CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761394Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 155696

MEETING MINUTES

AstraZeneca Pharmaceuticals LP
Attention: Allison Guy, MSc, RAC
Regulatory Affairs Director
One MedImmune Way
Gaithersburg, MD 20878

Dear Allison Guy:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Datopotamab deruxtecan (Dato-DXd; DS-1062a).

We also refer to the video conference between representatives of your firm and the FDA on November 28, 2023. The purpose of the meeting was to gain agreement on the suitability of the clinical data to support a BLA for Dato-DXd in the proposed indication.

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

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

If you have any questions, call Kim J. Robertson, Senior Regulatory Health Project Manager at (301) 796-1441, or kim.robertson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Senior Regulatory Health Project Manager
Oncology 1 Group
Division of Regulatory Operations – Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

{See appended electronic signature page}

Preeti Narayan, MD
Acting Clinical Team Leader
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date: November 28, 2023

Application Number: IND 155696
Product Name: Datopotamab deruxtecan (Dato-DXd; DS-1062a)

Indication: Treatment of adult patients with hormone receptor-positive, HER2 negative (IHC 0, IHC 1+, or IHC 2+/ISH-) breast cancer who have received prior (b) (4) for unresectable or metastatic disease

Sponsor Name: AstraZeneca
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Preeti Narayan, MD
Meeting Recorder: Kim J. Robertson

FDA ATTENDEES
Laleh Amiri-Kordestani, MD, Director, DO1
Daniel Suzman, MD, Deputy Director, DO1
Christy Osgood, MD, Acting Supervisory Associate Director, DO1
Preeti Narayan, MD, Acting Clinical Team Leader, DO1
Xin (Cindy) Gao, PhD, Biometrics Reviewer, DBV
Mallorie Fiero, PhD, Supervisory Mathematical Statistician, DBV
Hairat Sabit, PhD, Clinical Pharmacology Reviewer, DCPII
Hong Zhao, PhD, Clinical Pharmacology Team Leader, DCPII
Milos Dokmanovic, PhD, Product Quality Reviewer, OBP/DBRRI
Andrea George, PhD, Product Quality Team Leader, OBP/DBRRI
Kim J. Robertson, Senior Regulatory Project Manager, DRO-OD

ASTRA ZENECA ATTENDEES
Vikram Chand, MD, Vice President, Global Franchise Head, Dato-DXd
Hubo Li, PhD, Global Product Lead, Late Development, Oncology R&D
Karen McCullough, PhD, Vice President, Oncology Regulatory Science & Strategy
Paul McCleverty, BSc (Hons), Executive Director, Oncology Regulatory Science & Strategy
Shruti Kalra, PharmD, RAC, Senior Regulatory Affairs Director, Global Regulatory Lead, Oncology Regulatory Science & Strategy

ASTRA ZENECA ATTENDEES (cont.)
Allison Guy, MSc, RAC, Regulatory Affairs Director, US Regulatory Lead, Oncology Regulatory Science & Strategy
Neelima Denduluri, MD, FASCO, Global Clinical Head, R&D Oncology
Lu Xu, PhD, Senior Director, Statistics, Oncology
Lei Shi, PhD, Director, Statistics, Oncology
Nana Rokutanda, MD, PhD, Senior Global Development Medical Director, R&D Oncology
Manjunatha Ankathatti Munegowda, DVM, MS, PhD, Global Development Director, R&D Oncology
Hannah Dry, Senior Global Development Scientist Director, R&D Oncology
Karen Cui, Senior Global Development Medical Director, R&D Oncology
Yu Jiang, PhD, Associate Director, Clinical Pharmacology and Pharmacometrics
KyoungSoo Lim, MD, PhD, Director, Clinical Pharmacology and Pharmacometrics
Rick Fairhurst, MD, PhD, Senior Medical Director, Patient Safety Oncology
Kwame Atuah, PhD, Senior Director, Patient Safety Oncology
Aino Teleranta-Keerie, PhD, Senior Director, Precision Medicine
Danielle Carroll, PhD, Executive Director Global Head of ADC Franchise
Ananya Murali, PharmD, Associate Director Regulatory Affairs, Oncology Regulatory Science & Strategy
Marina Robin, PharmD, Regulatory Affairs Resident, Oncology Regulatory Science & Strategy

DAIICHI SANKYO ATTENDEES
Pranav Patel, PharmD, Associate Director, US Regulatory Lead
Joseph Rosamilia, MS, Senior Director, Global Regulatory Affairs
John Lee, MD, PhD, Senior Director, Global Oncology Clinical Development

1.0 BACKGROUND

AstraZeneca requested a pre-Biologics License Application (BLA) Type B meeting with the FDA to gain agreement on the suitability of their clinical data to support a BLA for datopotamab deruxtecan (Dato-DXd) for the following proposed indication:

> *Dato-DXd is indicated for the treatment of adult patients with HR-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) BC who have received prior* (b) (4) *for unresectable or metastatic disease*.

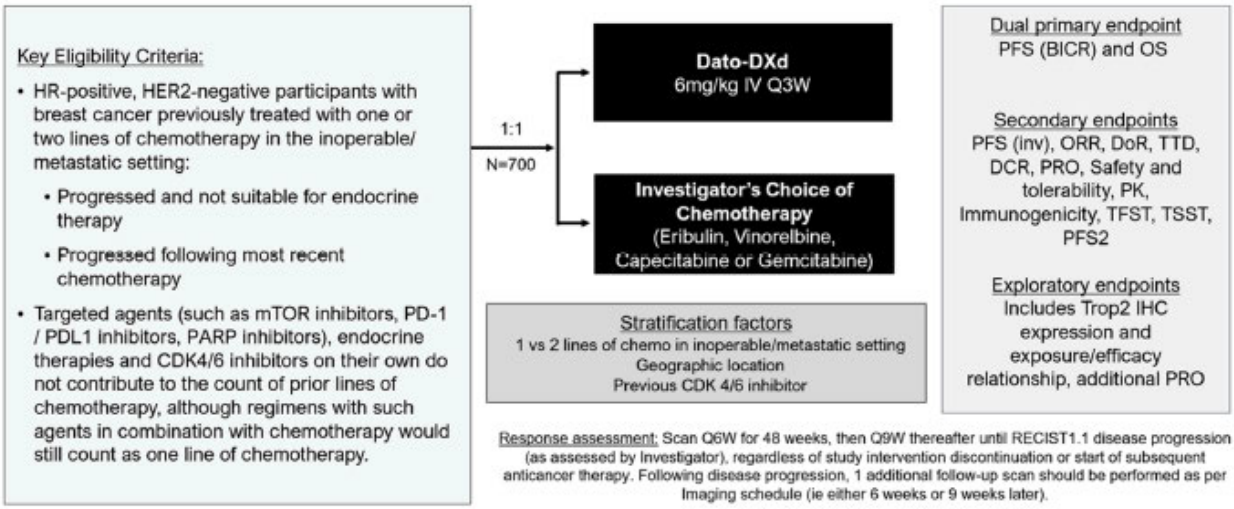
Dato-DXd is a TROP2-targeted ADC consisting of a humanized anti-TROP2 antibody connected via an enzymatically cleavable tetrapeptide linker to deruxtecan, a topoisomerase I inhibitor.

The primary trial to support the proposed indication is the TROPION-Breast01 study (TB-01), a phase 3, open-label, randomized trial of Dato-DXd versus single agent investigator's choice of chemotherapy (ICC) in patients with inoperable or metastatic HR-positive, HER2-negative (per ASCO/CAP criteria) breast cancer who had been

treated with 1 or 2 prior lines of systemic chemotherapy in the inoperable or metastatic setting. The dual primary endpoints of the study were progression free survival (PFS) by blinded independent central review (BICR) and overall survival (OS). Randomization was stratified according to the following factors:

- Number of previous lines of chemotherapy (1 vs 2; 50% recruitment cap applied to patients with 2 prior lines of chemotherapy for advanced disease)
- Geographic region (North America/Europe vs Rest of World)
- Prior use of CDK4/6 inhibitor (Yes vs No; 49% recruitment cap applied to patients without prior CDK4/6 inhibitor therapy).

Essential elements of TB-01 study design are depicted in the schema below:



Source: Sponsor Briefing Package, Figure 2, page 33

Eligible patients were randomized 1:1 to receive either:

- Dato-DXd at 6 mg/kg intravenously (IV) on Day 1, every 3 weeks (Q3W); or
- ICC from the following choices:
  - Capecitabine at 1000 or 1250 mg/m^2 (choice of dose per standard institutional practice) oral twice daily (BID) on Days 1 to 14, Q3W
  - Gemcitabine at 1000 mg/m^2 IV on Day 1 and Day 8, Q3W
  - Eribulin mesylate at 1.4 mg/m^2 IV on Days 1 and 8, Q3W
  - Vinorelbine at 25 mg/m^2 IV on Days 1 and 8, Q3W

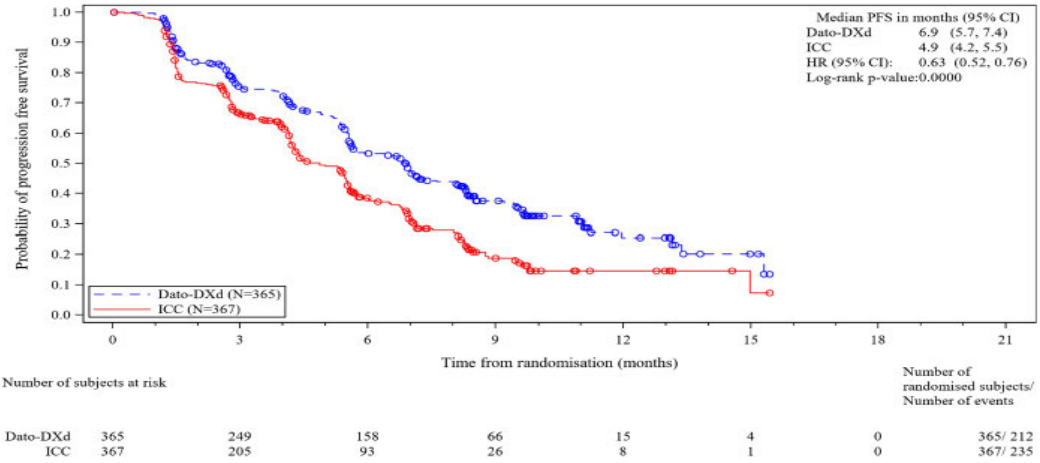
Trial treatment was administered until disease progression (per RECIST 1.1) or until unacceptable toxicity, withdrawal of consent, or another treatment discontinuation criterion per protocol was met. No crossover between study treatment arms was allowed.

