Definition
PREVIR	Previously Irradiated	Indication of previous irradiation to a tumor.
PREVIRP	Irradiated then Subsequent Progression	Indication of documented progression subsequent to irradiation.

TUMOR RESULTS - TR

tr.xpt, Tumor Results - Findings, Version 3..*x x* …….. One record per tumor measurement/assessment per tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App, 2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result records to the tumor identification record.	Exp	
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: LDIAM, DIAM. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: LONGEST DIAMETER, LONGEST PERPENDICULAR, AXIAL THICKNESS, VOLUME, AREA. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement Categorical	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRORRES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment as originally received or collected.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRORRESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TRORRES. Example: mm	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied or derived from TRORRES in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2 SDTMIG 4.1.5.1
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, or a tumor measurement was not taken. Should be Null if a result exists in TRORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor measurement or assessment.	Perm	SDTM 2.2.3
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TREVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. TREVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TREVALID variable would not be subject to CDISC Controlled Terminology. Note TREVAL must also be populated when TREVALID is populated. See Assumption 4	Perm	
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. where TREVALID has values of "RADIOLOGIST 1" & "RADIOLOGIST 2") provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

TR Definition: The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate back to an identification record in TU.

2. TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

TRTESTCD	TRTEST
AREA	Area
AXTHICK	Axial Thickness
DIAM	Diameter
LDIAM	Longest Diameter
LMAXSP	Major Axis Axial Plane, Long Diameter Target
LPERP	Longest Perpendicular
METVOLNO	Average Metabolic SUV
MJAX3SP	Major Axis 3D (All Planes)

MNAX3SP	Minor Axis 3D
MNAXSP	Minor Axis
MXSUVSSP	Maximum SUV (1 cm Spot)
MXSUVVSP	Maximum SUV (Single Voxel)
PCCHBL	Percent Change From Baseline
PCCHNAD	Percent Change From Nadir
PREVIR	Lesion Previously Irradiated
PREVIRP	Lesion Progressing Since Irradiated
PRODUCT	Product
RADDESP	Radio Density
SAXIS	Short Axis
SUMAREA	Sum of Area
SUMAXTHK	Sum of Axial Thickness
SUMLDIAM	Sum of Longest Diameter
SUMLPERP	Sum of Longest Perpendicular
SUMPDIAM	Sum of the product of the diameters
SUMPROD	Sum of Product
SUMVOL	Sum of Volume
VOLPETSP	Total Tumor Volume
VOLUME	Volume
XPRO3SP	Cross Product 3D
XPRODSP	Cross Product

Note: The sponsor should not derive results for any test indicated in the list above (e.g. “Percent Change From Nadir”) if the result was not collected. Tests would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external assessor as part of an electronic data transfer. It is not intended that the sponsor would create derived records to supply those values.

3. The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

4. The Evaluator Specified variable (TREVALID) is used in conjunction with TREVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TREVAL variable. For example TREVAL=”INDEPENDENT ASSESSOR” and TREVALID=”RADIOLOGIST 1”. The TREVALID variable is not subject to Controlled Terminology. TREVAL must also be populated when TREVALID is populated.

RESPONSE – RS

rs.xpt, Response - Findings, Version 3..*x x* ..... One record per response assessment per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the appropriate measurement records (in TR) used to determine the response result.	Perm	
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TRGRESP, BESTRESP, SYMPTPD	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. The value in RSTEST cannot be longer than 40 characters. Examples: Target Response, Best Overall Response, Symptomatic deterioration	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originally received, collected, or calculated.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTRESC	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response assessment, copied or derived from RSORRES in a standard format or standard units. RSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in RSSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was not performed. Should be Null if a result exists in RSORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not performed. Examples: Subject does not have target lesions. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the response assessment.	Perm	SDTM 2.2.3
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with RSEVAL to provide an additional level of detail. When multiple assessors play the role identified in RSEVAL, values of RSEVALID will attribute a row of data to a particular assessor. RSEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The RSEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5	Perm	
RSACPTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent assessor (e.g. independent Oncologist) provides an evaluation of response this flag identifies the record that is considered to be the accepted evaluation.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates of scans Exception: derived data in RS needed for reviewer	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. May be from rand date not first dose date 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

RS Definition: The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required when a response evaluation relates back to an individual tumor.

2. RSTESTCD / RSTEST values for this domain(this is for illustration purposes these values will be published as Controlled Terminology):

RSTESTCD	RSTEST	Definition
TRGRESP	Target Response	
NTRGRESP	Non-target Response	
OVRLRESP	Overall Response	
BESTRESP	Best Response	
LESNRESP	Lesion Response	
SYMPTPD	Symptomatic Deterioration	

3. When an evaluation of Symptomatic Deterioration is recorded (which is symptomatic of progressive Disease) and additional description of the clinical symptoms is collected then that information would be recorded in the following Supplemental Qualifier:

QNAM	QLABEL	Definition
CLSYMP	Clinical Symptoms of PD	Textual description of clinical symptoms that led to the evaluation of Symptomatic deterioration

4. TS – TSPARM/TSVAL needed to represent the Response Criteria used in the clinical trial.

5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the RSEVAL variable. For example RSEVAL="INDEPENDENT ASSESSOR" and RSEVALID="RADIOLOGIST 1". The RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

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/s/

MEREDITH LIBEG
03/20/2015