CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761381Orig1s000
761429Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 150904

MEETING REQUEST-
WRITTEN RESPONSES

Bristol Myers Squibb Company
Attention: Rick Spring, MSc
Director, Global Regulatory Lead, Oncology
P.O. Box 5326
Princeton, NJ 08543-5326

Dear Rick Spring:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMS-986298; nivolumab subcutaneous (SC).

We also refer to your July 14, 2023, submission requesting a meeting to obtain feedback from the Division of Oncology 3 on the proposed content and format of the planned Biologics License Application (BLA) in support of nivolumab SC.

Further reference is made to our August 3, 2023, Meeting Granted letter, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your August 11, 2023, background package.

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, MT
Senior Regulatory Health Project Manager
Division of Regulatory Operations-Oncologic Diseases for DO3
Office of Regulatory Operations
Office of New Drugs
Center for Drug

Enclosure:

- Written Responses

WRITTEN RESPONSES

Meeting Type:	C
Meeting Category:	Guidance
Application Number:	IND 150904
Product Name:	BMS-986298; nivolumab subcutaneous (SC)
Indication:	Renal Cell Carcinoma
Applicant Name:	Bristol Myers Squibb Company
Regulatory Pathway:	351(a) of the Public Health Service Act

BACKGROUND

On July 14, 2023, Bristol Myers Squibb Company (BMS) submitted a meeting request to obtain feedback on the proposed content and format for the planned Biologics License Application (BLA) in support of nivolumab subcutaneous (SC). The meeting package was submitted on August 11, 2023.

Nivolumab SC (BMS-986298) is a fixed-dose-combination product of nivolumab and recombinant human hyaluronidase.

- Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains and is a human IgG4 monoclonal antibody directed against the programmed death-1 (PD-1) receptor.

- Recombinant Human Hyaluronidase PH20 (rHuPH20) rHuPH20 is the active ingredient in the approved product HYLENEX.

BMS plans to seek approval, based on data from Study CA20967T (pivotal study), Study CA2098KX (supportive pharmacokinetic (PK)/safety and dose-finding study), and a model-based PK bridging strategy, for nivolumab SC for the following adult indications:

<u>Monotherapy</u>

- (b) (4)
- all currently approved solid tumor nivolumab maintenance monotherapy indications following completion of OPDIVO/ipilimumab combination therapy

<u>Combination therapy</u>

- all currently approved solid tumor indications where nivolumab is administered Q2W and/or Q4W with chemotherapy
- with cabozantinib for advanced renal cell carcinoma

The proposed dosage of nivolumab SC consists of nivolumab 600 mg with rHuPH20 10,000 units administered every 2 weeks (Q2W) or nivolumab 1200 mg with rHuPH20 20,000 units administered Q4W.

BMS is seeking FDA agreement on the proposed content and technical aspects of the proposed BLA. BMS plans to submit the BLA in March 2024. (b) (4) (b) (4) (b) (4) According to BMS, topline results from Study CA20967T are expected in October 2023 and will form the basis of a Type B pre-BLA meeting planned for December 2023.

CLINICAL
The proposed BLA submission for nivolumab SC will be supported by Study CA20967T and Study CA2098KX.

Study CA20967T, a multicenter, randomized, open-label, Phase 3 study that will evaluate PK and efficacy non-inferiority of nivolumab SC to nivolumab IV and safety and tolerability of nivolumab SC in patients with advanced or metastatic clear cell renal carcinoma (ccRCC) who have evidence of progression after having received no more than two prior systemic treatment regimens. The primary objectives are to demonstrate PK non-inferiority of nivolumab SC vs nivolumab IV administration. Key secondary objective is to demonstrate overall response rate (ORR) as determined by blinded independent central review (BICR) non-inferiority of nivolumab SC vs IV nivolumab.

Study CA2098KX will provide supportive PK and safety data in the proposed BLA submission. This is a multicenter, randomized, open-label, Phase 1/2 study that will evaluate the PK, safety, and tolerability of nivolumab SC administered with and without rHuPH20 SC in patients with NSCLC; RCC; unresectable or metastatic melanoma; HCC; or CRC (MSI-H or dMMR) in Parts A-D of the study and patients with metastatic urothelial cancer in Part E. The primary objectives are to describe the PK of nivolumab SC with or without rHuPH20.

The primary source of data for the summary of clinical efficacy (SCE) and summary of clinical safety (SCS) will be derived from Study CA20967T, while the data from Study CA2098KX will serve only as supplementary evidence. BMS does not intend to pool the two studies for safety or efficacy because they involve distinct dosing schedules, treatment durations, and tumor types.

The assessment of efficacy in CA20967T will be conducted based on the entire randomized population. The primary endpoint of ORR will be used to evaluate the non-inferiority of nivolumab SC in comparison to nivolumab IV.

Safety analyses will be performed on the treated population, including analysis of immune mediated adverse events (IMAEs) that occurred within 100 days of last dose of treatment. Descriptive statistics of safety will be presented by treatment group using NCI CTCAE v5.

BMS plans to submit case report forms (CRFs) for all treated patients in Study CA20967T who either died or experienced a serious adverse event (SAE) within 100 days of the last treatment dose or who developed an adverse event (AE) that lead to treatment discontinuation.

BMS also intends to submit a 120-day safety update report with a data cutoff in February 2024, which is 7 months after the data cutoff (July 2023) for the primary analysis that will be used for the initial BLA submission.

(b) (4)

SPONSOR QUESTIONS AND FDA RESPONSES

1. Does the FDA agree that BMS can provide additional data from the ongoing PPQ stability studies during BLA review (Section 12.1.1)?