A total of 732 eligible patients were randomized, 365 to Dato-DXd and 367 to ICC at 159 study sites globally across 20 countries, with 8.1% of total patients recruited from trial centers in the US. Most patients (82.4%) had received prior treatment with a CDK4/6 inhibitor. Approximately 62% of patients had received 1 prior line and 38% of patients received 2 prior lines of chemotherapy. The Sponsor reports that patient demographic, baseline characteristics and disease characteristics were similar between the 2 treatment arms.

As of the data cut off (DCO) on 7/17/2023, 132 patients were still receiving treatment, 93 patients (25.8%) in the Dato-DXd arm and 39 patients (11.1%) in the ICC arm.

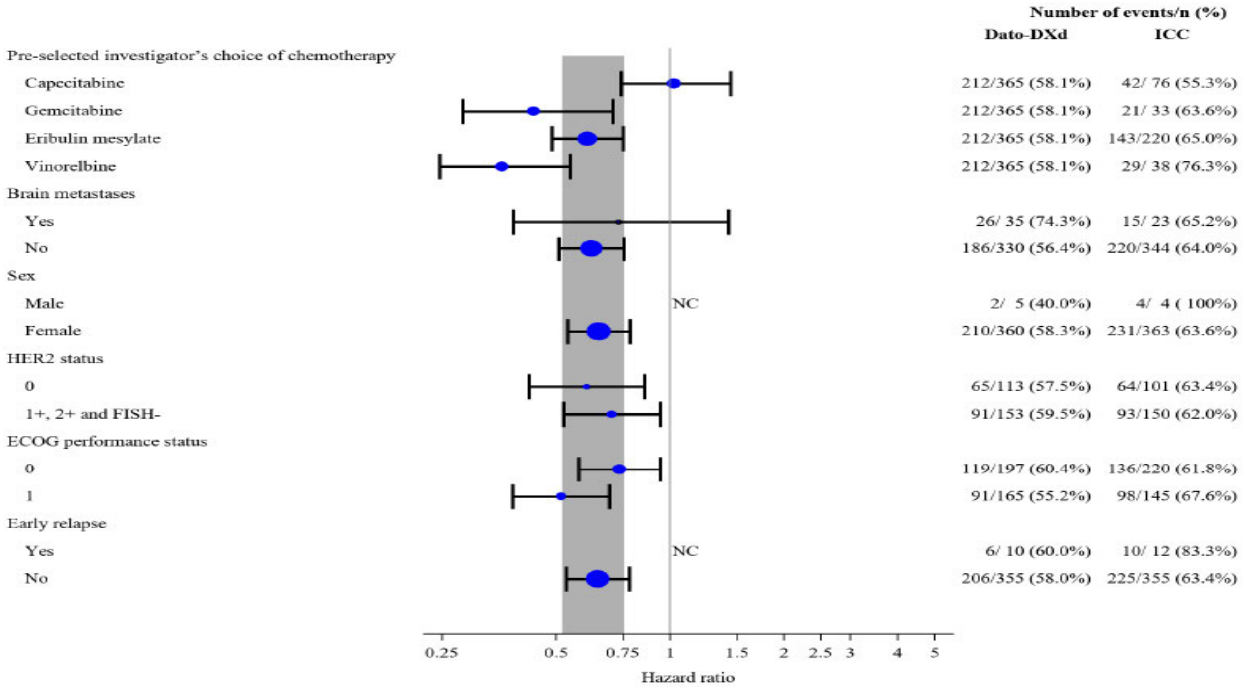
TB-01 Efficacy results

The primary analysis of PFS/first OS interim analysis was planned when approximately 419 PFS events (BICR) were observed. This has occurred as of the DCO of July 17, 2023, with a total of 447 BICR-assessed PFS events; median study follow-up was about 10.8 months. The stratified hazard ratio (HR) for PFS was 0.63 (95% CI: 0.52, 0.76) in favor of the Dato-DXd arm; 2-sided stratified log-rank P-value was <0.0001. The median PFS by BICR was 6.9 months (95% CI: 5.7, 7.4) in the Dato-DXd arm vs 4.9 months (95% CI: 4.2, 5.5) in the ICC arm. Kaplan-Meier plot of BICR-assessed PFS is shown below:



Source: Sponsor Briefing Package, Figure 4, page 39

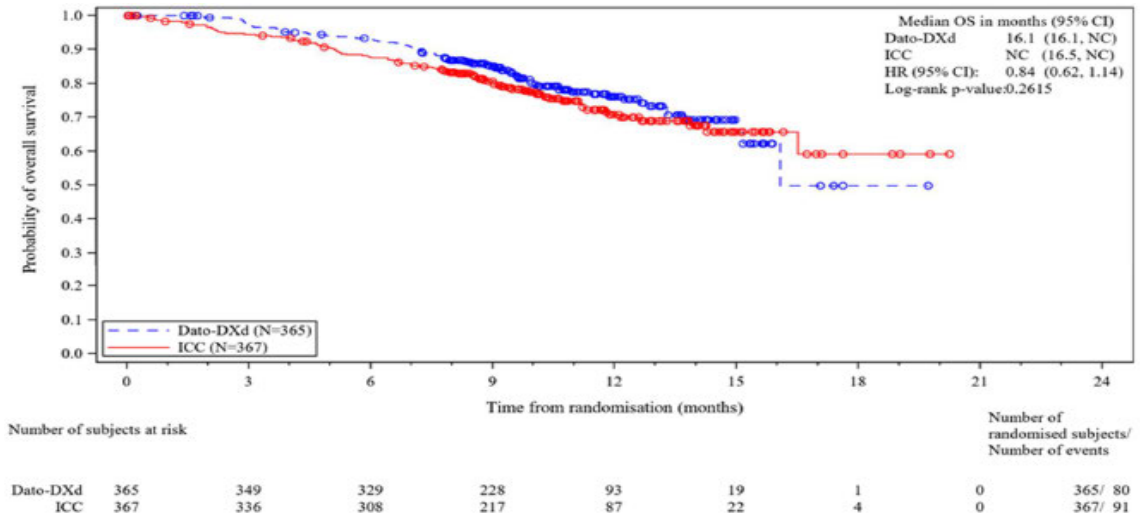
The Sponsor also states that results of investigator-assessed PFS are consistent with BICR-assessed PFS. A subgroup analysis of PFS for choice of control arm treatment is shown below:



Source: Sponsor Briefing Package, Figure 7, page 42

At OS IA1, the median OS for Dato-DXd arm = 16.1 months (16.1, not calculated [NC]) and the ICC arm = NC (16.5, NC); with an OS HR (95% CI) = 0.84 (0.62, 1.14), log-rank p-value = 0.2615. Data for OS were immature (23% maturity, 39% of information fraction), with a median follow-up of 9.7 months for OS. The trial will continue as planned until the next planned OS analysis when 355 and 444 events have occurred (for 2nd interim analysis and final analysis of OS, respectively). Current projected estimates indicate that DCO for OS IA2 will be in May 2024.

The Kaplan-Meier plot for OS is shown here:



Source: Sponsor Briefing Package, Figure 8, page 44

All other efficacy endpoints reported by the Sponsor also favor Dato-DXd over ICC:

- Confirmed objective response rate (ORR) for Dato-DXd = 36.4% vs. ICC = 22.9%, with an odds ratio of 1.95 (95% CI: 1.41, 2.71)

- Median duration of response (DOR) in months was numerically higher with Dato-DXd (6.7 [95% CI: 5.6, 9.8]) than for ICC (5.7 [95% CI: 4.9, 6.8])

TB-01 Safety results (Safety Analysis Set):

The median total treatment duration in the Dato-DXd arm was 6.7 months compared to 4.1 months in the ICC arm.

Summary of adverse events (AEs) noted in TB-01, regardless of attribution, are tabulated below:

AE category	**Dato-DXd N = 360 (%)**	**ICC N = 351 (%)**
Any AE	97	96
Any Grade ≥3 AE	33	54
Any AE with outcome = death	0	0.9*
Any serious adverse event (SAE)	15	18
Any SAE leading to treatment discontinuation	1.1	1.1
Any AE leading to discontinuation	3	3
Any AE leading to dose reduction	23	32
Any AE leading to dose interruption	22	34

*Of 3 fatal AEs, 1 event was considered to be possibly related to study treatment.
Source: Sponsor Briefing Package, adapted from Table 13, pages 49-50

The most frequently reported all grade TEAEs (≥ 20%) in the Dato-DXd treatment arm were nausea (56%), stomatitis (51%), alopecia (38%), constipation (34%), fatigue (28%), dry eye and vomiting (24% each). There was less neutropenia/neutrophil count decreased (11%), anemia (16%), and palmar-plantar erythrodysaesthesia syndrome (2%) were reported for the Dato-DXd arm compared to the ICC arm (47%, 25% and 12%, respectively).

