CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761174Orig1s006

Trade Name:	**JEMPERLI**
Generic or Proper Name:	(dosatarlimab-gxly)
Sponsor:	GLAXOSMITHKLINE LLC
Approval Date:	July 31, 2023

Indication:

JEMPERLI is a programmed death receptor-1 (PD-1) blocking antibody indicated:

Endometrial Cancer (EC)

- in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent for the treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatched repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H)
- as a single agent for the treatment of adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA- approved test, that has progressed on or following prior treatment with a platinum- containing regimen in any setting and are not candidates for curative surgery or radiation

Mismatch Repair Deficient Recurrent or Advanced Solid Tumors

- as a single agent for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

BLA 761174/S-006

SUPPLEMENT APPROVAL

GlaxoSmithKline LLC
Attention: Deanna Rubin, PharmD
1250 South Collegeville Road
Mailstop UP 4400
Collegeville, PA 19426

Dear Dr. Rubin:

Please refer to your supplemental biologics license application (sBLA), dated March 23, 2023, received March 23, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Jemperli (dostarlimab-gxly) Injection 500 mg/10mL.

This Prior Approval supplemental biologics license application (S-006) provides for approval of Jemperli, in combination with carboplatin and paclitaxel, followed by Jemperli as a single agent for the treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H).

APPROVAL & LABELING

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling text for the Prescribing Information

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (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, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

[2] 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.

4481-1 Complete the ongoing clinical trial, RUBY Part 1, titled “A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY)”, to provide the pre-specified interim and final overall survival (OS) analyses.

The timetable you submitted on July 19, 2023, states that you will conduct this study according to the following schedule:

Interim Report Submission:	12/2024
Trial Completion:	12/2028
Final Report Submission:	06/2029

Submit the datasets with the interim and final report.

4481-2 Commitment to establish and support the availability of a nucleic acid based in vitro diagnostic device that is essential to support the safe and effective use of Jemperli, in combination with carboplatin and paclitaxel, for patients with endometrial cancer (EC) that are microsatellite instability high (MSI-H) through an appropriate analytical and clinical validation study using clinical trial data.

The timetable you submitted on July 19, 2023, states that you will conduct this study according to the following schedule:

Study Completion:	03/2027
Final Report Submission:	09/2027

Submit a summary of study results in the final report submission.

Submit clinical protocols to your IND 126472 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Amy Tilley, Regulatory Project Manager, at amy.tilley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Laleh Amiri-Kordestani, MD
Director
Division of Oncology 1
Office of Oncologic Diseases
Center for Drug Evaluation & Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[3] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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

/s/

LALEH AMIRI KORDESTANI
07/31/2023 11:22:27 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JEMPERLI safely and effectively. See full prescribing information for JEMPERLI.

JEMPERLI (dostarlimab-gxly) injection, for intravenous use
Initial U.S. Approval: 2021

----------RECENT MAJOR CHANGES ----------

Indications and Usage (1)	7/2023
Dosage and Administration (2.1, 2.2)	7/2023
Warnings and Precautions, Severe and Fatal Immune-Mediated Adverse Reactions (5.1)	7/2023

---------- INDICATIONS AND USAGE----------

JEMPERLI is a programmed death receptor-1 (PD-1)–blocking antibody indicated:

Endometrial Cancer (EC)

- in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent for the treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H). (1.1, 2.1)
- as a single agent for the treatment of adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation. (1.1, 2.1)

Mismatch Repair Deficient Recurrent or Advanced Solid Tumors

- as a single agent for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.[1] (1, 2.1)

[1]This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (1)

----------DOSAGE AND ADMINISTRATION----------

- JEMPERLI, in combination with carboplatin and paclitaxel, for dMMR or MSI-H primary advanced or recurrent endometrial cancer: 500 mg every 3 weeks for 6 doses followed by 1,000 mg monotherapy every 6 weeks. (2.2)
- JEMPERLI, as a single-agent, for dMMR recurrent or advanced endometrial cancer: 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks. (2.2)
- JEMPERLI, as a single-agent, for dMMR recurrent or advanced solid tumors: 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks. (2.2)
- Administer as an intravenous infusion over 30 minutes. (2.2)
- For complete dosing instructions, see full prescribing information.

