CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761139Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
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 DS-8201a.

We also refer to the meeting between representatives of your firm and the FDA on June 10, 2019. The purpose of the meeting was to discuss results of studies DS8201-A-J101 and DS8201-A-U201 and your proposed submission strategy for a Biologics License Application (BLA) for your product, DS-8201a.

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.

If you have any questions, contact Sherry Hou, PharmD, Regulatory Project Manager, at (240) 402-1813.

Sincerely,

{See appended electronic signature page}

Sherry Hou, PharmD  
Regulatory Project Manager  
Division of Oncology Products  
Office of Hematology & Oncology Products  
Center for Drug Evaluation and Research

Harpreet Singh, MD  
Acting Clinical Team Leader  
Division of Oncology Products  
Office of Hematology & Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
- Meeting Minutes

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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.
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: June 10, 2019 from 12:00 – 1:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: IND 127553
Product Name: DS-8201a
Indication: Treatment of patients with unresectable or metastatic HER2-positive breast cancer who have received ado-trastuzumab emtansine (T-DM1)

Sponsor Name: Daiichi Sankyo, Inc.

Meeting Chair: Harpreet Singh, MD, Acting Clinical Team Leader, DOP1
Meeting Recorder: Sherry Hou, PharmD, Regulatory Project Manager, DOP1

FDA ATTENDEES
Julia Beaver, MD, Director, DOP1
Laleh Amiri-Kordestani, MD, Supervisory Associate Director, DOP1
Harpreet Singh, MD, Acting Clinical Team Leader, DOP1
Suparna Wedam, MD, Clinical Reviewer, DOP1
Sakar Wahby, PharmD, Clinical Analyst, DOP1
Preeti Narayan, MD, Clinical Reviewer, DOP1
Lijun Zhang, PhD, Acting Biostatistics Team Leader, OTS/OB/DBV
Wei Zhang, PhD, Biometrics Reviewer, DBV
Tiffany Ricks, PhD, Supervisory Pharmacologist/Toxicologist Reviewer, DHOT
Haw-Jyh Chiu, PhD, Pharmacologist/Toxicologist Reviewer, DHOT
Steven Bowen, PhD, Chemist, Team Leader, OPQ/OBP
Jun Liu, PhD, Biologist, OPQ/OBP
Joyce Weaver, PharmD, Senior Drug Risk Management Analyst, DRISK
Christy Cottrell, Chief, Project Management Staff, DOP1
Sherry Hou, PharmD, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES
Antoine Yver, MD, MSc, Executive Vice President, Global Head Oncology R&D
Gilles Gallant, Bpharm, PhD, Vice President, Global Team Lead, R&D Global Oncology
Javad Shahidi, MD, MSc, Executive Director, Clinical Development, R&D Global Oncology
Caleb Lee, MD, PhD, Director, Clinical Development, R&D Global Oncology

Reference ID: 4450397
1.0 BACKGROUND

The sponsor proposes to submit a BLA for accelerated approval to support the use of DS-8201a for the following indication:

*treatment of patients with unresectable or metastatic HER2-positive breast cancer who have received ado-trastuzumab emtansine (T-DM1)*

DS-8201a is an antibody-drug conjugate (ADC) comprised of a monoclonal antibody (MAb), MAAL-9001, conjugated with a drug-linker, MAAA-1162a. MAAL-9001 is a recombinant humanized anti-HER2 IgG1 MAb with the same amino acid sequence as trastuzumab.

The BLA will be based primarily on data from subjects in the target population of HER2-positive breast cancer treated at the target dose of 5.4 mg/kg from 2 studies, DS8201-A-J101 and DS8201-A-U201, along with a pooled subset from these 2 studies.

- **DS8201-A-J101**: Phase 1, two-part, first in human study of DS-8201a. A total of 292 subjects (27 from part 1 and 265 from part 2) were randomized in this study from August 28, 2015 to August 21, 2018 at 14 sites in 2 countries (Japan and United States).
  - Part 1(Dose Escalation)
  - Part 2 (Dose Expansion) multiple cohorts were included: subjects with pathologically documented advanced/unresectable or metastatic HER2-overexpressing breast cancer previously treated with T-DM1 (Part 2a); trastuzumab treated HER2 overexpressing gastric or gastroesophageal junction adenocarcinoma (Part 2b); HER2-low expressing breast cancer (Part 2c), HER2-expressing other solid malignant tumor or any tumor with HER2 mutation (Part 2d); and HER2-expressing breast cancer (Part 2e).
    - The data for HER2-positive breast cancer subjects from Part 1 + Part 2a + Part 2e (N=118) were pooled for subjects treated at a dose of 5.4
mg/kg (N=51) or 6.4 mg/kg (N=67) and form the basis of the primary analysis. Data cut-off (DCO) date was February 1, 2019.

- **DS8201-A-U201**: Phase 2, open-label, two-part, study designed to investigate the safety and efficacy of DS-8201a in HER2-positive, unresectable and/or metastatic breast cancer subjects who are resistant or refractory to T-DM1. The primary endpoint was confirmed best objective response (BOR) of overall response rate (ORR) as assessed by independent central review (ICR) using RECIST v1.1. A total of 253 subjects were randomized to the study between October 2, 2017 to September 21, 2018 at 72 sites in 8 countries (including the United States).
  
  - Part 1 (a PK Stage and a Dose Finding Stage) designed to define the RP2D to be evaluated in Part 2.
  
  - Part 2a planned to enroll approximately 100 subjects at the dose based on the analyses of Part 1 of this trial as well as the Phase 1 trial DS8201-A-J101. Part 2b was to enroll an open-ended number of subjects that received T-DM1 (considered T-DM1 intolerant) but were not eligible for the primary analysis.
  
  - The subjects with HER2-positive breast cancer treated at 5.4 mg/kg who are part of the analyses were enrolled in Part 1, Part 2a, and Part 2b (N=184) of the study. The data from the 5.4 mg/kg dose in Part 1 + Part 2a (N=180) were pooled and form the basis of the primary analysis. DCO date was March 21, 2019.

**Efficacy:**

ORR at the 5.4 mg/kg dose for the two studies is shown in the following table:
DS8201-A-J101:

- median duration of response (DOR) by ICR was 12.7 months (95% CI: 6.7, NR)
- median PFS based on ICR was 13.7 months (95% CI: 8.4, 19.6)

DS8201-A-U201:

- median DOR was not reached
- approximately 60% of subjects were still on study treatment at the DCO, therefore, the median PFS estimates are not available at this time

An efficacy update is planned for submission with the 90-day Safety Update.

Safety:

The safety database for DS-8201a includes 645 patients who have received at least 1 dose of DS-8201a, of which 253 patients had HER2-positive unresectable or metastatic breast cancer and were treated with 5.4 mg/kg. The median treatment duration for subjects with HER2-positive breast cancer at 5.4 mg/kg was 6.9 (0.7-16.1) months in DS8201-A-J101 and 6.9 (0.7-16.1) months in DS8201-AU201.

Across both studies, the most commonly reported TEAEs (≥30%) at 5.4mg/kg were nausea, alopecia, fatigue, vomiting, constipation, and decreased appetite. Grade 3 or above TEAEs were reported in 56.9% of patients. SAEs were reported in 19.8% of patients, and included pneumonia (n=5), pleural effusion (n=3), dyspnea (n=2), pneumonitis (n=2), and interstitial lung disease (n=2).

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Summary of ILD: An independent ILD adjudication committee was established for the DS-8201a clinical program. All potential ILD events were sent for adjudication. Events which were adjudicated as ILD and related to DS-8201a were summarized. As of May 2, 2019, preliminary results are summarized below, and final tables are pending:

- In DS8201-A-J101, among all subjects at all dose levels, 57 out of the 58 events were adjudicated. 43 events in 289 subjects (14.9%) have been adjudicated as ILD and related to DS-8201a. There were 2 (0.7%) Grade 3, 2 (0.7%) Grade 4 and 5 (1.7%) Grade 5 events. Among the HER2-positive breast cancer 5.4 mg/kg group, 7 events in 50 subjects (14%) have been adjudicated as ILD and related to DS-8201a. There were 2 (4.0%) Grade 5 and no Grade 3 or 4 events. One event has not been adjudicated: a Grade 3 acute respiratory failure (due to lung infection per Investigator; subject recovered after antibiotic treatment) in the HER2-positive breast cancer 5.4 mg/kg group.

- In DS8201-A-U201, among all subjects at all dose levels, 26 out of the 28 events were adjudicated. 23 events in 253 subjects (9.1%) have been adjudicated as ILD and related to DS-8201a. There were 1 (0.4%) Grade 3 and 3 (1.2%) Grade 5 events. Among the HER2-positive breast cancer 5.4 mg/kg group, 14 events in 184 subjects (7.6%) have been adjudicated as ILD and related to DS-8201a. There were 3 (1.6%) Grade 5 events and no Grade 3 or 4 events. Two events from two subjects have not been adjudicated: a Grade 5 pneumonitis in the 7.4 mg/kg group, and a Grade 5 acute respiratory failure (due to disease progression per Investigator) in the HER2-positive breast cancer 5.4 mg/kg group.