Notable details regarding observed AESIs in TB-01 were as follows:

- ILD/pneumonitis: The overall incidence was approximately 5% and 0.6% for Dato-DXd and ICC arms, respectively. There was one patient who experienced a grade 3 and one patient who experienced a grade 5 event.

- Ocular surface toxicity: The most common events (≥ 5%) within the Dato-DXd arm included dry eye (24%), punctate keratitis (11%), blepharitis, keratitis (8% each), lacrimation increased, and meibomian gland dysfunction (7% each). There were 1.7% of patients who experienced grade 3 eye disorders, including 2 patients with grade 3 dry eye, 1 patient each with grade 3 punctate keratitis and ulcerative keratitis. Overall, the reported incidence of ocular surface toxicity is

approximately 49% and 23% for Dato-DXd and ICC arms, respectively. Of note, the reported ~49% ocular surface toxicity rate may be an underestimation as additional events of conjunctivitis (4%, reported under SOC infections/infestations) may need be reclassified under ocular surface toxicity.

- Infusion related reactions (IRR): Overall, IRR was reported at a higher frequency in the Dato-DXd arm (approximately 9% versus 3%); one patient in the Dato-DXd arm had a Grade 3 event (bronchospasm).

- Oral mucositis/stomatitis: Oral mucositis/stomatitis was reported at a higher frequency in the Dato-DXd arm (approximately 57% versus 17%). The most common events (≥5%) for the Dato-DXd arm included stomatitis (51.1%, mostly Grades 1 and 2), and oropharyngeal pain (5.6%, Grades 1 and 2 only).

Supporting study – TROPION-PanTumor01 (TP-01):

The Sponsor intends to submit results from TP-01 to support the proposed BLA. TP-01 is an ongoing, first-in-human (FIH) phase I, 2-part, multicenter, non-randomized, open-label, multiple-dose study evaluating escalating doses of Dato-DXd (0.27 to 10 mg/kg) in patients with advanced solid tumors. Two expansion cohorts enrolled adult patients with breast cancer, one cohort with advanced/inoperable or metastatic triple-negative breast cancer (TNBC, per ASCO/CAP guidelines) and another cohort with HR-positive, HER2-negative breast cancer.

The FDA sent Preliminary Comments to AstraZeneca on November 22, 2023.

2.0 DISCUSSION

QUESTION 1
Does the Agency agree that the statistically significant and clinically meaningful PFS improvement along with manageable safety/tolerability profile for Dato-DXd, as demonstrated from the pivotal TB01 study with supportive data from the TP01 study, are sufficient to support a BLA for Dato-DXd in the proposed patient population?

FDA Response: Possibly. Whether the results from TB01 will support a favorable benefit-risk assessment for the proposed indication will be a review issue given the modest improvement in median PFS (~2 months), immature OS data, and the substantial toxicities including nausea, ocular toxicity, and mucositis associated with Dato-DXd. You should plan to submit updated OS results (based on IA2) during the review of your BLA, including the top-line results as soon as available and the datasets as soon as possible afterward.

In addition, in the PFS subgroup analysis, we note some differences in treatment effect based on investigator's choice of chemotherapy. You should provide OS subgroup analyses in your BLA submission, which include an analysis based on investigator's choice of chemotherapy.

We also noticed that PFS was censored due to the reason of withdrawal of consent for some patients in both arms, which may lead to informative censoring and potential bias in the analysis. You should perform sensitivity analyses to evaluate the impact on the efficacy findings. The sensitivity analyses should include but not limited to a tipping point analysis where you assume the patients who withdrew consent and were censored in the PFS analysis to have a reduction of hazard rate by x%. You should also perform analyses of demographics and baseline disease characteristics for these censored patients by treatment arm and compare to the overall study population. Please include the analyses results in the submission package. Ultimately, the impact of withdrawal of consent and potential informative censoring on the study results will be a review issue.

Furthermore, if detection of TROP2 expression is determined to be necessary for safe and effective use of your product, a diagnostic device for detection of TROP2 expression will be needed.

Regarding the Dato-DXd dosage, based on the data you have provided, you have not explored any Dato-DXd dose that is lower than your proposed dose as you only explored Dato-DXd as a single agent at 6 mg/kg Q3W (n= 42) and 8 mg/kg Q3W (n=2) in patients with triple negative breast cancer (TNBC), and 6 mg/kg Q3W dosage in patients with HR+/HER2- BC. In TB01, intended to support your planned BLA submission, you only explored a 6 mg/kg Q3W dosage. You do not have clinical data to support that you have optimized the dosage for your intended HR-/HER2+ BC patient population. Provide adequate justification(s) for your dosing selection. Alternatively, conduct further dose optimization by including a lower dosage cohort for Dato-DXd in your phase 3 trial or a separate dose randomization study in addition to the proposed 6 mg/kg Q3W dose to support your dose selection.

AstraZeneca's Response 1A; November 24, 2023:

The Sponsor acknowledges the Agency's comments, and no discussion is requested.

OS IA2 DCO will occur when approximately 355 OS events are observed. Based on current OS data and modeling projections, this is expected around August 2024 (range from May 2024 to Jan 2025).

Meeting Discussion: No discussion.

AstraZeneca's Response 1B; November 24, 2023:

The Sponsor acknowledges the Agency's comments regarding PFS subgroup analysis and would like to provide an update to the analysis provided in the briefing document. The TB01 protocol and SAP defined the ICC subgroup analysis by the pre-selected investigator's choice of chemotherapy, intended to compare patients who would be treated with each chemotherapy pre-selected by investigators prior to the

randomization. However, the subgroup analysis of the investigator's choice of chemotherapy included in the briefing document was performed comparing the Dato-DXd ITT population (all patients randomized to Dato-DXd arm, n=365) vs. each of the investigator's choice of chemotherapy (Figure 1a). After high-level results, the Sponsor has since re-run the analysis to follow the SAP, which compares patients who receive Dato-DXd to patients who receive the investigator's choice of chemotherapy within the same subgroup that was pre-specified before randomization. As an example, patients who receive capecitabine in the ICC arm (n=76) would be compared against patients who were randomized to Dato-DXd in the subgroup that was pre-specified to receive capecitabine before randomization (n=68), instead of compared against all patients who receive Dato-DXd (n=365). The results of this updated analysis are shown in Figure 1b and will be presented in the CSR. The comparison of the original analysis and updated analysis is shown in Table 1.

Table 1: Original and Updated Subgroup Analysis; pre-selected chemotherapy

	Original Analysis			**Updated Analysis**		
Pre-selected investigator's choice chemotherapy	**Dato-DXd Number of Events/N (%)**	**ICC Number of Events/N (%)**	**HR (95% CI)**	**Dato-DXd Number of Events/N (%)**	**ICC Number of Events/N (%)**	**HR (95% CI)**
Capecitabine	212/365 (58.1%)	42/76 (55.3%)	1.02 (0.74, 1.44)	35/68 (51.5%)	42/76 (55.3%)	0.83 (0.53, 1.31)
Gemcitabine	212/365 (58.1%)	21/33 (63.6%)	0.44 (0.28, 0.71)	18/33 (54.5%)	21/33 (63.6%)	0.51 (0.26, 0.98)
Eribulin mesylate	212/365 (58.1%)	143/220 (65.0%)	0.60 (0.49, 0.75)	129/210 (61.4%)	143/220 (65.0%)	0.62 (0.48, 0.79)
Vinorelbine	212/365 (58.1%)	29/38 (76.3%)	0.36 (0.25, 0.54)	30/54 (55.6%)	29/38 (76.3%)	0.39 (0.23, 0.66)

Figure 1a Original subgroup analysis; pre-selected chemotherapy

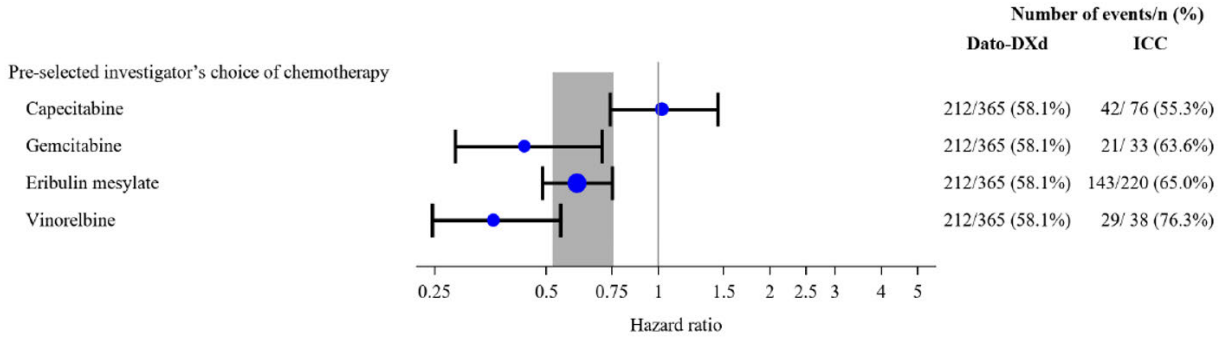
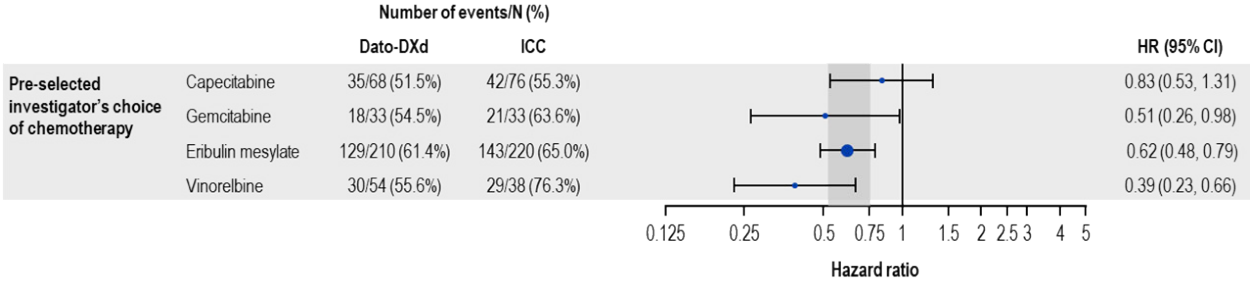