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 500 mg/10 mL (50 mg/mL) solution in a single-dose vial. (3)

---------- CONTRAINDICATIONS ----------

None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection. Monitor for signs and symptoms of immune-mediated adverse reactions. Evaluate clinical chemistries, including liver enzymes, creatinine, and thyroid function, at baseline and periodically during treatment. Withhold or permanently discontinue JEMPERLI and administer corticosteroids based on the severity of reaction. (2.3, 5.1)
- Infusion-related reactions: Interrupt, slow the rate of infusion, or permanently discontinue JEMPERLI based on severity of reaction. (2.3, 5.2)
- Complications of allogeneic hematopoietic stem cell transplantation (HSCT): Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1–blocking antibody. (5.3)
- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.4, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------

- Most common adverse reactions (≥20%) with JEMPERLI in combination with carboplatin and paclitaxel in patients with dMMR/MSI-H EC are rash, diarrhea, hypothyroidism, and hypertension. Most common Grade 3 or 4 laboratory abnormalities (≥10%) are decreased neutrophils, decreased hemoglobin, decreased white blood cell count, decreased lymphocytes, increased glucose, decreased sodium, and decreased platelets. (6.1)
- Most common adverse reactions (≥20%) with JEMPERLI as a single agent in patients with dMMR solid tumors are fatigue/asthenia, anemia, diarrhea, and nausea. Most common Grade 3 or 4 laboratory abnormalities (≥2%) are decreased lymphocytes, decreased sodium, increased alkaline phosphatase, and decreased albumin. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Endometrial Cancer

JEMPERLI, in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent, is indicated for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H) *[see Dosage and Administration (2.1)]*.

JEMPERLI, as a single agent, is indicated for the treatment of adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation *[see Dosage and Administration (2.1)]*.

1.2 Mismatch Repair Deficient Recurrent or Advanced Solid Tumors

JEMPERLI, as a single agent, is indicated for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options *[see Dosage and Administration (2.1)]*. This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.2)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Combination Therapy

For use of JEMPERLI in combination with carboplatin and paclitaxel, select patients for treatment with JEMPERLI based on dMMR/MSI-H status in tumor specimens *[see Clinical Studies (14.1)]*.

Single Agent

Select patients for treatment with JEMPERLI as a single agent based on the presence of dMMR in tumor specimens in:

- recurrent or advanced endometrial cancer *[see Clinical Studies (14.1)]*.
- recurrent or advanced solid tumors *[see Clinical Studies (14.2)]*.

Information on FDA-approved tests for the detection of dMMR status is available at https://www.fda.gov/companiondiagnostics.

- An FDA-approved test for the detection of MSI-H is not currently available *[see Clinical Studies (14.1)]*.

Because the effect of prior chemotherapy on test results for dMMR in patients with high-grade gliomas is unclear, it is recommended to test for this marker in the primary tumor specimen obtained prior to initiation of temozolomide chemotherapy in patients with high-grade gliomas.

2.2 Recommended Dosage

The recommended dosage for JEMPERLI is presented in Table 1.

Table 1. Recommended Dosage of JEMPERLI

Indication	Recommended Dosage	Duration/Timing of Treatment
Combination Therapy		
Adults with dMMR/MSI-H primary advanced or recurrent EC	500 mg[b] every 3 weeks for 6 doses[a] followed by 1,000 mg[b] monotherapy every 6 weeks Administer JEMPERLI prior to carboplatin and paclitaxel when given on the same day.	Until disease progression, unacceptable toxicity, or up to 3 years.
Monotherapy		
Adults with dMMR recurrent or advanced EC and dMMR recurrent or advanced solid tumors	500 mg[b] every 3 weeks for 4 doses followed by 1,000 mg[b] every 6 weeks	Until disease progression or unacceptable toxicity

dMMR = Mismatch Repair Deficient; MSI-H = Microsatellite Instability-High; EC = endometrial cancer.

[a] First 6 doses are administered in combination with carboplatin and paclitaxel. Refer to the Prescribing Information for the agents administered in combination with JEMPERLI, as appropriate.

[b] 30-minute intravenous infusion.