Potential confirmatory studies:

**DS8201-A-U301:** Phase 3, multicenter, randomized, open-label, active-controlled study of DS-8201a versus treatment of investigator's choice in HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with T-DM1. The primary objective is to compare the efficacy of DS-8201a compared to investigator’s choice by means of PFS based on blinded independent central review (BICR) after observing 372 events. An interim analysis for OS will be conducted at the time of the primary analysis. A final analysis of OS is planned when approximately 428 events have occurred. Approximately 600 subjects will be randomized 2:1 to DS-8201a vs. investigator’s choice. As of May 3, 2019, 72 subjects have been randomized. Enrollment is estimated to complete in approximately February 2020. The primary analysis is event-driven and based on the protocol assumptions is projected to occur in 2Q2020.

**DS8201-A-U302:** Phase 3 randomized, open-label, multicenter study to establish clinical benefit and compare the anti-tumor activity as well as the safety and efficacy of DS-8201a versus T-DM1 in HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and a taxane. The primary objective is to compare the efficacy of DS-8201a to T-DM1 as measured by PFS based on BICR after observing 331 PFS events. Approximately 500 subjects will be
randomized 1:1 to DS-8201a vs. T-DM1. As of May 3, 2019, 56 subjects have been randomized. Enrollment is estimated to complete in approximately December 2019. The primary analysis is event-driven and based on the protocol assumptions is projected to occur in 4Q2020.

FDA sent Preliminary Comments to Daiichi Sankyo, Inc. on May 30, 2019.

2. DISCUSSION

**Question 1:** Does the Agency agree that the results from studies DS8201-A-J101 and DS8201-A-U201 submitted as part of a BLA would support a filing under 21 CFR 601 Subpart E for the treatment of patients with unresectable or metastatic HER2-positive breast cancer who have received T-DM1?

**FDA Response to Question 1:** Results from studies DS8201-A-J101 and DS8201-A-U201 appear adequate to support submission of a BLA. A final filing decision will be made after BLA submission. Whether the results can support an accelerated approval will be a review decision.

**Sponsor’s Response to Question 1 [dated June 4, 2019]:** The sponsor acknowledges the Agency’s comments. As part of the background package for the meeting, ILD data was summarized for DS8201-A-J101 and DS8201-A-U201 and it was noted that there were cases pending adjudication. The sponsor would like to share the latest ILD data as ILD adjudication for the 2 studies (as of data cut-off per study) is complete and discuss our ILD management activities.

**Meeting Discussion:** FDA acknowledged the sponsor’s additional adjudicated cases of ILD. FDA also acknowledged the sponsor’s ongoing ILD management activities, including the ongoing education campaign. These will be further explored during the review process.

**Question 2:** Does the Agency agree with the content of the Financial Disclosure package?

**FDA Response to Question 2:** Yes. In addition, evidence of due diligence must be provided for investigators and sub-investigators for whom follow-up could not be completed.

**Sponsor’s Response to Question 2 [dated June 4, 2019]:** The sponsor acknowledges the Agency’s comments. No further discussion is required.

**Meeting Discussion:** No discussion took place.

**Question 3:** Does the Agency agree with the content and timing of the proposed Safety Update?

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FDA Response to Question 3: Yes.

Sponsor’s Response to Question 3 [dated June 4, 2019]: The sponsor acknowledges the Agency’s comments. No further discussion is required.

Meeting Discussion: No discussion took place.

Question 4: Does the Agency confirm that study DS8201-A-U301 or DS8201-A-U302 can serve as the confirmatory trial to verify the clinical benefit of DS-8201a for the treatment of patients with unresectable or metastatic HER2-positive breast cancer?

FDA Response to Question 4: Yes.

Sponsor’s Response to Question 4 [dated June 4, 2019]: The sponsor acknowledges the Agency’s comments. No further discussion is required.

Meeting Discussion: No discussion took place.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was not discussed as the meeting was focused on the discussion of ILD data.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Rolling review request has been granted per Granted Rolling Review Letter correspondence from June 10, 2019.

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.

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Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

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

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

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.

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

² https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm

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PREScribing INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant 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*.

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

**DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS**

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.
SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: NDA, ANDA, BLA, Master File (except Type III) and Commercial INDs must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.6

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification Specification for Transmitting Electronic Submissions using eCTD Specifications. For additional information, see FDA.gov.7

SECURE EMAIL COMMUNICATIONS

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

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

6 http://www.fda.gov/ectd
7 http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

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**OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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


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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\(^{10}\)

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor’s related analysis of proposed suffixes, which are considered a “collection of information” under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA’s current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

\(^9\) [https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612927.htm](https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612927.htm)
\(^{10}\) [https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612923.htm](https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612923.htm)
Your proposed 351(a) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION
None.

5.0 ACTION ITEMS
None.

6.0 ATTACHMENTS AND HANDOUTS
See Attached Slides.
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/

SHERRY C HOU
06/18/2019 11:13:31 AM

B HARPREET SINGH
06/18/2019 11:18:35 AM
MEETING PRELIMINARY COMMENTS

Daiichi-Sankyo, Inc.
Attention: Kruti Patel
Senior Director, Regulatory Affairs Oncology
211 Mount Airy Road
Basking Ridge, NJ 07920-2311

Dear Ms. Patel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DS-8201a.

We also refer to your September 13, 2018, correspondence, received September 13, 2018, requesting a meeting to discuss clinical data in your upcoming BLA submission in the third quarter of 2018 for DS-8201a in treatment of patients with HER2-positive unresectable, and/or metastatic breast cancer who have received T-DM1.

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, call Janice Kim, Regulatory Project Manager, at (301) 796-9628.

Sincerely,

[See appended electronic signature page]

‘Lola Fashoyin-Aje, MD
Clinical Team Leader (Acting)
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
ENCLOSURE:
  Preliminary Meeting Comments
Preliminary Meeting Comments

Meeting Type: Type B
Meeting Category: Pre-BLA
Meeting Date and Time: November 9, 2018; 9:00 AM – 10:00 AM
Meeting Location: Teleconference
Application Number: IND 127553
Product Name: DS-8201a
Indication: Human Epidermal Growth Receptor 2-positive unresectable, and/or metastatic breast cancer who have received T-DM1
Sponsor/Applicant Name: Daiichi-Sankyo, Inc.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 9, 2018, 9:00 AM – 10:00 AM, teleconference between Sponsor and the Division of Oncology Products 1. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference).

1.0 BACKGROUND

On September 13, 2018, the Sponsor submitted a Type B pre-Biologics License Application (BLA) meeting request to discuss the format, structure, and content of a proposed BLA for DS-8201a, with planned submission in 3rd quarter of 2019.

DS-8201a is an antibody drug conjugate (ADC) comprised of the human epidermal growth factor receptor 2 (HER2)-targeted antibody MAAL-9001, drug linker MAAA-1162, and the drug MAAA-1181a, which is a topoisomerase I inhibitor. The DS-8201a drug product, DS-8201a for injection 100mg, is a lyophilized powder containing 100mg of DS-8201a in a glass vial to be reconstituted in 5 mL of water for injection prior to use.
Based on preliminary clinical results from the first-in-human phase 1 study (DS8201-A-J101), a Fast Track Designation was granted in November 2016 and a Breakthrough Therapy Designation was granted in August 2017 for DS-8201a for the treatment of patients with HER2-positive, locally advanced or metastatic breast cancer who have been treated with trastuzumab and pertuzumab and have disease progression after T-DM1. The Phase 2 study, DS8201-A-U201, is currently ongoing.

The Sponsor plans to submit a BLA for the accelerated approval of DS-8201a, based upon the results of the Phase 2 study, and several supporting studies, including the Phase 1 study, for the following indication:

*DS-8201a is a HER2-targeted antibody and topoisomerase I inhibitor conjugate indicated, as a single agent, for the treatment of patients with HER2-positive, unresectable, and/or metastatic breast cancer who have previously received T-DM1*

Objective response rate (ORR) and duration of response (DoR) from Studies DS8201-A-J101 and DS8201-A-U201 will be used to support this BLA.