Figure 1b Updated subgroup analysis per protocol and SAP; pre-selected chemotherapy



Regarding the Agency's request to provide OS subgroup analyses in the BLA which include an analysis based on investigator's choice of chemotherapy, the Sponsor proposes not to include these analyses in the BLA. Due to the low maturity of the current OS events (23% overall OS maturity, 39% information fraction), the OS subgroup analysis at this IA1 is likely to not be meaningful or informative. Does the Agency agree with this approach?

Meeting Discussion: The FDA acknowledged the subgroup analyses of PFS per investigator's choice of chemotherapy. The FDA stated that the subgroup analysis of OS per investigator's choice of chemotherapy is informative and should be included in the BLA submission. AstraZeneca (AZ) clarified that this information will be included in the CSR and the data will be submitted to the FDA for review.

AZ's proposed approach to compare patients who receive Dato-DXd to patients who receive the investigator's choice of chemotherapy within the same subgroup that was pre-specified before randomization appears reasonable. However, as the investigator's choice was not a stratification factor, there is still risk of imbalanced patient characteristics between the treatment arms within each choice of chemotherapy. The FDA will review these results when the application is submitted, as this will be a review issue.

AZ stated that an update to the OS subgroup analysis will be provided at IA2, DCO anticipated around August 2024.

AstraZeneca's Response 1C; November 24, 2023:

The Sponsor acknowledges the Agency's comments, and no discussion is requested.

Meeting Discussion: No discussion.

AstraZeneca's Response 1D; November 24, 2023:

The Sponsor acknowledges the Agency's comments, and no discussion is requested. The results of the exploratory TROP2 analyses will be provided in the dossier.

Meeting Discussion: No discussion.

AstraZeneca's Response 1E; November 24, 2023:

The Sponsor acknowledges the Agency's comments and intends to provide a dose justification report in the BLA to support the dose selection. The 6 mg/kg Q3W Dato-DXd dose was selected based on results from the ongoing TROPION-PanTumor01 study in patients with solid tumours and is being used in ongoing Phase 3 studies (i.e., TROPION-Breast02, TROPION-Breast03, TROPION-Breast04, TROPION-Lung01, TROPION-Lung02, TROPION-Lung04, and AVANZAR). No discussion is requested.

Meeting Discussion: No discussion.

QUESTION 2
Does the Agency agree with the Applicant's proposal for the data cut-off, structure, and content of the safety update report to be submitted during the BLA review period?

FDA Response: Yes, your proposal appears acceptable.

AstraZeneca's Response; November 24, 2023
The Sponsor acknowledges the Agency's comments, and no discussion is requested.

Meeting Discussion: No discussion.

QUESTION 3
Does the Agency agree that the content of the proposed clinical pharmacology data package is acceptable to support the BLA review of Dato-DXd 6 mg/kg for the proposed indication?

FDA Response: As stated, in the Written Responses dated February 13, 2023, relative to the clinical pharmacology question in your Type C Pre-BLA meeting

package, your proposed content of clinical pharmacology data package appears acceptable for our review of your BLA.

Additionally:

- **In your planned BLA submission, provide sufficient justification(s) for not pooling TP01 TNBC cohort.**
- **The adequacy of the QTc data from Study TP01 to assess QTc effect will be assessed during our review of the BLA.**

AstraZeneca's Response; November 24, 2023

The Sponsor acknowledges the Agency's comments, and no discussion is requested.

Meeting Discussion: No discussion.

QUESTION 4
Does the Agency agree that the top-line safety and efficacy results from TB01 provide evidence of significant improvement in safety and effectiveness and fulfil an unmet medical need in HR+ HER2- metastatic BC, thereby qualifying this application for a Priority Review Designation?

FDA Response: A determination regarding priority review will be made at the time of filing.

AstraZeneca's Response; November 24, 2023

The Sponsor acknowledges the Agency's comments, and no discussion is requested.

Meeting Discussion: No discussion.

QUESTION 5
Does the Agency agree with the proposed comprehensive table of contents for the BLA?

FDA Response: Yes, your proposed table of contents (TOC) for the TB-01 BLA appears reasonable.

AstraZeneca's Response; November 24, 2023

The Applicant intends to submit two separate BLAs to the FDA for Dato-DXd, one for the treatment of patients with NSCLC (DO2) and one for patients with HR-positive, HER2-negative mBC (DO1). In an effort to reduce the review burden on the Agency, as proposed in the Type C, Content and Format meeting WRO (IND 155696, Reference ID: 5125924), the Sponsor intends to include Module 2.3 and Module 3 in the first BLA submitted and to cross-refer to the first BLA from the second BLA as the information in these modules will be identical for the two submissions. Does the Agency agree with this approach?

Meeting Discussion: The FDA stated the approach to provide Module 2.3 and the entire Module 3 sections in the initial BLA submission, and to provide a cross-reference in the subsequent BLA, appears reasonable provided all the information is identical.

QUESTION 6
Does the Agency agree that the Assessment Aid can be submitted within 30 days of receipt of the BLA?

FDA Response: Yes, this is acceptable.

AstraZeneca's Response; November 24, 2023

The Sponsor acknowledges the Agency's comments, and no discussion is requested.

Meeting Discussion: No discussion.

QUESTION 7
Does the Agency agree with the proposal for an Application Orientation Meeting in support of the BLA for Dato-DXd to occur shortly after the submission?

FDA Response: We acknowledge your request and encourage you to communicate your preferred timing for an AOM with the Regulatory Project Manager at the time of the BLA's submission. The timing of an AOM will be determined after we receive the BLA, and the review status granted to the application.

AstraZeneca's Response; November 24, 2023

The Sponsor acknowledges the Agency's comments, and no discussion is requested.

Meeting Discussion: No discussion.

ADDITIONAL COMMENTS

1. **Request feedback on dose selection for future trials and clinical pharmacology program during milestone meetings or during a clinical pharmacology-specific meeting. As part of the meeting package focused on selection of the optimal dosage(s), include the rationale for the selection of these dosages along with the following information, as appropriate:**

   a) **Tabular or graphical summary for each dosing regimen investigated in the completed and ongoing clinical trials to allow comparison of the following:**

   - **Safety data**

- **duration of exposure**
- **relative dose intensity**
- **dosage modifications for treatment-emergent adverse events, including time course and prevalence of interruptions, reductions and discontinuations and most common treatment-emergent adverse events leading to dosage modification**
- **dose-limiting toxicities**
- **serious adverse events, including fatal events**
- **grade 3 - 4 treatment-emergent adverse events**
- **all grade treatment-emergent adverse events**
- **patient-reported outcomes (PROs) regarding symptomatic adverse events (if collected)**
- **Preliminary anti-tumor activity or efficacy data for relevant indications**
- **Pharmacokinetic (PK) and pharmacodynamic data**

b) Integrated dose- and exposure-response analyses using the anti-tumor activity or efficacy and safety and tolerability data from multiple dosages

c) Summary of modeling and simulations, if applicable, that incorporates relevant data to select and support dosing regimens

d) Summary of the potential for drug interactions or overlapping toxicity with proposed combination therapy

e) Summary of the effects of intrinsic (e.g., organ impairment, age, body size, race, ethnicity, polymorphisms) and extrinsic factors (e.g., common concomitant medications) on the safety and pharmacokinetics

f) Summary of relevant nonclinical data (e.g., target engagement)

AstraZeneca's Response; November 24, 2023

The Sponsor acknowledges the Agency's comments, and no discussion is requested.

Meeting Discussion: No discussion.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- 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.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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 the 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 the 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 guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

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

FDARA REQUIREMENTS

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

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

PRESCRIBING INFORMATION

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

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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

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

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and Sponsor/monitor/CRO inspection assignments,

and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

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

NONPROPRIETARY NAME

On January 13, 2017, the FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the FDA 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

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

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. The 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 the 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.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, the FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as the FDA approves the BLA.

SUBMISSIONS WITH REAL-WORLD EVIDENCE

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

None.

[9] https://www.fda.gov/media/124795/download

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

/s/

AMY R TILLEY
12/07/2023 10:04:28 AM

PREETI NARAYAN
12/08/2023 10:27:33 AM

IND 155696

MEETING REQUEST-
WRITTEN RESPONSES

Astra Zeneca
Attention: Saloni Vor Goradia, MS
Regulatory Affairs Director
35 Gatehouse Drive
Waltham, MA 02451

Dear Ms. Goradia:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Datopotamab deruxtecan (Dato-DXd; DS-1062a).