   FDA Response: Yes, FDA agrees with the strategy to provide additional stability data from the PPQ drug product (DP) lots during BLA review.

2. Does the FDA agree with the approach to cross reference Halozyme's BLA 76313 for rHuPH20 drug substance information of the nivolumab SC BLA (Section 12.1.2)?

   FDA Response: BMS' approach to cross reference Halozyme's BLA 761313 for rHuPH20 drug substance information of the nivolumab SC BLA appears to be acceptable. Clearly identify and delineate the sections and subsections (if applicable) cross-referenced from BLA 761313 in the nivolumab SC BLA submission. The adequacy of the cross-referenced data in BLA 761313 to support the proposed BLA submission will be a review issue. In addition to the appropriate LOA, include a copy of the Shared Manufacturing Agreement (SMA) in module 1 of the BLA.

   Section 12.1.2 of the Type C Meeting Package states that BMS and Halozyme intend to have a "Shared Manufacturing Agreement." Submit all license applications/supplements that pertain to a particular product to be manufactured under a shared manufacturing arrangement concurrently (i.e., on the same date) to facilitate FDA's complete review of the product; note that the lack of one or

more related license applications may be a basis for a refusal to file action. Refer *to FDA Guidance for Industry - Cooperative Manufacturing Arrangements for Licensed Biologics, November 2008* for guidance on shared manufacturing agreements.

3. Does the FDA agree that the nonclinical data package is sufficient to support review of the nivolumab SC BLA (Section 12.2.1)?

   FDA Response: The nonclinical data package appears sufficient to support a marketing application. A final determination of the adequacy of the nonclinical data will a review issue.

4. Does the FDA agree with the approach to cross reference both BLA 125554 (nivolumab intravenous) and Halozyme's BLA 021859 (rHuPH20) for nonclinical information of the nivolumab SC BLA (Section 12.2.2)?

   FDA Response: FDA does not object.

5. Does the FDA agree with the proposed plans for the efficacy presentation in the SCE (Section 12.3.1)?

   FDA Response: The proposed plan for the efficacy presentation appears reasonable.

6. Does the FDA agree with the proposed plans for the safety presentation in the SCS including IMAE analysis (Section 12.3.2)?

   FDA Response: The proposed plan for the safety presentation appears reasonable.

7. Does the FDA agree with the scope of the narratives and CRFs to be included in the BLA (Section 12.3.3)?

   FDA Response: The proposed plan for the safety narratives appears reasonable. Additional safety narratives may be requested during the BLA review. However, BMS should plan to include CRFs for all patients in the pivotal study, in the BLA submission.

8. Does the FDA agree that the proposed data cutoff for the primary efficacy/safety analysis is appropriate to support the BLA (Section 12.3.4)?

   FDA Response: FDA does not object to the proposed data cutoff for the primary efficacy/safety analysis.

9. Does the FDA agree with the proposed approach for the 120-day safety update (Section 12.3.5)?

FDA Response: The proposed plan for the 120-day safety update appears reasonable.

10. Does the FDA agree with the proposed plans for the presentation of clinical pharmacology and pharmacometrics information in the SCP (Section 12.4.1)?

FDA Response: FDA agrees.

11. Does the FDA agree with the proposed analysis method for the primary PK endpoints non-inferiority analyses (Section 12.4.2)?

FDA Response: The proposed analysis method for the primary PK endpoints appears reasonable. The acceptability of including derived PK endpoints after treatment discontinuation or death in the analysis will be a review issue. The adequacy of dosing and nivolumab serum concentration-time data from these patients will also be reviewed.

12. Does the FDA agree with the proposed SDTM and ADaM data packages for the pivotal study CA20967T and supportive study CA2098KX (Section 12.5.1)?

FDA Response: The proposal appears acceptable. FDA acknowledges BMS' proposal to exclude intermediate datasets from the data submission package, however, BMS should be prepared to submit these datasets during the review of the application, should FDA request them. .

13. Does the FDA agree that the planned contents of the BLA constitute a complete application for the proposed indications (Section 12.6.1)?

FDA Response: In general, the planned contents of the proposed BLA appears complete, however, a final determination regarding the adequacy of the proposed submission will be made during the pre-BLA meeting when top line results will be available.

14. Does the FDA agree with the proposed nivolumab SC prescribing information in accordance with precedent established with the FDA's PD-1/PD-L1 Class Labeling initiative (Aug. 2018 to Nov. 2020) with respect to the following:

- treatment modification recommendations due to specific immune-mediated adverse reactions in Section 2 Dosage and Administration?

- immune-mediated adverse reactions in Section 5 Warnings and Precautions (Section 12.6.2)?

FDA Response: FDA agrees with the proposal to submit nivolumab SC prescribing information in accordance with the PD1/L1 Blocking Antibody Label Harmonization effort. A final decision regarding the acceptability of the nivolumab SC PI will be made during labeling negotiations.

15. (b) (4)

16.

17.

18.

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.[1]

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

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided.

Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**"

These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review.

Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[3].

---

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[4]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG.
For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[5]

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[6]

---

[4] http://www.fda.gov/ectd
[5] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[6] https://www.fda.gov/media/85061/download

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

(1) Study phase

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

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

(4) Population

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

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

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

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

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental).

An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

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

- Assessment Aid[8]

SUBMISSIONS WITH REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to identify uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.*[9] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

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

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/

GINA M DAVIS
09/27/2023 07:16:58 PM