An overview of the 5 studies to be included in the BLA is shown in the following table:

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Phase</th>
<th>Countries</th>
<th>Study Title</th>
<th>Study Design</th>
<th>Study Population</th>
<th>FSFV*</th>
<th>Planned Enrollment (TE/UE/WE)*</th>
<th>Subject Exposure* (Sex, Age group [years])*</th>
</tr>
</thead>
</table>

Reference ID: 4344736
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Phase</th>
<th>Countries</th>
<th>Study Title</th>
<th>Study Design</th>
<th>Dosing Regimen</th>
<th>Study Population</th>
<th>FSFV</th>
<th>Planned Enrollment (T/E/C/W)</th>
<th>Subject Exposure (Sex, Age group [years])</th>
</tr>
</thead>
<tbody>
<tr>
<td>DS8201-A102</td>
<td>1</td>
<td>Japan</td>
<td>Phase 1, Multicenter, Open-Label, Multiple Dose Study of DS-8201a to Assess the Effect on the QT Interval and Pharmacokinetics in Subjects with HER2-Expressing Metastatic and/or Unresectable Breast Cancer</td>
<td>Phase 1, Multicenter, Open-Label, Multiple Dose Study of DS-8201a</td>
<td>6.4 mg/kg Q3W</td>
<td>Subjects with pathologically documented unresectable or metastatic breast cancer with HER2 expression</td>
<td>11 Jan 2018</td>
<td>T: 50/E: 29/C: 10/W: 6</td>
<td>Exposed: 23 Male: 0; Female: 23 Age Group: 165:15; ≥65:3; Missing: 5</td>
</tr>
<tr>
<td>DS8201-A104</td>
<td>1</td>
<td>Japan, Korea, and Taiwan</td>
<td>A Phase 1, Multicenter, Open-Label, Single Sequence Crossover Study to Evaluate Drug-Drug Interaction Potential of OATP1B3/CYP3A Inhibitor on the Pharmacokinetics of DS-8201a in Subjects with HER2-Expressing Advanced Solid Malignant Tumors</td>
<td>Phase 1, multicenter, open-label, single sequence crossover study</td>
<td>The study will consist of Cohort 1 and Cohort 2. DS-8201a in Cohort 1 and Cohort 2. DS-8201a for injection 100 mg is provided as a sterile lyophilized powder containing 100 mg of DS-8201a in a glass vial (Lyo-DS-8201a) will be administered as an IV solution at 5.4 mg/kg Q3W. Cohort 1: Ritonavir 200 mg BID on Day 17 of Cycle 2 until Day 21 of Cycle 3. Cohort 2: Ritonavir 200 mg BID on Day 17 of Cycle 2 followed by 200 mg QD until Day 21 of Cycle 3.</td>
<td>Subjects with pathologically documented unresectable or metastatic solid malignant tumors with HER2 expression</td>
<td>12 Jan 2018</td>
<td>T: 32/E: 46/C: 5/W: 1</td>
<td>Exposed: 34 Male: 3; Female: 21 Age Group: 165:15; ≥65:10</td>
</tr>
<tr>
<td>DS8201-A201</td>
<td>2</td>
<td>North America, Europe, Japan, and other Asian countries</td>
<td>A Phase 1, Multicenter, Open-Label Study of DS-8201a to Assess Safety and Pharmacokinetics in Subjects with HER2-Positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated With T-DMM</td>
<td>Phase 2, open-label, 2 part, global, multicenter trial</td>
<td>DS-8201a to be administered as a 5.4 mg/kg, 6.4 mg/kg or 7.4 mg/kg IV dose for Part 1 of the trial. The dose for Part 2 will be determined based on results from Part 1.</td>
<td>HER2-Positive, Unresectable and/or Metastatic Breast Cancer Subjects Previously Treated With T-DMM</td>
<td>14 Sep 2017</td>
<td>T: 230/E: 94/C: 3/W: 1</td>
<td>Exposed: 98 Male: 0; Female: 94 Age group: 16 to 40: 10; ≥60 to &lt;65: 60; ≥65 to ≥75: 21; ≥75: 3</td>
</tr>
<tr>
<td>DS8201-A103</td>
<td>1</td>
<td>Taiwan (Republic of China)</td>
<td>Phase 1, Multicenter, Open-Label Study of DS-8201a to Assess Safety and Pharmacokinetics in Subjects with HER2 Positive Advanced and/or Refractory Gastric, Gastroesophageal Junction Adenocarcinoma, or Breast Cancer</td>
<td>Phase 1, multicenter, open-label study</td>
<td>6.4 mg/kg Q3W</td>
<td>Subjects with pathologically documented HER2 positive advanced unresectable or metastatic gastric, gastroesophageal junction adenocarcinoma or breast cancer, with both</td>
<td>02 Apr 2018</td>
<td>T: 12/E: 15/C: 2/W: 0</td>
<td>Exposed: 11 Male: 0; Female: 11; Age group: 165:10; ≥65:1</td>
</tr>
</tbody>
</table>

* Date of First Subject: First Visit
* Number of targeted subjects (T), enrolled subjects (E), completed subjects (C) and withdrawn subjects (W). The enrolled subjects are defined as those who signed the informed consent. Completed was defined as the subjects who discontinued due to neurological or clinical progression or study drug death due to progression. Withdrawn was defined as discontinuations for other reasons including AEs, protocol deviation, withdrawal of consent or other reasons such as p53 mutation.
* Based upon total number of subjects enrolled as of 08 Jun 2018 and applied randomization schemes. Subject exposure (enrolled subject) is defined as the subject who received at least one study drug (DS-8201a, comparator or placebo).
* Number of exposed subjects by sex and age are provided as overall. Age range (ie, minimum and maximum) is calculated based on all exposed subjects.
* ADC: antibody drug conjugate; HD: twice a day; HER2: human epidermal growth factor receptor 2; IV: intravenous; T-DMM: trastuzumab emtansine; NSCLC: Non-Small cell Lung Cancer; OATP: organic anion transporting polypeptide; Q3W: once every 3 weeks; QD: once a day.
The sponsor plans to include the five studies which will be completed (all listed in the table above) at the time of BLA submission. Three Phase 3 studies (DS8201-A-U301, DS8201-A-U302 and DS8201-A-U303) in patients with unresectable and/or metastatic HER2-expressing breast cancer, or any studies evaluating DS-8201a in other tumor types, or in combination with other agents which are ongoing at the time of the BLA submission and will not be included in the planned BLA submission.

The Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety (ISS) will include data from studies DS8201-A-U201 and DS8201-A-J101. Both studies enrolled patients what match the proposed indication and dose for the planned BLA (i.e., HER2-positive, unresectable and/or metastatic breast cancer who have previously received T-DM1, assigned a dose of DS-8201a at 5.4 mg/kg). Data from studies DS8201-A-A103, DS8201-A-A104, and DS8201-A-J102 will not be included in either the ISE or ISS. For the pooled safety analysis, safety data will be presented for the 5.4 mg/kg dose as well as higher doses in the target patient population and other tumor types. A total of 9 patients received doses ≤3.2 mg/kg in the study DS8201-A-J101 and will not be included in the analysis. The pooled safety analysis will be presented in tables with the following format:

<table>
<thead>
<tr>
<th>HER2+ BC, 5.4 mg/kg</th>
<th>HER2+ BC, 6.4, 7.4, 8.0 mg/kg</th>
<th>All Tumor Types 5.4 mg/kg</th>
<th>All Tumor Types 6.4, 7.4, 8.0 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated 216 subjects</td>
<td>Estimated 143 subjects</td>
<td>Estimated 263 Subjects</td>
<td>Estimated 262 Subjects</td>
</tr>
</tbody>
</table>

Pooled groups of Preferred Terms (PT) will be used for the following adverse events of special interest (AESI):

<table>
<thead>
<tr>
<th>Medical concept</th>
<th>Selected PT’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILD/pneumonitis</td>
<td>Intersitial lung disease, Pneumonitis, Organising pneumonia, Acute interstitial pneumonitis</td>
</tr>
<tr>
<td>LVEF decrease</td>
<td>Acute left ventricular failure, Acute right ventricular failure, Cardiac failure, Cardiac failure acute, Cardiac failure chronic, Cardiac failure congestive, Chronic left ventricular failure, Chronic right ventricular failure, Ejection fraction decreased, Left ventricular failure, Right ventricular failure, Ventricular failure</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>Electrocardiogram QT prolonged, Electrocardiogram QT interval abnormal, Torsade de points, Sudden cardiac death, Sudden death, Syncope, Ventricular arrhythmia, Ventricular fibrillation, Ventricular flutter, Ventricular tachycardia, Ventricular tachyarrhythmia, Seizure</td>
</tr>
<tr>
<td>IRR (defined as any of these pre-selected PT’s within the same day of an infusion at any cycle)</td>
<td>Infusion related reaction, Flushing, Anaphylactic reaction, Dyspnea, Hypotension, Wheezing, Hypersensitivity, Bronchospasm, Pruritus, Angioedema, Urticaria, Skin exfoliation, Oedema, Rash</td>
</tr>
</tbody>
</table>
An interstitial lung disease (ILD) data analysis plan analysis will be conducted for two sets of ILD data: (1) investigator-reported events and (2) for events which have been adjudicated as both ILD and related to DS-8201a by the ILD adjudication committee. A summary table will be presented by worst Common Terminology Criteria for Adverse Events (CTCAE) grade for both the aforementioned sets of ILD event data.