2.3 Dosage Modifications for Adverse Reactions

No dose reductions of JEMPERLI are recommended. In general, withhold JEMPERLI for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue JEMPERLI for life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for JEMPERLI for adverse reactions that require management different from these general guidelines are summarized in Table 2.

Table 2. Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity[a]	Dosage Modification
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold[b]
	Grade 3 or 4 or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[b]
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold[b]
	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver[c]	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold[b]
	AST or ALT increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue

Endocrinopathies	Grade 2, 3, or 4	Withhold until clinically stable or permanently discontinue, depending on severity[b]
Nephritis with renal dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[b]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative dermatologic conditions	Suspected SJS, TEN, or DRESS	Withhold[b]
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological toxicities	Grade 2	Withhold[b]
	Grade 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-related reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; DRESS = drug rash with eosinophilia and systemic symptoms.

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0.

[b] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to less than 10 mg/day (or equivalent) within 12 weeks of initiating steroids.

[c] If AST and ALT are less than or equal to ULN at baseline in patients with liver involvement, withhold or permanently discontinue JEMPERLI based on recommendations for hepatitis with no liver involvement.

2.4 Preparation and Administration

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to yellow. Discard the vial if visible particles are observed.
- Do not shake.

- For the 500-mg dose, withdraw 10 mL of JEMPERLI from a vial using a disposable sterile syringe made of polypropylene and dilute into an intravenous infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 2 to 10 mg/mL (maximum 250 mL). JEMPERLI is compatible with an infusion bag made of polyolefin, ethylene vinyl acetate, or polyvinyl chloride with di(2-ethylhexyl) phthalate (DEHP).
- For the 1,000-mg dose, withdraw 10 mL from each of 2 vials (withdraw 20 mL total) and dilute into an intravenous bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 4 to 10 mg/mL (maximum 250 mL).
- Mix diluted solution by gentle inversion. Do not shake.
- Discard any unused portion left in the vial.

Storage of Infusion Solution

Store in the original carton until time of preparation in order to protect from light. The prepared dose may be stored either:

- At room temperature for no more than 6 hours from the time of preparation until the end of infusion.
- Under refrigeration at 2°C to 8°C (36ºF to 46ºF) for no more than 24 hours from time of preparation until end of infusion. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Discard after 6 hours at room temperature or after 24 hours under refrigeration.

Do not freeze.

Administration

Administer infusion solution intravenously over 30 minutes through an intravenous line using tubing made of polyvinyl chloride or platinum cured silicon; fittings made of polyvinyl chloride or polycarbonate; and a sterile, non-pyrogenic, low-protein binding, 0.2-micron, in-line or add-on filter.

JEMPERLI must not be administered as an intravenous push or bolus injection. Do not co-administer other drugs through the same infusion line.

3 DOSAGE FORMS AND STRENGTHS

Injection: 500 mg/10 mL (50 mg/mL) clear to slightly opalescent, colorless to yellow solution in a single-dose vial for intravenous infusion after dilution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

JEMPERLI is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death receptor-1 (PD-1) or PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance, and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed in WARNINGS AND PRECAUTIONS may not include all possible severe and fatal immune-mediated reactions.

Immune-mediated adverse reactions, which can be severe or fatal, can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting a PD-1/PD-L1–blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1–blocking antibodies, they can also manifest after discontinuation of PD-1/PD-L1–blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1–blocking antibodies. Monitor closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function tests at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue JEMPERLI depending on severity *[see Dosage and Administration (2.3)]*. In general, if JEMPERLI requires interruption or discontinuation, administer systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies, dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

JEMPERLI can cause immune-mediated pneumonitis, which can be fatal. In patients treated with other PD-1/PD-L1–blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation.

Immune-mediated pneumonitis occurred in 2.3% (14/605) of patients receiving JEMPERLI, including Grade 2 (1.3%), Grade 3 (0.8%) and Grade 4 (0.2%) pneumonitis. Pneumonitis led to discontinuation of JEMPERLI in 1.3% of patients.

Systemic corticosteroids were required in 79% (11/14) of patients with pneumonitis. Pneumonitis resolved in 11 of the 14 patients. JEMPERLI was withheld for 9 patients. Five patients reinitiated JEMPERLI after symptom improvement; of these, 2 patients had recurrence of pneumonitis.