We also refer to your submission dated November 30, 2022, containing a meeting request. The purpose of the requested meeting was to discuss the structure and content of a potential BLA for Datopotamab deruxtecan (Dato-DXd; DS-1062a) for the treatment of adult patients with [redacted] (b) (4) or metastatic HR+/HER2- breast cancer [redacted] (b) (4), based on results from the TROPION-Breast01 study.

Further reference is made to our Meeting Granted letter dated December 19, 2022, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your December 21, 2022, background package.

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

If you have any questions, call Kim J. Robertson, Senior Regulatory Health Project Manager, at (301) 796-1441, or kim.robertson@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Senior Regulatory Health Project Manager
Oncology 1 Group
Division of Regulatory Operations for Oncologic Diseases
Center for Drug Evaluation and Research

{See appended electronic signature page}

Mirat Shah, MD
Acting Clinical Team Leader
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type:	C
Meeting Category:	Guidance
Application Number:	IND 155696
Product Name:	Datopotamab deruxtecan (Dato-DXd; DS-1062a).
Indication:	Adult patients with (b) (4) or metastatic HR+/HER2- breast cancer (b) (4)
Sponsor Name:	Astra Zeneca
Regulatory Pathway:	351(a) of the Public Health Service Act

1.0 BACKGROUND

AstraZeneca Pharmaceuticals LP (AstraZeneca) requested a Type C meeting to obtain guidance on their planned Biologics License Application (BLA) for Datopotamab deruxtecan (Dato-DXd), based on the TROPION-Breast01 (TB01) phase 3 trial, currently targeted for submission in **Q4 of 2023** for the following indication:

> *Dato-DXd is indicated for the treatment of adult patients with* (b) (4) *or metastatic HR-positive (HR+), HER2-negative (HER2-) breast cancer (BC)* (b) (4)

The specific objectives of the meeting are to seek feedback and alignment with the FDA on the:

- Format, structure, and content of the clinical components of the planned BLA for Dato-DXd based on the TB01 phase 3 trial, currently targeted for submission in Q4 of 2023; and
- Planned statistical analysis for the integrated summary of safety (ISS).

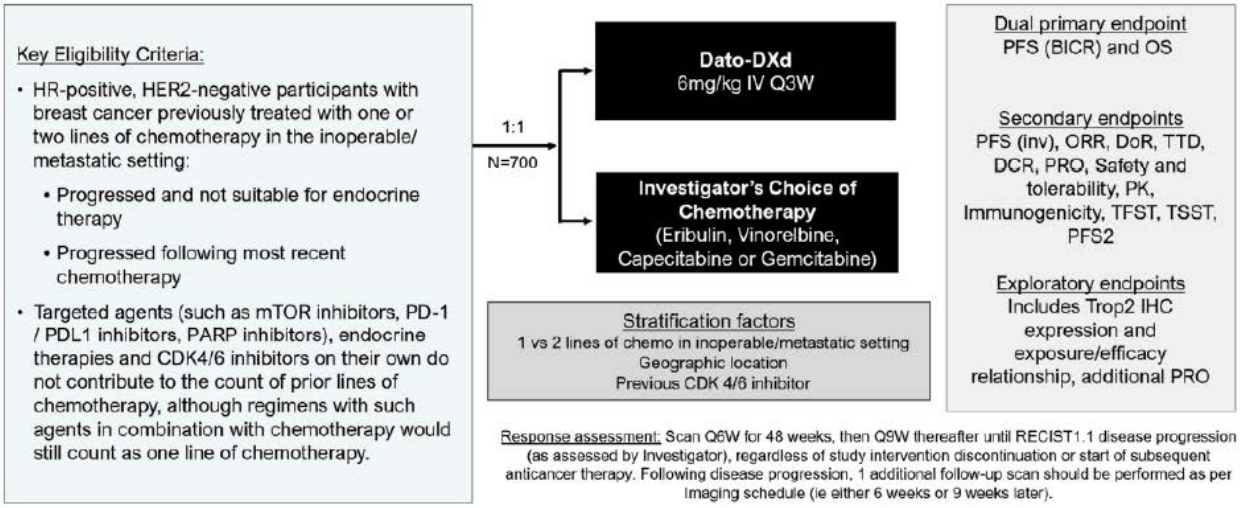
There are no topline results included in this meeting package.

Dato-DXd is an antibody-drug conjugate (ADC) that comprises a recombinant humanized anti-trophoblast cell surface protein 2 (TROP2) immunoglobulin 1 (IgG1) monoclonal antibody, MAAP-9001a, which is covalently conjugated to a drug-linker, MAAA-1162a, via thioether bonds. The released drug, MAAA-1181a, inhibits DNA topoisomerase I and leads to apoptosis of the target cells. Clinical evaluation of Dato-DXd was initiated with the first-in-human (FIH), open-label, phase 1, dose-escalation/dose-expansion study of Dato-DXd in advanced adult solid tumors (TROPION-PanTumor01; TP01). Thereafter, development of Dato-DXd has progressed

to a phase 3 trial in HR+HER2- advanced breast cancer (TB01; described below) as well as a phase 3 trial (TROPION LUNG01; TL01) in non-small cell lung cancer (NSCLC).

The pivotal study of Dato-DXd in metastatic BC (TB01) is an **ongoing** phase 3, open-label, randomized study, comparing Dato-DXd versus Investigator's choice of single-agent chemotherapy in patients with inoperable or metastatic HR+, HER2- BC who have been treated with one or two prior lines of systemic chemotherapy. The trial has dual primary endpoints of PFS per BICR as assessed according to RECIST v1.1 and OS.

The study design and fundamental elements of TB01, including key eligibility criteria, stratification factors, and key endpoints are shown in the figure below:



Stratification factors for randomization include:

- 1 vs. 2 prior lines of chemotherapy in the inoperable/metastatic setting (50% cap on patients with 2 prior lines)
- Geographic location
- Previous CDK4/6 inhibitor (49% cap on patients without prior CDK4/6i)

Dato-DXd is administered at 6 mg/kg IV Q3W. Investigator's choice chemotherapy (ICC) options include eribulin, vinorelbine, capecitabine, or gemcitabine. The ICC is predefined prior to randomization and is administered per USPI except for capecitabine which has two dose options (1000 or 1250 mg/m2 oral BID on Days 1 to 14, Q3W per standard institutional practice). Treatment is given until RECIST 1.1-defined radiological progression, or unacceptable toxicity, withdrawal of consent, or another criterion for discontinuation is met.

Tumor imaging occurs every 6 weeks for 48 weeks, then every 9 weeks until RECIST 1.1 disease progression. Survival follow-up thereafter occurs every 3 months relative to the date of the last safety evaluation post-treatment discontinuation (~30 days). There is no crossover allowed between study treatment arms.

Based on safety data from the Dato-DXd clinical development program, the important identified risks are drug-induced interstitial lung disease (ILD)/pneumonitis and infusion related reaction (IRR). Additional adverse events of special interest (AESI) are oral mucositis/stomatitis, other non-oral mucosal inflammation, and ocular surface toxicity such as dry eye and keratitis. Other identified or potential risks of Dato-DXd include anemia, lymphopenia, fatigue, nausea, vomiting, diarrhea or constipation, decreased appetite, alopecia, skin rash and increase in ALT/AST. Monitoring and mitigation strategies pertinent to mucositis, ocular toxicity, and pneumonitis are briefly described below:

- **Oral care:** Oral care kits and oral care protocol [OCP] guides will be provided to patients. Daily OCP will be started before study drug initiation and continued until 28 days after last study dose. The OCP includes daily use of a steroid-containing mouthwash for prophylaxis.
- **Ophthalmologic evaluations:** Assessments to be done by an ophthalmologist, or another licensed eye care provider to include visual acuity testing, fluorescein staining, intraocular pressure, slit lamp examination and fundoscopy. Assessments will be performed at screening, and then every 3 cycles from C1D1, as well as clinically indicated while on trial, and at end of treatment (EoT).
- **Pulmonary evaluation:** Pulmonary function tests will be conducted at baseline and as clinically indicated while on trial.

Statistical Considerations for TB01

TB01 is designed with dual primary endpoints: PFS (BICR assessment by RECIST 1.1) and OS. The trial is planned to enroll ~700 patients.

Approximately 419 PFS BICR events from the ITT population (60% maturity) are anticipated to provide >99% power to demonstrate statistical significance at the 2-sided alpha level of 1.0%. This assumes a hazard ratio (HR) of 0.55 for Dato-DXd versus ICC and corresponding median PFS of 8.5 months and 4.7 months (or 3.8-month median PFS improvement). The smallest treatment difference that could be statistically significant is a hazard ratio (HR) of 0.775 or a minimum detectable difference (MDD) in median PFS of 1.4 months. Approximately 444 OS events from the ITT population (63% maturity) will provide ~83% power to demonstrate statistical significance at the 2-sided alpha level of 4.0%. This assumes a HR of 0.75 for Dato-DXd versus ICC, and a median OS of 19.0 months for ICC (or MDD in OS of 6.3 months). The smallest treatment difference that is statistically significant will be a HR of 0.817 or a MDD in OS of 4.3 months.

If the PFS primary analysis crosses the efficacy threshold, OS will be tested at the 2-sided alpha level of 5.0% and the analysis will have 85% power to demonstrate statistical significance. The smallest treatment difference that is statistically significant will be a HR of 0.824 or a MDD in OS of 4.1 months.

There is 1 planned analysis for PFS, and there are 2 planned interim analyses and 1 final analysis for OS. The Sponsor expects the final PFS analysis /interim overall survival analysis 1 (OS) to read-out in mid-2023.