General summary statistics (i.e. severity, outcome, time to first onset, duration of the event) will be generated on the two sets of ILD event data for the pooled groups in the target population (HER2+ BC at 5.4 mg/kg and HER2+ BC at doses ≥6.4 mg/kg) from the DS8201-AJ101 and DS8201-A-U201 studies and overall for the 5 studies in the BLA.

2.0 DISCUSSION


**FDA Response to Question 1:** Yes.

**Question 2:** Does the Agency agree with the Sponsor’s proposal for the Integrated Summary of Efficacy (ISE) statistical analysis plan (SAP)?

**FDA Response to Question 2:** (stats): Yes.

**Question 3:** Does the Agency agree with the Sponsor’s proposal for the Integrated Summary of Safety (ISS) Statistical Analysis Plan (SAP)?

**FDA Response to Question 3:** Yes.

**Question 4:** Does the Agency agree with the Sponsor’s proposal for the selected relevant MedDRA Preferred Terms (PT) for reviewing the following adverse events of special interest (AESI) in the pooled groups as described in the ISS SAP?

**FDA Response to Question 4:** Yes.

**Question 5:** Does the Agency agree with the Sponsor’s proposal for the ILD data analysis plan in the ISS SAP?

**FDA Response to Question 5:** Yes.

**Question 6:** Does the Agency agree with the Sponsor’s proposal to use CTCAE Version 4.03 and MedDRA Version 20.1 for the pooled analyses in the BLA submission?

**FDA Response to Question 6:** Yes.
**Question 7:** Does the Agency agree with the Sponsor’s proposal for Study Data Tabulation Model (SDTM) and analysis data model (ADaM) datasets in the electronic submission data plan?

**FDA Response to Question 7:** In general, your proposal appears acceptable, however your data submission should include data from study DS8201-A-A103.

**Question 8:** Does the Agency agree with the proposal for the scope of CSR narratives and associated CRFs in the submission?

**FDA Response to Question 8:** Yes. In addition, submit CSR narratives for deaths and subjects with adverse events of special interest (AESIs) in the post study follow-up period that the Investigator considers related to DS-8201a.

**Question 9:** Does the Agency agree with the Sponsor’s use of a modified RECIST 1.1 for independent central review of imaging?

**FDA Response to Question 9:** Yes. Submit response results and datasets based on both investigator assessment based on RESCIST 1.1 and central review assessment using modified RECIST 1.1.

**Question 10:** Does the Agency agree with the proposed ER analyses (exposure-efficacy and exposure safety) endpoints?

**FDA Response to Question 10:** Your proposed strategy appears to be acceptable. For E-R for safety analysis, we recommend that you also consider additional endpoints with emerging data including but not limited to AEs of special interest/important identified risks that have not been mentioned in the package, as well as AEs of Grade >3, serious AEs, and dose interruptions due to AE. In addition, include data from study DS8201-A-A103 for E-R analysis.

**Question 11:** Does the Agency agree with the proposal for presentation for the data to be provided in the Summary of Biopharmaceutics and Associated Bioanalytical Methods?

**FDA Response to Question 11:** Your proposal is acceptable. To facilitate review of the BLA, we recommend you also provide an Integrated Summary of Immunogenicity. Currently the data relevant to the assessment of immunogenicity are dispersed throughout different locations of the eCTD including 2.7.4 Summary of Clinical Safety, 5.3.1.4 Reports on Biopharmaceutical Studies and 5.3.5 Reports of Efficacy and Safety Studies. For the BLA file we recommend that the applicant provide the Integrated Summary of Immunogenicity in eCTD section 2.7.2.4:Special Studies or Section 5.3.5.3 :Reports of Analysis of Data from More than One Study. This Integrated Summary of Immunogenicity should provide:

a) Immunogenicity Risk Assessment- this section should provide a concise immunogenicity risk assessment specific to the therapeutic product, in accordance to the principles discussed in the FDA Guidance (2014)
Immunogenicity Assessment for Therapeutic Protein Product. This section should include discussions on product quality-related factors and how these may impact the immunogenic potential of the product; patient-related factors including a discussion on how likely is the patient population and clinical indication to result in immunogenic responses to the product, and a section on trial design-related factors, with a discussion of how the clinical study conditions may facilitate an immunogenic response to the product.

b) Tiered strategy and Stage-Appropriate Bioanalytical Assays- This section should provide details on the tiered immunogenicity strategy that the applicant followed in the clinical program, and validation summaries for the various immunogenicity assay methods that were developed throughout the program. In addition, this section should provide links to method development and validation reports for all the immunogenicity assays used in the various clinical studies supporting the application, particularly those used to test immunogenicity samples from the pivotal clinical study(ies).

c) Clinical Study Design and Sampling Strategy: this section should provide the immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed. This section should include a justification for pre-treatment, in-treatment, and post-treatment sampling time points for immunogenicity and pharmacokinetics, where applicable. This section should discuss how the immunogenicity program aims to reveal the incidence, persistence and clinical significance of anti-drug antibodies.

d) Clinical Immunogenicity Data Analysis- This section should provide summary results of immunogenicity analysis for all clinical studies having an immunogenicity component, including the results of linear and/or non-linear correlation analysis between anti-drug antibody status and titers with PK/PD/efficacy/safety (adverse-events) data. This section should include drug levels measured in the samples tested for anti-drug antibodies, and trace drug product lots used in the individual clinical studies. Discussion should examine the impact of any pre-existing antibodies on pharmacokinetics, safety and efficacy and the impact of treatment-emergent anti-drug antibodies on pharmacokinetics, pharmacodynamics, safety and efficacy.

e) Conclusions and Risk Evaluation and Mitigation Strategies, if applicable. This section should discuss how product immunogenicity impacts the benefit/risk ratio of the therapeutic biologic for the patient population. In addition, consideration should be given to how product immunogenicity will be monitored in post-marketing stage, and how this will be incorporated into the planned REMS. Lastly, a discussion should be provided regarding life-cycle management of approved immunogenicity assays including assay requalification schedule, and assay transfer plans to any contract testing laboratories for post-marketing surveillance.

**Question 12:** Does the Agency agree that the proposed comprehensive table of contents for the BLA with regards to Module 1, 2, 4, and 5 will constitute a complete application for filing?
FDA Response to Question 12: In general, yes. In addition, see FDA response to Question 11. Please note that the final decision on the adequacy of the data will be determined following review of your BLA.

Question 13: Does the Agency agree with the Sponsor’s proposal to include the ISE within Module 2.7.3 (SCE) as well as the ISS within Module 2.7.4 (SCS), and all corresponding tables, appendices, and datasets in Module 5.3.5.3?

FDA Response to Question 13: Yes.

ADDITIONAL COMMENTS

Clinical Pharmacology

1. We recommend the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” (available at https://go.usa.gov/xn4qB). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Address the following questions in the Summary of Clinical Pharmacology:

1. Please include a dedicated section to explain the rationale for dose/dosing regimen selection for the following stages of drug development: first-in-human starting dose, the dose range in phase 1, the dose range in phase 2, the dose(s) in phase 3 and the final proposed dose(s) in the proposed product label.
2. 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.
3. What are the exposure-response relationships for efficacy, safety and biomarkers?
4. How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?
5. What is the impact of immunogenicity on exposure, efficacy and safety?

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

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

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

Refer to the following pharmacometric data and models submission guidelines:

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

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

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 21, 2018 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore,
at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

Information on the Program is available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

**PREA REQUIREMENTS**

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

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include
plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

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

For the latest version of the molecular target list, please refer to https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.
PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

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

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

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

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Site or Type of Testing [Establishment function]</th>
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</table>

Corresponding names and titles of onsite contact:

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
<th>Phone and Fax number</th>
<th>Email address</th>
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<td>1.</td>
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OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in
submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:


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/

IBILOLA A FASHOYIN-AJE
11/02/2018
IND 127553

MEETING MINUTES

Daiichi-Sankyo, Inc.
Attention: Irene Nunes, OD, PhD
Senior Director, Regulatory Affairs Oncology
211 Mount Airy Road
Basking Ridge, NJ 07920-2311

Dear Dr. Nunes:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DS-8201a.

We also refer to your May 23, 2018, correspondence, received May 23, 2018, requesting a meeting to discuss your design and study population for your proposed Phase 3 protocol.

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

If you have any questions, call Janice Kim, Regulatory Project Manager, at (301) 796-9628.