Immune-Mediated Colitis

JEMPERLI can cause immune-mediated colitis. Cytomegalovirus infection/reactivation have occurred in patients with corticosteroid-refractory immune-mediated colitis treated with PD-1/PD-L1–blocking antibodies. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated colitis occurred in 1.3% (8/605) of patients receiving JEMPERLI, including Grade 2 (0.7%) and Grade 3 (0.7%) adverse reactions. Colitis led to discontinuation of JEMPERLI in 1 (0.2%) patient.

Systemic corticosteroids were required in 75% (6/8) of patients with colitis. Colitis resolved in 5 of the 8 patients. Of the 4 patients in whom JEMPERLI was withheld for colitis, all reinitiated treatment with JEMPERLI; of these, 1 patient had recurrence of colitis.

Immune-Mediated Hepatitis

JEMPERLI can cause immune-mediated hepatitis, which can be fatal.

Immune-mediated hepatitis occurred in 0.5% (3/605) of patients receiving JEMPERLI, all were Grade 3. Hepatitis led to discontinuation of JEMPERLI in 1 (0.2%) patient. Systemic corticosteroids were required in 2 patients with hepatitis and the events resolved in 2 of the 3 patients.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency: JEMPERLI can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment per institutional guidelines, including hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity *[see Dosage and Administration (2.3)]*.

Adrenal insufficiency occurred in 1.2% (7/605) patients receiving JEMPERLI, including Grade 2 (0.5%) and Grade 3 (0.7%). Adrenal insufficiency resulted in discontinuation in 1 (0.2%) patient and resolved in 4 of the 7 patients. Of the 4 patients in whom JEMPERLI was withheld for adrenal insufficiency, all reinitiated treatment with JEMPERLI. Systemic corticosteroids were required in 5 of the 7 patients with adrenal insufficiency.

Hypophysitis: JEMPERLI can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field

cuts. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity *[see Dosage and Administration (2.3)]*.

JEMPERLI in Combination with Carboplatin and Paclitaxel: Hypophysitis (Grade 3) occurred in 0.4% (1/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel. Systemic corticosteroids were required and the event resolved. JEMPERLI was withheld and the patient reinitiated treatment.

JEMPERLI as a Single Agent: Hypophysitis (Grade 2) occurred in 0.2% (1/605) of patients receiving JEMPERLI as a single agent. Systemic corticosteroids were required and the event did not resolve. JEMPERLI was withheld and the patient reinitiated treatment.

Thyroid Disorders: JEMPERLI can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate thyroid hormone replacement or medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity *[see Dosage and Administration (2.3)]*.

Thyroiditis: Thyroiditis occurred in 0.5% (3/605) of patients receiving JEMPERLI; all were Grade 2. Systemic corticosteroids were required in 1 of 3 patients and anti-thyroid therapy was required for 2 of 3 patients with thyroiditis. JEMPERLI was withheld for 1 patient and the patient reinitiated treatment. None of the events of thyroiditis resolved; there were no discontinuations of JEMPERLI due to thyroiditis.

Hypothyroidism: JEMPERLI in Combination with Carboplatin and Paclitaxel: Hypothyroidism occurred in 12% (28/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel, all of which were Grade 2. Hypothyroidism led to discontinuation of JEMPERLI in 1 patient and resolved in 18% (5/28) of patients. JEMPERLI was withheld for 5 patients and all reinitiated treatment with JEMPERLI. Thyroid hormone replacement was required for 26 of the 28 patients with hypothyroidism.

JEMPERLI as a Single Agent: Hypothyroidism occurred in 8% (46/605) of patients receiving JEMPERLI as a single agent, all of which were Grade 2. Hypothyroidism did not lead to discontinuation of JEMPERLI and resolved in 37% (17/46) of patients. JEMPERLI was withheld for 2 patients and both reinitiated treatment. Thyroid hormone replacement therapy was required for 45 of the 46 patients with hypothyroidism.

Hyperthyroidism: JEMPERLI in Combination with Carboplatin and Paclitaxel: Hyperthyroidism occurred in 3.3% (8/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel, including Grade 2 (2.9%) and Grade 3 (0.4%). Hyperthyroidism did not lead to discontinuation of JEMPERLI and resolved in 63% (5/8) of patients. JEMPERLI was withheld for 1 patient and the patient reinitiated treatment. Anti-thyroid therapy was required for

2 of the 8 patients while systemic corticosteroids were required for 1 of the 8 patients with hyperthyroidism.