Integrated Analyses and Cross-reference

Efficacy: Along with clinical efficacy data from TB01, supportive data from the breast cancer cohorts in TROPION-PanTumor01 (TP01), including 41 patients with HR+HER2- breast cancer and 44 patients with TNBC, will be included in the planned BLA submission. The Sponsor proposes to present efficacy results from the trials separately and as pooled analyses.
Safety: In addition to clinical safety data from TB01, the safety database will include data from patients enrolled to the trials listed:

- TP01: Pan-tumor trial, patients with either breast cancer or NSCLC and have received doses of 4-6 mg/kg will be included.
- TL01: NSCLC trial comparing Dato-DXd 6 mg/kg to docetaxel.
- TL05: NSCLC trial. All patients to receive Dato-DXd 6 mg/kg.

The proposed pooled safety populations for the planned BLA are shown in the table below:

	Pivotal study data (TB01) (N = 350)	**Pooled BC (TNBC; HR+/HER2-) (N = 433)**	**Pooled NSCLC (N = 482)**	**Pooled BC + NSCLC (N = 915)**	**Pooled BC and NSCLC (N = 1055)**
Dato-DXd dose	6 mg/kg	6 mg/kg	6 mg/kg	6 mg/kg	All doses (≥ 4 mg/kg)
Studies	TB01 HR+/HER2- BC (n=350)	TB01 (n=350) TP01 BC (n=83)	TP01 NSCLC (n=50) TL05 (n=137) TL01 (n=295)	TB01 (n=350) TP01 BC n=83) TP01 NSCLC (n=50) TL05 (n=137) TL01 (n=295)	TB01 (n=350) TP01 BC (n=85) TP01 NSCLC (n=188) TL05 (n=137) TL01 (n=295

Source: Sponsor Briefing Package, Table 2, page 15

The Sponsor intends to cross-reference the clinical study reports (CSRs) from TL01, TL05 and TP01 (BC and NSCLC cohorts) contained in the TL01 BLA which is targeted to be under review by DO2 at the time of the planned TB01 BLA submission.

TROP2:

An exploratory objective of TB01 is the assessment of tumor TROP2 expression and relationship to Dato-DXd exposure/efficacy. Tumor TROP2 expression levels by immunohistochemistry (IHC) with a validated assay using a mAb (clone EPR20043) directed against the intracellular domain of TROP2. Clinical response associations will include BC participants from TB01 and TP01 and be presented graphically and as a listing.

2.0 QUESTIONS AND RESPONSES

FDA Preamble: We recommend that you request an additional meeting once the topline results from TB01 are available as we may provide additional advice regarding your planned BLA submission. We remain concerned that the PFS results may not be clinically meaningful given that your trial could reach statistical significance with only a 1.4-month improvement in median PFS and has a 1.5 month scanning interval. Whether the results from this trial could support an approval will depend on the totality of data including the magnitude of PFS benefit, OS information, information from other secondary endpoints, and the acceptability of the toxicity profile.

We also remain concerned that there may be a substantial proportion of patients who have not received prior treatment with a CDK4/6 inhibitor, which is standard of care treatment for patients with HR+HER2- advanced breast cancer in the U.S. We acknowledge that a 49% cap will be applied to patients who have not received prior CDK4/6 inhibitor. However, whether the trial population is sufficiently representative of a U.S. population with HR+HER2- advanced breast cancer with respect to prior therapies will be a review issue.

Question 1
Does the Agency agree with the Sponsor's proposal that Study TB01, supported by data from Study TROPION-PanTumor01 (referred to as TP01; DS1062-A-J101), can serve as the basis for the BLA submission?

FDA Response: See the FDA Preamble.

In addition, it appears that you plan to include integrated efficacy assessments for PFS and OS from TB01 and TP01 in your submission. You should note that we are not planning to focus on pooled efficacy analyses during our review at this time as interpretation of pooled PFS and OS data may be particularly challenging in a heterogenous population.

Question 2
Does the Agency agree with the proposed content of the SCE?

FDA Response: Yes, the proposed content for the summary of clinical efficacy (SCE) is generally acceptable. Please also see the FDA's response to Question 1.

Question 3
Does the Agency agree with the proposed content of the SCS, including the analyses for the ISS?

FDA Response: Yes, the proposed content for the summary of clinical safety (SCS) is acceptable.

Question 4
Does the Agency agree with the Sponsor's proposal for the safety update report?

FDA Response: No. It is premature for us to comment on whether your BLA will qualify for priority review. If your BLA is granted priority review, your plan to submit a 90-day safety update mirroring the content of the SCS appears reasonable.

Question 5
Does the Agency agree with the proposal for the scope of CSR narratives and associated CRFs in the submission?

FDA Response: Yes, your submission plan for CSR narratives and associated CRFs for events from TB01 is acceptable. You should also be prepared to provide any additional narratives from TB01 or other trials if requested by us during the review of your BLA.

Question 6

Does the Agency agree with the proposed clinical pharmacology data package, including the popPK, exposure-response analysis, PBPK modeling, concentration-QT analysis, and an integrated summary of immunogenicity, is acceptable for a BLA review?

FDA Response: No. In addition to the proposed exposure-response (E-R) analyses using clinical data from TB01, you should consider additional E-R analysis for efficacy by pooling data from TB01 with the data obtained from TP01 in patients with HR+HER2- BC (n=41) only and with the data obtained from TP01 in all patients with breast cancer (HR+HER2BC and TNBC; n=85).

Regarding the concentration-QT analysis, you have not provided sufficient information to assess whether QTc data from Study TP01 are adequate to support assessment of QTc effects of your product. Specifically, you have not stated how the maximum tested dose with QTc data from study TP01 covers the anticipated therapeutic Cmax or high clinical Cmax. Similarly, you have not stated the methods for ECG acquisition and reading and whether the PK and ECG collection schedules capture the QT effects at steady state Tmax for your product. You should submit your QT assessment plan for review.

The adequacy of the PBPK analysis to waive clinical DDI studies will be a review issue. Based on the limited data you provided, we have the following major concerns:

1. **If you plan to use the clinical DDI study of T-DXd (Takahashi et al 2021) to verify the contribution of CYP3A and OATP1B in the unconjugated MAAA-1181a model, the observed effects of itraconazole and ritonavir may be too small to be used for this purpose.**

2. **The results from an interaction study with ritonavir are not sufficient to support the statement that DDI with other inhibitors of CYP3A and OATP1B are not expected to be clinically meaningful because ritonavir only has a weak effect on the known OATP1B substrate pravastatin, whose AUC only increased 33% following a single dose of 100 mg ritonavir (PubMed 23381882). In addition, ritonavir is an inhibitor of CYP3A and an inhibitor or/and an inducer of P-gp. It is likely that the effect of ritonavir on MAAA-1181a observed in the clinical DDI study of T-DXd was the net effect of inhibition and induction of ritonavir on CYP3A, P-gp and OATP1B because MAAA-1181a is a substrate of CYP3A, P-gp and OATP1B and the effect of multiple doses of ritonavir was assessed in this study (Takahashi et al 2021).**

Otherwise, the proposed contents of clinical pharmacology data package appear acceptable for our review of your BLA.

Question 7
Does the Agency agree with the Sponsor's proposal for Study Data Tabulation Model and analysis data model datasets in the electronic submission data plan?

FDA Response: No, it is not clear if datasets from TP01 will be included in your submission or cross-referenced. As TP01 results are planned to provide supportive evidence of efficacy and safety for your application, you should also submit these datasets in your BLA. For datasets, programs, and define files entirely including patients with NSCLC, you may cross-reference these to the TL01 BLA.

Question 8
Does the Agency agree with the proposed comprehensive table of contents for the BLA and the Sponsor's proposal to cross-reference information in the TL01 BLA that is targeted to be under review by DO2 at the time of the TB01 BLA submission?

FDA Response: No. In your BLA submission, you should also include the following:

- **For TB01, you should include the protocol and amendments, a summary of the changes of the protocol amendments, the SAP and the amendments, a summary of the changes of the SAP amendments, and IDMC meeting minutes in Module 5.3.5.1.**
- **Your submission should contain a mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses. Variables used for sensitivity analyses of the efficacy endpoints should be included as well.**
- **Your submission should include the following additional items:**
  - **SAS programs that produced all key efficacy results reported in the CSR efficacy section**
  - **All raw as well as derived variables in .xpt format**
  - **SAS programs by which the derived variables were produced from the raw variables.**

In addition, you should include the TP01 CSR in your BLA submission rather than cross-referencing this information. Please also see the FDA's response to Q7.

Question 9
Does the Agency agree that the Sponsor can submit the BLA under Project Orbis if another original application for the same molecule is already being reviewed under Project Orbis?

FDA Response: Yes, multiple applications (including supplemental applications) for the same product can qualify for Project Orbis. We remind you that applications eligible for Project Orbis are typically those considered high impact and clinically significant due to improvement in efficacy and/or safety.

To request participation in Project Orbis, we recommend that when you submit your topline results for an additional meeting, you also submit a global submission plan (GSP) that provides details and timelines for submission to the other regulatory authorities. Once we review your topline results, we can provide more advice regarding Project Orbis eligibility. For more details on Project Orbis, refer to this website: https://www.fda.gov/about-fda/oncology-center-excellence/project-orbis.

Question 10
Does the Agency agree with the content of the Financial Disclosure package?

FDA Response: Yes.

Additional Clinical Comment

We note that you will be exploring associations between clinical response and tumor TROP2 expression by IHC. If detection of TROP2 expression is determined to be necessary for safe and effective use of your product, a diagnostic device for detection of TROP2 expression will be needed. In that situation, consultation with CDRH is strongly recommended.