Sincerely,

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Supervisory Associate Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2
Meeting Date and Time: July 24, 2018; 12:00 PM – 1:00 PM EST
Meeting Location: teleconference
Application Number: IND 127553
Product Name: DS-8201a
Indication: (b)(4) HR-positive unresectable and/or metastatic breast cancer
Sponsor/Applicant Name: Daiichi Sankyo, Inc.
Meeting Chair: Laleh Amiri-Kordestani, MD
Meeting Recorder: Janice Kim, PharmD, MS

FDA ATTENDEES
Julia Beaver, MD, Director, DOP1
Amna Ibrahim, MD, Deputy Director, DOP1
Laleh Amiri-Kordestani, MD, Supervisory Associate Director, DOP1
Suparna Wedam, MD, Clinical Reviewer, DOP1
Shenghui Tang, PhD, Statistics Team Leader, DBV
Janice Kim, PharmD, MS, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES
Allison Allen, Postdoctoral Fellow, Regulatory Affairs
Gilles Gallant, Vice President, Global Team Leader
Sean Ge, Senior Director, Biostatistics
Caleb Lee, Associate Director, Clinical Development
Irene Nunes, Senior Director, Regulatory Affairs
Kruti Patel, Associate Director, Regulatory Affairs
Eric Richards, Vice President, Regulatory Affairs
Jayad Shahidi, Executive Director, Global Clinical Leader
Kongming Wang, Director, Biostatistics
Lin Zhang, Executive Director, Clinical Safety

1.0 BACKGROUND

The sponsor has requested a Type B meeting with the agency to seek input on a proposed
Phase 3 study designed to evaluate the safety and efficacy of DS-8201a in subjects with human epidermal growth factor receptor 2 (HER2)-low unresectable and/or metastatic breast cancer. DS-8201a is an antibody drug conjugate (ADC) comprised of a HER2-targeted antibody and topoisomerase I inhibitor.

Clinical development of DS-8201a began in August 2015 with the first-in-human (FIH) study DS8201-A-J101. The following table shows ongoing and planned studies with DS8201a:

<table>
<thead>
<tr>
<th>Trial (status)</th>
<th>Study Design</th>
<th>Study Population</th>
<th>Planned Sample Size (N)</th>
<th>Study Start Date</th>
</tr>
</thead>
</table>
| DS8201-A-J101 (ongoing) | Phase 1, Multi-cohort, open-label basket study, monotherapy | Part 1 (dose escalation): Advanced breast cancer or gastric/gastroesophageal junction adenocarcinoma  
Part 2 (dose expansion): Cohort 2a: T-DM1 treated HER2-positive breast cancer  
Cohort 2b: trastuzumab treated HER2-positive gastric/gastroesophageal junction adenocarcinoma  
Cohort 2c: HER2 low breast cancer  
Cohort 2d: other HER2 expressing solid cancers  
Cohort 2e: HER2 expressing breast cancer (PK cohort) | Total: ~287  
Part 1: 27  
Part 2:  
Cohort 2a: 100  
Cohort 2b: 40  
Cohort 2c: 40  
Cohort 2d: 60  
Cohort 2e: 20 | Aug 2015 |
| DS8201-A-J102 (ongoing) | Phase 1, Multiple-dose, open-label, multicenter study, monotherapy | Subjects with HER2 expressing metastatic and/or unresectable breast cancer | ~50 | Jan 2018 |
| DS8201-A-J104 (ongoing) | Phase 1, Multiple-dose, open-label, multicenter study, monotherapy, DDI study; Single sequence crossover study to evaluate drug-drug interaction | Subjects with HER-2 expressing advanced, malignant solid tumors | ~32 | Jun 2018 |
| DS8201-A-U301 (planned) | Phase 3, Randomized, Controlled, Multicenter, Open-label vs. investigator’s choice | HER2-positive, unresectable and/or metastatic breast cancer subjects who progressed after prior standard of care HER2 therapies, including T-DM1 | ~600 | Q3 2018 |
| DS8201-A-U302 (planned) | Phase 3, Randomized, Controlled, Open-label vs. T-DM1 | HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and a taxane | ~500 | Q3 2018 |
| DS8201-A-U303 (planned) | Phase 3, Randomized, Controlled, Multicenter, Open-label vs. treatment of physician’s choice | HER2-low, HR-positive, unresectable and/or metastatic breast cancer subjects, who have exhausted endocrine therapy and have been previously treated with 1 or 2 prior lines of chemotherapy | ~480 | TBD |
DS8201-A-J101 is a phase 1, two-part, multicenter, open-label, multiple-dose study of DS-8201a in subjects with advanced solid malignant tumors. Part 1 initiated enrollment in June 2015 while Part 2 initiated enrollment in June 2016. Enrollment in Parts 1, 2a, 2b, 2d, and 2e is complete as of April 9, 2018 and the study continues to enroll subjects in Part 2c as of April 18, 2018. All subjects in the dose escalation phase and in cohorts 2a, 2b, 2c, and 2d received the frozen liquid drug product 1 (FL-DP1) formulation of DS-8201a. To support the growing DS-8201a clinical development program, drug product FL-DP2 was developed.

The added cohort Part 2e opened June 2017 and enrolled 21 HER2 expressing breast cancer subjects for treatment with FL-DP2. The preliminary information from Cohort 2e suggests that FL-DP1 and FL-DP2 are comparable.

As of April 18, 2018, a total of 254 subjects have been treated in the DS8201-A-J101 study (part 1 and part 2 combined), of whom 123 were subjects with breast cancer previously treated with T-DM1. Overall efficacy results from all dose cohorts in Part 1 of DS8201-A-J101 demonstrate an ORR of 43.5%. Subjects in the higher dose levels in Part 1 (≥5.4 mg/kg, 13 subjects) were associated with an ORR of 66.7%.

Confirmed responses from Study DS8201-A-J101 (Parts 1 and 2 at doses ≥5.4 mg/kg) are summarized in the following table:

<table>
<thead>
<tr>
<th></th>
<th>Complete Response (CR)</th>
<th>Partial Response (PR)</th>
<th>Objective Response Rate (CR + PR)</th>
<th>Disease Control Rate (CR + PR + SD)</th>
<th>Estimated Median Duration of Response (DOR)</th>
<th>Estimated Median Progression Free Survival (mPFS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All breast cancer (n=140)</td>
<td>1.5% (2/133)</td>
<td>51.9% (69/133)</td>
<td>53.4% (71/133) 95% CI (44.5, 62.1)</td>
<td>91.7% (122/133)</td>
<td>13.6 months</td>
<td>13.7 months</td>
</tr>
<tr>
<td>HER2-positive breast cancer (n=106)</td>
<td>2.0% (2/99)</td>
<td>52.5% (52/99)</td>
<td>54.5% (54/99) 95% CI (44.2, 64.6)</td>
<td>93.9% (93/99)</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>Breast cancers with HER2-low (n=34)</td>
<td>0.0% (0/34)</td>
<td>50.0% (17/34)</td>
<td>50.0% (17/34) 95% CI (24.4, 67.6)</td>
<td>85.3% (29/34)</td>
<td>11.0 months</td>
<td>12.9 months</td>
</tr>
<tr>
<td>HR-positive breast cancers with HER2-low (n=29)</td>
<td>0.0% (0/29)</td>
<td>55.3% (16/29)</td>
<td>55.2% (16/29) 95% CI (35.7, 73.6)</td>
<td>89.7% (26/29)</td>
<td>11.0 months</td>
<td>13.6 months</td>
</tr>
<tr>
<td>HR-positive breast cancers with HER2-low and ≥1 line of prior chemotherapy (n=28)</td>
<td>0.0% (0/28)</td>
<td>53.6% (15/28)</td>
<td>53.6% (15/28) 95% CI (33.9, 72.5)</td>
<td>89.3% (25/28)</td>
<td>11.0 months</td>
<td>13.6 months</td>
</tr>
</tbody>
</table>

* Analysis set: efficacy evaluable subjects for time to event.
* A majority of subjects in these groups remain on treatment. These numbers represent estimated durations of response or PFS based on Kaplan-Meier method.
* An estimate of median duration of response and PFS cannot be calculated in this population due to immature data.
CR = complete response; HER2 = human epithelial growth factor 2; PR = partial response; SD = stable disease.
No dose limiting toxicity was observed and the maximum tolerated dose was not reached in the dose escalation part of DS8201-A-J101. The recommended dose levels for the expansion were 5.4 and 6.4 mg/kg based on tolerability, efficacy, pharmacokinetic data and exposure-response analysis.

As of April 18, 2018, 251 (98.8%) subjects experienced at least one treatment-emergent adverse events (TEAE), of which 246 (96.9%) were related to DS-8201a per investigator assessment. The most common (>20%) adverse events reported were: nausea (185 subjects [72.8%]), decreased appetite (145 subjects [57.1%]), vomiting (99 subjects [39.0%]), alopecia (90 subjects [35.4%]), anemia (87 subjects [34.3%]), diarrhea (82 subjects [32.3%]), constipation (81 subjects [31.9%]), fatigue (79 subjects [31.1%]), platelet count decreased (73 subjects [28.7%]), neutrophil count decreased (63 subjects [24.8%]), white blood cell count decreased (62 [24.4%]), and malaise (55 subjects [21.7%]).

Based on current preclinical and clinical experience and information on class medications of the monoclonal antibody and payload of DS-8201a, the adverse events of special interest (AESI) include interstitial lung disease (ILD)/pneumonitis, cardiotoxicity, and infusion related reactions.