JEMPERLI as a Single Agent: Hyperthyroidism occurred in 2.3% (14/605) of patients receiving JEMPERLI as a single agent, including Grade 2 (2.1%) and Grade 3 (0.2%). Hyperthyroidism did not lead to discontinuation of JEMPERLI and resolved in 71% (10/14) of the 14 patients. JEMPERLI was withheld for 2 patients and both reinitiated treatment. Anti-thyroid therapy was required for 10 of the 14 patients with hyperthyroidism.

Type 1 Diabetes Mellitus, Which Can Present with Diabetic Ketoacidosis: JEMPERLI can cause type 1 diabetes mellitus, which can present with diabetic ketoacidosis. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue JEMPERLI depending on severity *[see Dosage and Administration (2.3)]*.

JEMPERLI in Combination with Carboplatin and Paclitaxel: Type 1 diabetes mellitus (Grade 3) occurred in 0.4% (1/241) of patients receiving JEMPERLI in combination with carboplatin and paclitaxel. Type 1 diabetes mellitus led to withholding JEMPERLI; the patient reinitated treatment and required long-term insulin therapy.

JEMPERLI as a Single Agent: Type 1 diabetes mellitus occurred in 0.2% (1/605) of patients receiving JEMPERLI as a single agent, which was Grade 3. Type 1 diabetes mellitus did not result in treatment discontinuation and did not resolve.

Immune-Mediated Nephritis with Renal Dysfunction

JEMPERLI can cause immune-mediated nephritis, which can be fatal. Nephritis, including tubulointerstitial nephritis, occurred in 0.5% (3/605) of patients receiving JEMPERLI; all were Grade 2. Nephritis led to discontinuation of JEMPERLI in 1 (0.2%) patient and resolved in all patients. JEMPERLI was withheld for 1 patient and the patient reinitiated treatment. Systemic corticosteroids were required in 2 of the 3 patients experiencing nephritis.

Immune-Mediated Dermatologic Adverse Reactions

JEMPERLI can cause immune-mediated rash or dermatitis. Bullous and exfoliative dermatitis, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS), have occurred with PD-1/PD-L1–blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue JEMPERLI depending on severity *[see Dosage and Administration (2.3)]*.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred in <1% of the 605 patients treated with JEMPERLI or were reported with the use of other PD-1/PD-L1–blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

Nervous System: Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy.

Cardiac/Vascular: Myocarditis, pericarditis, vasculitis.

Ocular: Uveitis, iritis, other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

Gastrointestinal: Pancreatitis, including increases in serum amylase and lipase levels, gastritis, duodenitis.

Musculoskeletal and Connective Tissue: Myositis/polymyositis, rhabdomyolysis and associated sequelae including renal failure, arthritis, polymyalgia rheumatica.

Endocrine: Hypoparathyroidism.

Other (Hematologic/Immune): Autoimmune hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenia, solid organ transplant rejection.

5.2 Infusion-Related Reactions

Severe or life-threatening infusion-related reactions have been reported with PD-1/PD-L1–blocking antibodies. Severe infusion-related reactions (Grade 3) occurred in 0.2% (1/605) of patients receiving JEMPERLI. All patients recovered from the infusion-related reactions.

Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion or permanently discontinue JEMPERLI based on severity of reaction *[see Dosage and Administration (2.3)]*.

5.3 Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1–blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1–blocking antibody prior to or after an allogeneic HSCT.

5.4 Embryo-Fetal Toxicity

Based on its mechanism of action, JEMPERLI can cause fetal harm when administered to a pregnant woman. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus, resulting in fetal death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Severe and fatal immune-mediated adverse reactions *[see Warnings and Precautions (5.1)]*
- Infusion-related reactions *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety population described in the *Warnings and Precautions* for use of JEMPERLI in combination with carboplatin and paclitaxel was evaluated in 241 patients with primary advanced or recurrent endometrial cancer (EC) in the randomized, double-blind, active-controlled RUBY trial.