Additional Clinical Pharmacology Comments

Regarding the USPI for the proposed BLA:

The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with the FDA's Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format". 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. **What is the basis for selecting the dosages used in the registration trials to support your marketing application? Identify individuals who required dosage modifications and provide time to the first dosage modification and reasons for the dosage modifications in support of the proposed dosage.**

2. **What are the exposure-response relationships for efficacy, safety, and biomarkers of interest?**

3. **How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, and safety of your drug? What dose modifications are recommended?**

4. **What is the impact of immunogenicity on exposure, efficacy, and safety?**

<u>Apply the following advice in preparing the clinical pharmacology sections of the BLA submission:</u>

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

2. **Provide the 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 dosage modifications; the time to the first dose reduction, interruption or discontinuation; and the reasons for dosage 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 this data format information: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format.

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 safety) relationships in the targeted patient population. Refer to Guidance for Industry for population PK: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/population-pharmacokinetics, exposure-response relationships: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exposure-response-relationships-study-design-data-analysis-and-regulatory-applications, and pharmacometric data and models submission guidelines: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format.**

7. **Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (using individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.**

8. **Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in the laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in the adverse event analysis dataset (adae.xpt) to**

support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide, and this should be consistent with common pooled terms used to inform labeling if applicable.

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 any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that the 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 the FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

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

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

FDARA REQUIREMENTS

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

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

---

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

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*.[4]

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 the 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[5]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[6]

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

---

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/

KIM J ROBERTSON
02/13/2023 05:59:36 PM

MIRAT S SHAH
02/13/2023 07:06:12 PM

PIND 155696

MEETING PRELIMINARY COMMENTS

Astra Zeneca
Attention: Martin Mao, MS, RAC
Director, Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Mao:[1]

Please refer to your pre-investigational new drug application (PIND) file for Datopotamab deruxtecan (Dato-DXd).

We also refer to your April 14, 2021, correspondence, received April 19, 2021, requesting a meeting to receive advice on the design of a phase 3 study (D9268C00001; TROPION-Breast 01) that would evaluate Dato-DXd versus Investigator's choice of single-agent chemotherapy in patients with inoperable, or metastatic hormone receptor-positive/HER2-negative breast cancer who have been treated with one or two prior lines of systemic chemotherapy.

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 the FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

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

If you have any questions, call Kim J. Robertson, Senior Regulatory Health Project Manager, at (301) 796-1441, or kim.robertson@fda.hhs.gov .

Sincerely,

{See appended electronic signature page}

Kim J. Robertson
Senior Regulatory Health Project Manager
Oncology 1 Group
Division of Regulatory Operations for Oncologic Diseases
Office of Oncologic Diseases
Center for Drug Evaluation and Research

{See appended electronic signature page}

Gwynn Ison, MD
Acting Clinical Team Leader
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type:	B, EOP
Meeting Category:	Pre-IND
Application Number:	IND 155696
Product Name:	Datopotamab deruxtecan (Dato-DXd)
Indication:	(b) (4) metastatic hormone receptor-positive/ HER2-negative breast cancer
Sponsor Name:	Astra Zeneca
Regulatory Pathway:	505(b)(1) of the Public Health Service Act

INTRODUCTION:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for Tuesday, June 29, 2021, 11:00am – 12:00pm, EST between Astra Zeneca and the Division of Oncology 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 teleconference. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the teleconference (contact the regulatory project manager (RPM)). If you choose to cancel the teleconference, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The Sponsor requested a Type B EOP meeting to gain feedback on TROPION-Breast01, a proposed registration trial for their investigational agent datopotamab deruxtecan (Dato-DXd) in patients with inoperable or metastatic HR-positive, HER2-negative breast cancer following 1-2 prior lines of systemic chemotherapy. The Sponsor seeks the following indication:

Dato-DXd is indicated for the treatment of adult patients with (b) (4) metastatic HR-positive, HER2-negative breast cancer (b) (4)

Dato-DXd is an antibody-drug conjugate containing an anti-TROP2 monoclonal antibody, cleavable linker, and a MAAA-1181a payload. MAAA-181a is a DNA topoisomerase I inhibitor. The Sponsor is developing this therapy for NSCLC, TNBC, and HR-positive/HER2-negative breast cancer. The Sponsor includes safety and efficacy data from the 4 mg/kg, 6 mg/kg, and 8 mg/kg doses in NSCLC to support selection of the 6 mg/kg dose. Per the Sponsor, the 8 mg/kg dose was associated with higher frequencies of grade 3+ TEAEs, SAEs, dose modifications, and AESIs compared to the other doses. **The Sponsor is proposing to utilize the 6 mg/kg dose in the proposed phase 3 trial.**

Preliminary efficacy data are available for the NSCLC and TNBC expansion cohorts from an ongoing trial DS1062-A-J101. There were 21 patients evaluable for response in the TNBC cohort at a data cutoff of January 8, 2021. Two patients had received the 8 mg/kg dose, and 19 patients had received the 6 mg/kg dose. Five patients out of 21 patients experienced a disease response, four patients who received the 6 mg/kg dose and 1 patient who received the 8 mg/kg dose.

Lung, skin, and corneal toxicities were predicted from animal studies. ILD/pneumonitis is an identified risk of Dato-DXd, affecting 10% of patients enrolled in the development program to date and causing 3 deaths. All deaths were in patients who received the 8 mg/kg dose. Other adverse events of special interest for the development program are Infusion-related reactions, stomatitis, and combined elevations in AST/ALT and bilirubin. Although 8% of patients have experienced ALT and/or AST elevation, there has only been 1 case of G3 elevation, and no cases of Hy's law. Other identified risks include nausea, vomiting, diarrhea, fatigue, alopecia, decreased appetite, anemia, rash, and dry eye. Other potential risks include keratitis, skin pigmentation changes, constipation, and increased AST/ALT.

The Sponsor plans to conduct the proposed trial, TROPION-Breast01, a phase 3, randomized (1:1), open-label trial, in 700 patients with unresectable or metastatic HR-positive, HER2-negative breast cancer. The endpoints are:

Co-Primary Endpoints:

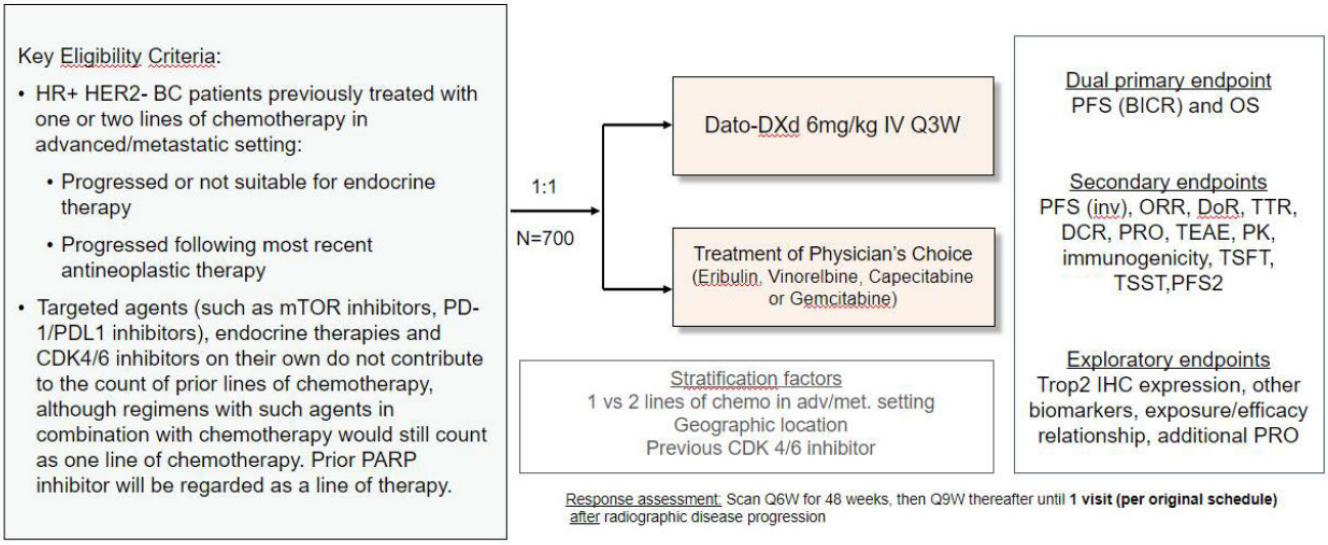
- Progression-free survival (PFS) as assessed by blinded independent central review (BICR) according to RECIST v1.1
- Overall survival (OS)

Secondary Endpoints (selected):

- ORR and DOR per BICR and investigator according to RECIST v1.1

- PFS per investigator per RECIST v1.1
- PROs including EORTC QLQ-C30 physical functioning subscale, EORTC QLQ-C30 pain scale, and EORTC QLQ-BR45 breast symptoms scale

The study schema is shown here:



Key eligibility criteria include:

- Inoperable or metastatic HR-positive, HER2-negative breast cancer
- Progression of disease following 1 or 2 prior lines of chemotherapy in the inoperable or metastatic setting
- Progressed on or not suitable for endocrine therapy per investigator
- PARPi do count as one of the prior lines of chemotherapy. Other targeted agents such as mTOR inhibitors, PD-1/PD-L1 inhibitors, and CDK4/6 inhibitors will not count towards the 1-2 prior lines of chemotherapy.
- Measurable disease as per RECIST v1.1
- Patients with brain metastases that are asymptomatic and not requiring corticosteroids or anticonvulsants may be eligible. There must be >2 weeks between WBRT and study enrollment.
- Patients who received prior ADC with topoisomerase 1, TROP2-targeted therapy, or trastuzumab deruxtecan are not eligible.
- Patients with history of ILD/pneumonitis requiring steroids, or current or suspected ILD/pneumonitis, or clinically severe pulmonary compromise are not eligible.