As of April 18, 2018, 30 subjects have experienced 31 events of ILD/pneumonitis/organizing pneumonia. Of these 30 subjects, 8 subjects experienced ILD (5 grade 1, 1 grade 2, 1 grade 3 and 1 grade 5), 17 subjects experienced pneumonitis (8 grade 1, 5 grade 2, 2 grade 3, 1 grade 4 and 1 grade 5) and 5 subjects experienced organizing pneumonia (1 grade 1 and 4 grade 2). Outcome was reported as fatal in 2 subjects, not recovered in 13 subjects, recovered in 6 subjects, recovering/resolving in 3 subjects, and not reported in 6 subjects. Of the 30 subjects, 4 subjects were from US and 26 subjects were from Japan. As of April 18, 2018, a total of 5 subjects have experienced a fatal outcome of ILD/pneumonitis. Two of the 5 have been reported as grade 5 in the clinical database and the remaining 3 have been reported as Grade 2, 3 and 4 pneumonitis. The sponsor states that sites have been contacted for clarification and updates in the clinical database.

An independent ILD adjudication committee has been established and is adjudicating all potential ILD cases. Among the 31 reported events, 21 events have been adjudicated as of April 25, 2018, of which 15 have been adjudicated to be ILD and considered related to DS-8201a, 3 were considered ILD but not related to DS-8201a and 3 were considered not an ILD and not related to DS-8201a.

The proposed Phase 3 study DS8201-A-U303 is a randomized, active-controlled, open-label study designed to evaluate the safety and efficacy of DS-8201a versus treatment of physician’s choice in subjects with HER2-low, HR-positive, unresectable and/or metastatic breast cancer. The dose identified as the RP2D based on DS8201-A-J101 and DS8201-A-U201 studies will be the DS-8201a dose evaluated in this Phase 3 study.

The overall study design is shown below:
The primary objective of the study is to compare efficacy of DS-8201a compared to treatment of physician’s choice on PFS per blinded independent central review (BICR). The secondary endpoints include OS, ORR, duration of response (DoR), clinical benefit rate (CBR), health economics and outcomes research (HEOR) endpoints, and safety endpoints.

Approximately 480 subjects will be randomized in a 2:1 ratio to DS-8201a or 1 of the following physician’s choice treatments: capecitabine, eribulin, gemcitabine, paclitaxel, or nab-paclitaxel.

Randomization will be stratified by:
- HER2 IHC status (HER2 IHC 1+, HER2 IHC 2+/ISH-) of archived samples confirmed by a central laboratory
- Number of prior lines of chemotherapy (1, 2)
- Region (Asia, non-Asia)

Daiichi Sankyo has partnered with [to develop a CDx for HER2-low breast cancer patients based on](b) (4) The commercial test configurations will be used to select HER2-low breast cancer patients (defined as IHC 1+ or 2+ without evidence of ISH positivity) for enrollment into DS-8201a trials using investigational scoring and interpretation guidelines for HER2-low. The enrollment testing will be conducted centrally at three regional [](b) (4)
Key Exclusion Criteria:
1. Ineligible for the 5 options in the physician’s choice arm either due to previously receiving treatment in the metastatic setting with the comparator or having a contraindication to treatment.
2. Prior treatment with ADC which consists of an exatecan derivative that is a topoisomerase I inhibitor.
3. Has spinal cord compression or clinically active central nervous system metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms.
4. Current treatment with strong cytochrome P450 (CYP3A4) and organic anion transporting polypeptide (OATP) inhibitors and any mAb treatment (washout period of $\geq 3$ elimination half-lives of the inhibitor/antibody is required).
5. Has clinically significant cardiovascular or pulmonary disease as defined per protocol.

The sample size for the study is determined based on PFS endpoint. Assuming median PFS in the physician’s choice arm is 4.2 months and median PFS in DS-8201a arm is 6.2 months, a total of 318 PFS events are needed to detect a hazard ratio of 0.68 for PFS with 1-sided alpha of 0.025 and power of 90%. A total of approximately 480 subjects will be randomized (320 subjects to DS-8201a and 160 subjects to physician’s choice). The primary analyses will be the event driven, and the primary analyses for PFS will be performed when approximately 318 PFS events per BICR are observed.

2.0 DISCUSSION

**Question 1:** Does the Agency agree that the study population as defined by the inclusion/exclusion criteria in the protocol DS8201-A-U303 is acceptable?

**FDA Response to Question 1:** Yes, your population is acceptable. You should define “documented refractory to endocrine therapy” in the protocol. Whether your study population as defined by the inclusion/exclusion criteria in the protocol DS8201-A-U303.

You could consider enrolling all patients with HER2-low unresectable and/or metastatic breast cancer regardless of HR status, and HR status could be included as one of the stratification factors.
Sponsor Response to Question 1 [July 23, 2018]:

The definition of endocrine refractory will be provided in the protocol as requested. The Sponsor thanks the Agency for the feedback on enrolling all patients with HER2-low unresectable and/or metastatic breast cancer regardless of HR status. We would like to discuss the need to potentially change the inclusion criteria, stratification approach and list of comparators. The updated inclusion criteria could be changed to enroll subjects regardless of HR status as proposed below.

Pathologically documented breast cancer that:

- Is unresectable or metastatic.
- Has a history of low HER2 expression, defined as IHC 2+/ISH- or IHC 1+ (ISH- or untested).
- Is assessed as low HER2 expression, defined as IHC 2+/ISH- or IHC 1+ according to American Society of Clinical Oncology – College of American Pathologists (ASCO-CAP) guidelines evaluated at a Central Laboratory.
- If HR-positive (either estrogen receptor positive or progesterone receptor positive), is documented refractory to endocrine therapy.
- Has had at least 1 and at most 2 prior lines of chemotherapy in the metastatic setting. If progression of disease occurred within 6 months of adjuvant chemotherapy, adjuvant therapy would count as 1 line of chemotherapy.
- Was never previously HER2-positive (IHC 3+ or ISH+) on prior pathology testing (per ASCO-CAP guidelines).
- Was never previously treated with anti-HER2 therapy.

1. Does the Agency agree with the proposed potential inclusion criteria to expand the study population to include HER2-low mBC regardless of HR status in the primary analyses for this study?

Discussion: FDA acknowledges the sponsor’s response. The sponsor’s proposal to enroll patients with hormone receptor negative HER2 low tumors is acceptable and ultimately the sponsor’s choice. FDA recommends sponsor defines ER/PR positive status in the eligibility criteria as well as hormone refractory population.

To account for the inclusion of HR-negative HER2-low mBC, the number of strata would be increased to include HR status. The potential revised strata would be HER2 IHC (1+ vs. 2+), # of prior chemotherapy (1 vs. 2), HR status and prior CDK4/6 therapy (HR+ with prior CDK4/6 therapy vs. HR+ without prior CDK4/6 therapy vs. HR-). We would remove the region stratum from the analysis, which was included in the briefing book. We would like to obtain Agency’s
input on this approach, which could potentially jeopardize the validity of the statistical testing or discuss alternate approaches that the Agency may provide.

2. Does the Agency agree with the proposed strata or does the Agency have an alternate approach given the # of strata that could impact the validity of statistical analyses? The third element for discussion with the Agency is the list of comparators. The Sponsor considers that the list of comparators (capecitabine, eribulin, gemcitabine, paclitaxel, and nab-paclitaxel) could remain unchanged given that single agent chemotherapy is considered standard of care for subjects with metastatic triple negative breast cancer after 1 or 2 lines of chemotherapy.

**Discussion:** FDA stated that the sponsor’s stratification factors are acceptable. FDA recommended the stratification factors for analysis be pre-specified.

3. Does the Agency agree with keeping the same comparator list (capecitabine, eribulin, gemcitabine, paclitaxel, and nab-paclitaxel) for subjects with HER2-low, HR-negative unresectable and/or metastatic breast cancer who have progressed after one or two prior chemotherapies?

**Discussion:** FDA agreed with the sponsor’s proposed comparator list.

**Question 2:** Does the Agency agree with the proposed Phase 3 (DS8201-A-U303) clinical study design to evaluate the safety and efficacy of DS-8201a when compared to physician’s choice in HER2-low, HR-positive, unresectable and/or metastatic breast cancer subjects?

**FDA Response to Question 2:** Yes.

**Sponsor Response to Question 2 [July 23, 2018]:** We acknowledge the Agency’s guidance

**Discussion:** None.

**Question 3:** Does the Agency agree with the physician’s choice comparator options of capecitabine, eribulin, gemcitabine, paclitaxel or nab-paclitaxel?

**FDA Response to Question 3:** Yes.

**Sponsor Response to Question 3 [July 23, 2018]:** We acknowledge the Agency’s guidance and will provide in the protocol as requested.

**Discussion:** None.

**Question 4:** Does the Agency agree with the planned primary and secondary statistical analyses as presented for study DS8201-A-U303?

**FDA Response to Question 4:** Your primary analysis using PFS assessed by a BICR is acceptable.
For ORR, you should use confirmed response rate, whereby responses are confirmed at a subsequent follow-up visit.