Additionally, the pooled safety population described in *Warnings and Precautions* reflects exposure to JEMPERLI as a single-agent in 605 patients with advanced or recurrent solid tumors in the non-randomized, open-label, multicohort GARNET trial that enrolled 314 patients with EC and 291 patients with other solid tumors. JEMPERLI was administered intravenously at doses of 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks until disease progression or unacceptable toxicity. Among the 605 patients, 32% were exposed for >1 year and 19% were exposed for >2 years.

Mismatch Repair Deficient (dMMR) or Microsatellite Instability-High (MSI-H) Primary Advanced or Recurrent EC: JEMPERLI In Combination with Carboplatin and Paclitaxel

The safety of JEMPERLI in patients with primary advanced or recurrent dMMR/MSI-H EC was evaluated in RUBY *[see Clinical Studies (14.1)]*. Patients received JEMPERLI 500 mg (n = 52) or placebo (n = 65) in combination with carboplatin and paclitaxel every 3 weeks for 6 doses followed by JEMPERLI 1,000 mg or placebo every 6 weeks until disease progression or unacceptable toxicity. Among the 52 patients, 56% were exposed for >1 year and 31% were exposed for >2 years.

Serious adverse reactions occurred in 13% of patients receiving JEMPERLI in combination with carboplatin and paclitaxel; the most common serious adverse reaction was sepsis, including urosepsis (6%). Fatal adverse reactions occurred in 6% of patients receiving JEMPERLI including septic shock (3.8%), and myelosuppression (1.9%).

In patients receiving JEMPERLI in combination with carboplatin and paclitaxel, JEMPERLI was permanently discontinued due to adverse reactions in 8 patients (15%) including 1 case (1.9%) each of rash maculo-papular, fatigue, general physical health deterioration, acute kidney injury, infusion-related reaction, keratitis, muscular weakness, and myelosuppression.

Dosage interruptions due to an adverse reaction occurred in 35% of patients who received JEMPERLI in combination with carboplatin and paclitaxel. Adverse reactions that required dosage interruption in ≥5% of patients who received JEMPERLI in combination with carboplatin and paclitaxel were anemia, thrombocytopenia, platelet count decreased, peripheral neuropathy, and rash.

The most common adverse reactions, including laboratory abnormalities (≥20%), were decreased hemoglobin, decreased white blood cell count, decreased platelets, decreased lymphocytes, increased glucose, increased alkaline phosphatase, decreased neutrophils, rash, diarrhea, increased aspartate aminotransferase, increased alanine aminotransferase, decreased sodium, hypothyroidism, and hypertension.

Table 3 summarizes the adverse reactions that occurred in ≥10% of patients with primary advanced or recurrent dMMR/MSI-H EC receiving JEMPERLI in combination with carboplatin and paclitaxel in RUBY.

Table 3. Adverse Reactions (≥10%) in Patients with dMMR/MSI-H Endometrial Cancer Who Received JEMPERLI with Carboplatin and Paclitaxel in RUBY

Adverse Reaction	JEMPERLI with Carboplatin and Paclitaxel N = 52		Placebo with Carboplatin and Paclitaxel N = 65	
	All Grades %	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Skin and subcutaneous tissue				
Rash[a]	42	8	20	0
Dry skin	12	0	8	0
Gastrointestinal disorders				
Diarrhea	40	1.9	31	0
Endocrine Disorders				
Hypothyroidism[b]	23	0	6	0
Vascular disorders				
Hypertension	21	10	11	6
General and administration site				
Pyrexia	14	0	1.5	0

dMMR = Mismatch Repair Deficient; MSI-H = Microsatellite Instability-High.
Graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

[a] Includes rash, rash maculo-papular, palmar-plantar erythrodysesthesia syndrome, rash pustular, skin exfoliation, vulvovaginal rash, and dermatitis bullous.

[b] Includes hypothyroidism and immune-mediated hypothyroidism.

Clinically relevant adverse reactions in <10% of patients with primary advanced or recurrent dMMR/MSI-H EC who received JEMPERLI in combination with carboplatin and paclitaxel included:

Endocrine Disorders: Hyperthyroidism, thyroiditis.

Eye Disorders: Keratitis.

Gastrointestinal Disorders: Colitis, pancreatitis.

Metabolism and Nutrition Disorders: Type 1 diabetes mellitus.