- Patients with clinically significant corneal disease are not eligible.

Stratification factors for randomization include:

- Geographic region (US/Europe vs. Rest of World)
- Prior use of CDK4/6 inhibitor (yes vs. No)
- Number of prior lines of therapy (1 vs. 2)

The Sponsor plans to cap enrollment of patients who have received 2 prior lines of therapy at 50%.

The dosing regimen for Dato-DXd is 6 mg/kg IV every 3 weeks. Options for Physician's Choice treatment include:

- Eribulin 1.4 mg/m2 IV on Days 1 and 8, every 3 weeks
- Vinorelbine 25 mg/m2 IV on Days 1 and 8, every 3 weeks
- Capecitabine 1000 or 1250 mg/m2 PO on Days 1-14 every 3 weeks
- Gemcitabine 1000 mg/m2 on Day 1 and 8, every 3 weeks

Imaging assessments will occur every 6 weeks for the first 48 weeks and then every 9 weeks thereafter. For safety assessments for ILD/pneumonitis, the Sponsor will perform baseline pulmonary function tests in all participants. The Sponsor will use an independent, blinded, ALT adjudication committee to evaluate potential cases of ILR/pneumonitis.

The Sponsor states that they will collect tumor tissue to retrospectively evaluate TROP2 expression by IHC. In the Sponsor's analysis to date, >90% of HR-positive breast cancer samples have TROP2 expression.

The Sponsor plans to enroll 900 patients and randomize 700 patients, and PFS and OS are co-primary endpoints. There is one PFS analysis planned and three OS analyses planned. The primary (and final) PFS analysis will occur ~2 months after the last patient is randomized. The Sponsor anticipates that PFS data will be ~60% mature with ~419 events having occurred at that time. The final OS analysis will occur when ~444 events have occurred. The Sponsor will maintain an overall 2-sided alpha of 5%, split between PFS and OS. The Sponsor will allocate 1% alpha to the PFS endpoint and 4% alpha to the OS endpoint. If the PFS endpoint is met, the 1% alpha from PFS will be passed to OS.

The Sponsor predicts a median PFS of 4.7 months on the control arm and is targeting a HR of 0.55, which translates to a median PFS of 8.5 months on the experimental arm. The Sponsor will have 99% power to detect this HR and the minimum detectable HR is 0.775 which translates to a median PFS of 6 months on the experimental arm. The Sponsor predicts a median OS of 19 month on the control arm and is targeting an OS HR of 0.75, which translates to median OS of 25 months on the experimental arm. The Sponsor will have 83% power to detect this HR and the minimum detectable HR is

0.817 at an alpha of 4% which translates to a median OS of 23 months on the experimental arm. The minimum detectable HR is 0.824 at an alpha of 5%.

2.0 DISCUSSION

List of Questions for TROPION-Breast01

Question 1 (Overall study design)

Does the Agency agree that the proposed overall phase 3 study design is appropriate to support registration of Dato-DXd for the treatment of adult patients with (b) (4) metastatic HR-positive / HER2-negative breast cancer (b) (4)

FDA Response: Possibly. The proposed phase 3 randomized clinical trial appears acceptable. Whether the results of this study could support an approval would be based upon the totality of data, including magnitude of benefit, and acceptability of the adverse event profile for the proposed population. The minimum detectable difference in median PFS on your proposed trial is ~(b) (4) months, and it is unlikely that this result would be considered clinically meaningful, especially given that your imaging interval is every 6 weeks.

Question 2 (Patient population)

Does the Agency agree that the patient population proposed in this study is appropriate to support registration of Dato-DXd for the proposed indication of "Dato-DXd is indicated for the treatment of adult patients with (b) (4) metastatic HR-positive/HER2-negative breast cancer (b) (4) "?

FDA Response: Your proposed patient population for this trial in general is acceptable; however, we are concerned that there may be a substantial proportion of patients enrolled to your trial who have not received a CDK4/6i. Your study population must be generalizable a US-based population with HR-positive, HER2-negative metastatic breast cancer, including that the majority of patients must have received treatment with a CDK4/6i, as this therapy is standard-of-care treatment and is associated with an OS benefit. Whether or not your study population is reflective of a US-based population with HR-positive, HER2-negative metastatic breast cancer will be a review issue.

In addition, you may consider enrolling patients without measurable disease to your trial, as overall response rate (ORR) is not one of your primary efficacy endpoints.

Question 3 (Stratification factors)

Does the Agency agree that the proposed stratification factors are appropriate for the proposed study?

FDA Response: Your proposed stratification factors are acceptable.

Question 4 (Choice of comparator)
Does the Agency agree the proposed comparator options of eribulin, vinorelbine, capecitabine, and gemcitabine are appropriate for the proposed study?

FDA Response: Yes, these comparator options are acceptable. If patients have not received a prior taxane, this would be an option for standard-of-care treatment, and you may consider including this as a treatment option for the comparator arm.

Question 5 (Safety considerations)
Does the Agency agree that the planned safety measures to be implemented in the study are sufficient to support the proposed treatment regimen?

FDA Response: The safety measures you propose with respect to ILD/pneumonitis and IRRs seem reasonable at this time, however we will review these more thoroughly when you submit your formal protocol.

Additionally, if dry eye is an identified risk associated with your investigational product, and keratitis is a potential risk, in your protocol, you should clarify what ocular assessments you will conduct at baseline and throughout the trial.

Question 6 (Statistical considerations)
Does the Agency agree that the sample size and statistical approach to evaluate the efficacy endpoints, including the MTP to control the overall Type I error rate and the proposed analysis are appropriate?

FDA Response: The sample size and statistical approach including the MTP appear to be acceptable. We recommend you follow all patients for OS until the final OS analysis, even if an interim OS analysis crosses the efficacy threshold.

Question 7 (Patient-reported outcomes assessment)
Does the Agency agree that [redacted (b) (4)] from the EORTC QLQ-C30 is appropriate to measure pain, [redacted (b) (4)] in the proposed study?

FDA Response: We have concerns about [redacted (b) (4)] from the EORTC QLQ-C30 will be clinically meaningful or interpretable. First, not all patients who enroll on the trial will have pain, and of those patients, they could have wide range of causes of pain. [redacted (b) (4)]

Generally, use of the EORTC-QLQ-C30 and BR-45, along with the PGIS and PGIC anchors is reasonable for exploratory assessment of disease symptoms, treatment related symptoms, physical function, and role function.

Additional Comments

Clinical Pharmacology:

Regarding the proposed protocol,

1. **Consider expanding the eligibility criteria to include patients with moderate hepatic impairment.**

2. **Per the package insert of eribulin mesylate (HALAVEN®), reduce the starting dose for patients with mild or moderate hepatic impairment (Child-Pugh).**

3. **Per the package insert of eribulin mesylate (HALAVEN®), reduce the starting dose for patients with moderate renal impairment.**

4. **Per the package insert of capecitabine (XELODA®), reduce the starting dose for patients with moderate renal impairment.**

5. **Per the package insert of vinorelbine (NAVELBINE®), include cautionary language of potential earlier onset and/or an increased severity of adverse reactions for patients concurrently taking drugs known to inhibit CYP3A and vinorelbine.**

6. **Include a detailed PK sampling plan to collect sparse PK samples in the final protocol submission. Include a detailed plan for conducting population pharmacokinetic analyses and exploratory exposure-response analyses for efficacy, safety and relevant biomarkers.**

7. **Include a detailed immunogenicity sampling plan in the final protocol submission. Due to the relative high incidence of ADA (11%) observed in ongoing clinical trials, we recommend that you develop a nAb assay as soon as possible. You should submit reports on the impact of neutralizing ADA on the PK, efficacy and safety of DS-1603a in the initial BLA.**

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 any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that the 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 the FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

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

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

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

FDARA REQUIREMENTS

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

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

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 the [FDA]." The FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the FDA can process, review, and archive. Currently, the FDA can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[4]

On December 17, 2014, the FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards.

---

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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 started on or before December 17, 2016, CDER strongly encourages IND Sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND Sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to the FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist the FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to the FDA supported electronic submission and data standards; there is no scientific review of content.

The FDA encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the the FDA. The FDA strongly encourages the Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study

[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.
Additional information can be found at FDA.gov.[6]

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.

---

[6] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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[7] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[8]

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[9]

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

[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[8] https://www.fda.gov/media/109533/download
[9] https://www.fda.gov/media/85061/download

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.

UNITED STATES PATIENT POPULATION

The FDA expects the Sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

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

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate the 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[10]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[11]

ADVANCING ONCOLOGY DECENTRALIZED TRIALS

The FDA Oncology requests that applicants submitting data to support NDA/BLA applications to voluntarily add flags to datasets in order to discriminate between REMOTE assessments and TRIAL SITE assessments. The intent is to allow the FDA to learn from trials conducted in the COVID-19 pandemic that permitted some aspects of trial conduct to be performed remote from trial sites to reduce potential COVID exposure. The FDA hopes to learn more about the opportunities and challenges of these REMOTE modifications in order to foster use of "decentralize" aspects of clinical trials prospectively in the post-COVID era.

For details please refer to: https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials.

[10] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[11] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

---

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/

KIM J ROBERTSON
06/23/2021 06:33:47 PM

GWYNN ISON
06/23/2021 09:48:53 PM