You should treat CBR as an exploratory endpoint only.

You should plan for an interim analysis of OS at the time of your PFS analysis.

In your protocol, please clarify whether patients will come off study drug after progression as determined by the BICR or by the local investigator.

**Sponsor Response to Question 4 [July 23, 2018]**: We acknowledge the Agency’s guidance and will provide in the protocol as requested.

**Discussion**: None.

**ADDITIONAL COMMENTS**

- One important clinical trial objective is the collection of PRO data that can inform tolerability. FDA remains open to assessment of symptomatic adverse events and their descriptive analyses for patients on therapy including impact of treatment on patient’s functioning (i.e., physical function) and other aspects of HRQL. To provide adequate data on acute toxicities, assessment frequency should be higher within the first few cycles and can be less frequent in later cycles.

- If there is an appropriate symptom or functional concept that is being considered for a marketing claim of treatment benefit (e.g., drug X improves disease symptoms or function, or has a comparative reduction in symptomatic side effects), FDA strongly recommends a clear endpoint definition and formal statistical testing with adjustment for multiplicity.

**Discussion**: None.

### 3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.
Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).
On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (ceder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

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

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

**LABORATORY TEST UNITS FOR CLINICAL TRIALS**

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting
mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

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: http://www.fda.gov/ectd.

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 http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION
N/A

5.0 ACTION ITEMS
N/A

6.0 ATTACHMENTS AND HANDOUTS
Sponsor’s slides dated July 23, 2018 are attached

8 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LALEH AMIRI KORDESTANI
08/07/2018
CDER Breakthrough Therapy Designation Determination Review Template

<table>
<thead>
<tr>
<th>IND/NDA/BLA #</th>
<th>IND 127553</th>
</tr>
</thead>
<tbody>
<tr>
<td>Request Receipt Date</td>
<td>June 30, 2017</td>
</tr>
<tr>
<td>Product</td>
<td>DS-8201a</td>
</tr>
<tr>
<td>Indication</td>
<td>HER2-positive locally advanced or metastatic breast cancer</td>
</tr>
<tr>
<td>Drug Class/Mechanism of Action</td>
<td>anti-HER2 antibody drug conjugate</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Daiichi Sankyo, Inc.</td>
</tr>
<tr>
<td>ODE/Division</td>
<td>DOP1</td>
</tr>
<tr>
<td>Breakthrough Therapy Request Goal Date (within 60 days of receipt)</td>
<td>August 29, 2017</td>
</tr>
</tbody>
</table>

Note: This document should be uploaded into CDER’s electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (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.*Section I to be completed within 14 days of receipt for all BTDRs*

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):

   DS-8201 is a HER2-targeted antibody and topoisomerase I inhibitor conjugate indicated for the treatment of patients with HER2-positive, locally advanced or metastatic breast cancer who have been treated with trastuzumab and pertuzumab and have disease progression after T-DM1.

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

   □ YES  ☒ NO

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:

3. Consideration of Breakthrough Therapy Criteria:

   a. Is the condition serious/life-threatening?  ☒ YES  □ NO

   If 3a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:

   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):

---

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 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 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. 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.

6. 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.

Breast cancer is the most commonly diagnosed malignancy in women, and the second leading cause of cancer deaths in women in the United States (US), with 255,180 new cases of breast cancer and 41,070 deaths estimated in 2017. Approximately 20% of breast cancers overexpress HER2. Tumors that overexpress HER2 are more aggressive and historically have been associated with poorer overall survival (OS) compared to HER2 negative cancers. Four HER2-targeting therapies have been approved up to now in the EU and US for HER2-positive metastatic breast cancer: two antibodies (trastuzumab and pertuzumab), an antibody-drug-conjugate (ADC) ((ado-)trastuzumab emtansine, T-DM1), and a small molecule kinase inhibitor (lapatinib). With the exception of (ado-) trastuzumab emtansine these HER2-

Reference ID: 4141781
targeting treatments are used in combination therapy regimens in the locally advanced or metastatic setting. Despite the marked improvements in progression free survival (PFS) and OS with the introduction of new agents for the treatment of HER2-positive breast cancer, patients with unresectable locally advanced or metastatic breast cancer (MBC) are not cured with currently available therapy and represent an ongoing medical need. Continued targeting of the HER2 pathway is beneficial for patients whose tumour has progressed on an anti-HER2 therapy.

The first targeted agent for HER2 therapy, trastuzumab, was approved by the FDA in 1998 on the basis of significant improvements in PFS and OS when combined with chemotherapy. The current standard of care in the US for patients with HER2-positive MBC consists of treatment with pertuzumab plus trastuzumab and a taxane as first-line treatment based on results from the CLEOPATRA trial. The CLEOPATRA trial randomized patients to receive trastuzumab plus docetaxel with or without the addition of pertuzumab as first line therapy for metastatic HER2-positive breast cancer. The addition of pertuzumab to trastuzumab and a taxane improved median PFS from 12.4 to 18.5 months and median OS from 40.8 to 56.5 months. Results from the EMILIA trial established T-DM1 as the standard second line therapy for this patient population. T-DM1 is an ADC linking the trastuzumab antibody to emtansine, a tubulin inhibitor. In the EMILIA trial, T-DM1 was compared with the combination of lapatinib and capecitabine for the treatment of patients who had progressed after treatment with a trastuzumab and taxane combination. In this trial, T-DM1 improved median PFS from 6.4 to 9.6 months and median OS from 25.1 to 30.9 months. Of note, this trial was conducted prior to the introduction of pertuzumab to first line therapy, so it is unclear what outcomes would result with T-DM1 when given after pertuzumab-containing regimens.

There is no current approved standard of care therapy for HER2-positive metastatic breast cancer after progressing on pertuzumab and T-DM1-containing regimens. Following progression on T-DM1, clinical practice typically consists of changing the chemotherapy component at the time of progression while continuing trastuzumab treatment. The National Comprehensive Cancer Network (NCCN) guidelines recommend several options for trastuzumab-exposed HER2-positive disease, including: lapatinib+capecitabine, trastuzumab+capecitabine, trastuzumab+lapatinib, or trastuzumab+other agents. Currently, no single regimen is considered the standard of care in this setting.

The only study to report outcomes after two lines of anti-HER2 therapy was the THERESA study, which compared T-DM1 in the third-line setting to physician’s choice therapies. The two prior lines of anti-HER2 therapy in this case were regimens containing trastuzumab and lapatinib. In this setting, although 81% of physician’s choice treatments consisted of combining an anti-HER2 agent with chemotherapy, the ORR for the physician’s choice treatment was only 9% and the median PFS was 3.3 months. The ORR for the T-DM1 arm was 31% with a median PFS of 6.2 months. None of these patients in the THERESA study received prior pertuzumab or T-DM1 therapy.

DS-8201a is an ADC consisting of a HER2-targeted antibody and a topoisomerase I inhibitor. DS-8201a has a different mechanism of cytotoxic drug component from that of T-DM1.

7. Information related to endpoints used in the available clinical data:
Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The Sponsor is using overall response rates (along with duration of response) results from Study DS8201-A-J101 to support this BTDR. ORR is the primary endpoint in part 2 of the phase 1 study. ORR has been used by the FDA previously to give regular approval for drugs used in the treatment of metastatic breast cancer.

Study DS8201-A-J101
- Phase 1, two-part, open-Label, First-in-Human study of DS-8201a, in subjects with advanced solid malignant tumor.
- Ongoing
- Primary objectives of Part 1 were to assess safety and tolerability and to determine the maximum tolerated dose (MTD); Primary objectives of Part 2 (dose expansion) are to assess safety and tolerability and to evaluate the efficacy (ORR) of DS-8201a at the MTD or recommended dose for expansion (RDE).

The Sponsor has planned two additional studies which include:

Study DS8201-A-U201
- Phase 2, open-label, 2 part, monotherapy study
- Patient population: HER2+, unresectable and/or metastatic breast cancer subjects who are resistant or refractory to T-DM1
- Part 1 objective: dose finding; Part 2 objective: primary is ORR. Secondary objectives include disease control rate (DCR), clinical benefit rate (CBR), PFS, OS, PK, and safety
- Approximately 230 patients
- Planned for August 2017

Study DS8201-A-J102
- Phase 1, open-label, clinical pharmacology study
- Patient population: Subjects with HER2-expressing metastatic and/or unresectable breast cancer
- Primary objectives will be to assess the effect of DS-8201a on the QTc interval and the PK parameters after multiple doses of DS-8201a (using 6.4 mg/kg with newer formulation)
- Approximately 50 patients
- Planned for January 2018

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

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

   None other than tumors that are HER2+.

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.

8. 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.

   There are no drugs specifically approved for patients with metastatic HER2+ breast cancer that have had progression following pertuzumab+trastuzumab and T-DM1 therapy. The following tables show FDA-approved agents for metastatic HER2+ breast cancer.