Nervous System Disorders: Encephalopathy.

Table 4 summarizes the laboratory abnormalities in patients with primary advanced or recurrent dMMR/MSI-H EC receiving JEMPERLI in combination with carboplatin and paclitaxel in RUBY.

Table 4. Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 Occurring in ≥10% of Patients with dMMR/MSI-H Endometrial Cancer Receiving JEMPERLI with Carboplatin and Paclitaxel in RUBY

	JEMPERLI with Carboplatin and Paclitaxel N = 52		Placebo with Carboplatin and Paclitaxel N = 65	
Laboratory Test	**All Grades[a] %**	**Grade 3 or 4[a] %**	**All Grades[a] %**	**Grade 3 or 4[a] %**
Hematology				
Decreased hemoglobin	77	17	86	25
Decreased white blood cell count	73	15	68	14
Decreased platelets	54	10	57	12
Decreased lymphocytes	52	13	51	25
Decreased neutrophils	46	21	58	23
Chemistry				
Increased glucose	50	13	54	11
Increased alkaline phosphatase[b]	48	6	26	0
Increased aspartate aminotransferase[b]	40	8	25	0
Increased alanine aminotransferase[b]	40	4	26	0
Electrolytes				
Decreased sodium	29	12	26	5

dMMR = Mismatch Repair Deficient; MSI-H = Microsatellite Instability-High.

[a] Consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality.

[b] Increased alkaline phosphatase, increased aspartate aminotransferase and increased alanine aminotransferase worsened from baseline to Grade 3 or 4 in <10% of patients.

dMMR Recurrent or Advanced EC: JEMPERLI as a Single Agent

The safety of JEMPERLI was evaluated in GARNET in 150 patients with advanced or recurrent dMMR EC who received at least 1 dose of JEMPERLI *[see Clinical Studies (14.1)]*. Patients received JEMPERLI 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks as an intravenous infusion until disease progression or unacceptable toxicity. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Among patients receiving JEMPERLI, 41% were exposed for >1 year and 23% were exposed for >2 years.

A fatal adverse reaction occurred in one patient (0.7%) who received JEMPERLI, due to concurrent immune-mediated encephalitis and urinary tract infection.

Serious adverse reactions occurred in 38% of patients receiving JEMPERLI. Serious adverse reactions in >2% of patients included urinary tract infection (4%), sepsis (3.3%), acute kidney injury (2.7%), and abdominal pain (2.7%).

JEMPERLI was permanently discontinued due to adverse reactions in 15 (10%) patients, including increased transaminases, sepsis, bronchitis, pneumonitis, rash, pruritus, pancreatitis, encephalitis, and nephritis. Dosage interruptions due to an adverse reaction occurred in 28% of patients who received JEMPERLI. Adverse reactions that required dosage interruption in >1% of patients who received JEMPERLI were anemia, diarrhea, asthenia, colitis, sepsis, and pneumonitis.

The most common adverse reactions (≥20%) were fatigue/asthenia, anemia, nausea, diarrhea, constipation, vomiting, and rash.

Table 5 summarizes the adverse reactions that occurred in ≥10% of patients with dMMR EC on JEMPERLI in GARNET.

Table 5. Adverse Reactions (≥10%) in Patients with dMMR Endometrial Cancer Who Received JEMPERLI in GARNET

Adverse Reaction	JEMPERLI N = 150	
	All Grades %	Grade 3 or 4 %
General and administration site		
Fatigue[a]	49	3.3
Pyrexia	13	0
Blood and lymphatic system		
Anemia[b]	35	18
Gastrointestinal		
Nausea	32	0.7
Diarrhea	29	2.7
Constipation	23	0.7
Vomiting	23	0.7
Skin and subcutaneous tissue		
Rash[c]	21	0
Pruritus	19	1.3
Infections		
Urinary tract infection	19	4

Metabolism and nutrition Decreased appetite	15	0
Respiratory, thoracic, and mediastinal Cough	15	0
Musculoskeletal and connective tissue Myalgia	10	0
Investigations Increased transaminases[d]	13	4
Endocrine Disorders Hypothyroidism	11	0

dMMR = Mismatch Repair Deficient.
Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.
[a] Includes fatigue and asthenia.
[b] Includes anemia, decreased hemoglobin, iron deficiency, and iron deficiency anemia.
[c] Includes rash, rash maculo-papular, rash pruritic, erythema, and pemphigoid.
[d] Includes increased alanine aminotransferase, increased aspartate aminotransferase, increased transaminases, and hypertransaminasemia.