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

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

9. A brief description of any drugs being studied for the same indication, or very similar indication, that
10. Information related to the preliminary clinical evidence:

There is a single phase 1 study (DS8201-A-J101) to support this BTDR. DS8201-A-J101 is an ongoing phase 1, two-part, multicenter, open-label, multiple-dose, first-in-human (FIH) trial in subjects with advanced solid malignant tumors. Part 1 (dose escalation) enrolled subjects with either advanced breast cancer or gastric/gastroesophageal junction adenocarcinoma that is refractory or intolerable to standard treatment, or for which no standard treatment is available. The primary objectives of Part 1 were to assess safety and tolerability and to determine the maximum tolerated dose (MTD). The primary objectives of Part 2 (dose expansion) are to assess safety and tolerability and to evaluate the efficacy of DS-8201a at the MTD or recommended dose for expansion (RDE). The pharmacokinetic (PK) profile and anti-drug antibody are assessed as secondary objectives. Part 2 is enrolling subjects in five cohorts: T-DM1 treated HER2-positive breast cancer (cohort 2a), trastuzumab-treated HER2-positive gastric/gastroesophageal junction adenocarcinoma (cohort 2b), HER2 low expressing breast cancer (cohort 2c), subjects with other HER2 expressing solid cancers (cohort 2d), and a recently opened PK cohort (cohort 2e). Cohort 2e was opened so that PK comparisons could be made within the trial using two different formulations. The formulation for DS-8201a has changed since the study was initiated to support new clinical studies, as well as commercial development. Enrollment in Part 1 and Part 2b is complete and the study continues to enroll patients in Parts 2a, 2c, 2d, and 2e in two doses of 5.4 mg/kg and 6.4 mg/kg.

The study design is shown below:

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

Reference ID: 4141781
As of June 8, 2017, a total of 148 subjects (median age: 60 years; median tumor size: 5.6 cm; 23% with tumors \( \geq 10 \) cm) have been treated in Study DS8201-A-J101 (24 patients in part 1 and 124 patients in part 2 c). This includes 55 subjects with HER2 positive MBC previously treated with T-DM1. 45 of these 55 patients had also been previously treated with pertuzumab. The median number of prior regimens in the subjects who have received pertuzumab for metastatic disease was 5.

The confirmed ORR for the 55 HER2 positive MBC previously treated with T-DM1 was 36.4% and for the 45 patients also treated with prior pertuzumab (in addition to T-DM1) the confirmed ORR was 40%. The median PFS and duration of response for the subset of 55 HER2 positive breast cancer patients was 10.4 months and 7.2 months respectively.

The following table shows how results with DS-8201a from the 55 patients with HER2 positive MBC compared to results from the THERESA study (the only study to report outcomes after two lines of anti-HER2 therapy). Of note, no patients on the THERESA study had received prior pertuzumab or T-DM1 therapy; therefore, it is expected that results with currently available therapy would be even worse than that seen with physician’s choice therapy in the 3rd line.

<table>
<thead>
<tr>
<th>Drug</th>
<th>ORR (%)</th>
<th>DOR (months)</th>
<th>PFS (months)</th>
<th>Line of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-DM1 3rd line (THERESA study)</td>
<td>31 vs 9 (physician’s choice)</td>
<td>9.7 vs NR</td>
<td>6.2 vs 3.3</td>
<td>3</td>
</tr>
<tr>
<td>DS-8201a (results from Study DS8201-A-J101)</td>
<td>36.4%</td>
<td>7.1</td>
<td>10.4</td>
<td>3+</td>
</tr>
</tbody>
</table>

The Safety dataset included all patients who received at least one dose of study drug in DS8201-A-J101 (n=148). No dose limiting toxicity (DLT) was observed and the MTD was not reached in the dose escalation part of DS8201-A-J101. The recommended dose levels for the expansion were 5.4 and 6.4 mg/kg based on tolerability, efficacy, and PK.

For 148 subjects enrolled across all parts and cohorts in the study, the most common AEs (>10%) of any grades are shown in Table 9.4.

<table>
<thead>
<tr>
<th>Total (Part 1 and Part 2) (n=148)</th>
<th>Grade 1 n(%)</th>
<th>Grade 2 n(%)</th>
<th>Grade 3 n(%)</th>
<th>Grade 4 n(%)</th>
<th>Grade 5 n(%)</th>
<th>Grade &lt;3 n(%)</th>
<th>Grade 3+ n(%)</th>
<th>Missing n(%)</th>
<th>All n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>74 (50.0)</td>
<td>19 (12.3)</td>
<td>4 (2.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>52 (35.2)</td>
<td>2 (1.4)</td>
<td>0 (0.0)</td>
<td>96 (64.0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>46 (31.1)</td>
<td>28 (18.9)</td>
<td>5 (3.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>74 (50.0)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>79 (55.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>41 (27.7)</td>
<td>7 (4.7)</td>
<td>2 (1.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>46 (32.4)</td>
<td>2 (1.4)</td>
<td>0 (0.0)</td>
<td>50 (33.9)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>17 (11.5)</td>
<td>13 (8.8)</td>
<td>11 (7.4)</td>
<td>5 (3.4)</td>
<td>0 (0.0)</td>
<td>30 (20.3)</td>
<td>16 (10.8)</td>
<td>0 (0.0)</td>
<td>45 (31.1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (2.7)</td>
<td>10 (6.7)</td>
<td>21 (14.2)</td>
<td>2 (1.4)</td>
<td>0 (0.0)</td>
<td>18 (12.6)</td>
<td>23 (15.5)</td>
<td>0 (0.0)</td>
<td>42 (30.4)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>20 (13.8)</td>
<td>8 (5.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>38 (26.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>38 (26.5)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>27 (18.2)</td>
<td>8 (5.4)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>35 (23.6)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>38 (26.4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>26 (16.6)</td>
<td>5 (3.4)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>34 (23.0)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>35 (23.3)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>1 (0.7)</td>
<td>10 (6.8)</td>
<td>17 (11.5)</td>
<td>4 (2.7)</td>
<td>0 (0.0)</td>
<td>14 (9.5)</td>
<td>21 (14.2)</td>
<td>0 (0.0)</td>
<td>35 (23.9)</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>2 (1.4)</td>
<td>17 (11.5)</td>
<td>13 (8.8)</td>
<td>3 (2.0)</td>
<td>0 (0.0)</td>
<td>10 (6.8)</td>
<td>10 (6.8)</td>
<td>0 (0.0)</td>
<td>35 (23.9)</td>
</tr>
<tr>
<td>Maligne</td>
<td>25 (16.9)</td>
<td>9 (6.1)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>31 (21.0)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>33 (22.3)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>20 (13.5)</td>
<td>3 (2.0)</td>
<td>2 (1.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>23 (15.5)</td>
<td>2 (1.4)</td>
<td>0 (0.0)</td>
<td>25 (16.9)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>19 (12.8)</td>
<td>2 (1.4)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>21 (14.2)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>22 (14.9)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>16 (11.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>16 (11.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>16 (11.8)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>17 (11.5)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>18 (12.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>18 (12.2)</td>
</tr>
<tr>
<td>Aspartate aminotransferase erase increased</td>
<td>16 (10.8)</td>
<td>2 (1.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>15 (10.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>15 (10.1)</td>
</tr>
</tbody>
</table>

Reference ID: 4141781
The safety profiles in the breast cancer patients were similar to the overall safety data observed from both part 1 and 2. There have been no treatment related deaths on study to date.

11. Division’s recommendation and rationale (pre-MPC review):

☑ GRANT:

Provide brief summary of rationale for granting:

HER2-positive MBC is an incurable disease with currently available therapies and represents an ongoing medical need. DS-8201a is an ADC consisting of a HER2-targeted antibody and a topoisomerase I inhibitor, exhibiting activity in a patient population previously treated with T-DM1, trastuzumab and pertuzumab (median of 5 previous treatments). DS-8201a offers an additional treatment option for patients with HER2-positive MBC that have progressed after current first and second line standard of care options. The confirmed ORR in Study DS8201-A-J101 among 55 patients with HER2-positive breast cancer was 36.4% with a median PFS of 10.4 months and DOR of 7.1 months. This is significantly higher than what would be expected with currently available treatment options for this patient population.

☐ DENY:

Provide brief summary of rationale for denial:

12. 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):

   Based on the results from study DS8201-A-J101, the Sponsor is planning to start a phase 2 study (Study DS8201-A-U201 described above) to confirm these results and potentially gain accelerated approval for DS-8201a. The Sponsor states that the design for a confirmatory phase 3 study will be decided as results from the phase 2 study become available and will be discussed with the Agency.

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:

13. List references, if any:

American Cancer Society Statistics 2017:


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

15. 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}

5-7-15/M. Raggio
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUPARNA B WEDAM
08/21/2017

LALEH AMIRI KORDESTANI
08/21/2017

AMNA IBRAHIM
08/22/2017