Clinically relevant adverse reactions in <10% of patients who received JEMPERLI included:

Endocrine Disorders: Hyperthyroidism, adrenal insufficiency, hypophysitis.

Eye Disorders: Iridocyclitis, uveitis.

Gastrointestinal Disorders: Colitis, pancreatitis, enterocolitis, gastritis.

General Disorders and Administration Site Conditions: Chills.

Musculoskeletal and Connective Tissue Disorders: Immune-mediated myositis, immune-mediated arthritis.

Nervous System Disorders: Encephalitis.

Renal and Urinary Disorders: Nephritis.

Respiratory, Thoracic, and Mediastinal Disorders: Pneumonitis, interstitial lung disease.

Table 6 summarizes laboratory abnormalities worsening from baseline to Grade 3 or 4 in ≥1% of patients with dMMR EC on JEMPERLI in GARNET.

Table 6. Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 Occurring in ≥1% of Patients with dMMR Endometrial Cancer Receiving JEMPERLI in GARNET

Laboratory Test	JEMPERLI N = 150	
	All Grades[a] %	Grade 3 or 4[a] %
Hematology		
Decreased lymphocytes	46	15
Decreased leukocytes	21	2
Decreased neutrophils	17	2.7
Chemistry		
Decreased albumin	36	2.7
Increased creatinine	33	3.4
Increased alkaline phosphatase	31	2.7
Increased aspartate aminotransferase	31	2
Increased alanine aminotransferase	25	4.7
Electrolytes		
Decreased sodium	29	5
Decreased magnesium	28	2
Decreased potassium	22	2
Increased calcium	8	2

[a] Consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality.

dMMR Recurrent or Advanced Solid Tumors

The safety of JEMPERLI was investigated in 267 patients with recurrent or advanced dMMR solid tumors enrolled in GARNET *[see Clinical Studies (14.2)]*. Patients received JEMPERLI 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks as an intravenous infusion until disease progression or unacceptable toxicity. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. The median duration of exposure to JEMPERLI was 25 weeks (range: 1 to 139 weeks).

Serious adverse reactions occurred in 34% of patients receiving JEMPERLI. Serious adverse reactions in >2% of patients included abdominal pain (3.7%), sepsis (2.6%), and acute kidney injury (2.2%). Fatal adverse reaction occurred in 1 patient who received JEMPERLI due to respiratory failure.

JEMPERLI was permanently discontinued due to adverse reactions in 9% patients; the most common adverse reaction (≥1%) leading to discontinuation was increased alanine aminotransferase (1.1%).

Dosage interruptions due to an adverse reaction occurred in 23% of patients who received JEMPERLI. Adverse reactions that required dosage interruption in ≥1% of patients who received JEMPERLI were anemia, pneumonitis, diarrhea, adrenal insufficiency, increased alanine aminotransferase, and increased aspartate aminotransferase.

The most common adverse reactions (≥20%) were fatigue/asthenia, anemia, diarrhea, and nausea.

Table 7 summarizes the adverse reactions that occurred in ≥10% of patients with dMMR recurrent or advanced solid tumors in GARNET.

Table 7. Adverse Reactions (≥10%) in Patients with dMMR Recurrent or Advanced Solid Tumors in GARNET

Adverse Reaction	JEMPERLI N = 267	
	All Grades %	Grade 3 or 4 %
General and administration site		
Fatigue[a]	42	3.4
Pyrexia	12	0
Blood and lymphatic system		
Anemia[b]	30	11
Gastrointestinal		
Diarrhea	25	1.5
Nausea	22	0.4
Vomiting	17	1.5
Constipation	16	0.4
Skin and subcutaneous tissue		
Pruritus	15	0.4
Rash[c]	14	0.4
Respiratory, thoracic, and mediastinal		
Cough	13	0
Metabolism and nutrition		
Decreased appetite	12	0.4
Investigations		
Increased transaminases[d]	12	3

dMMR = Mismatch Repair Deficient.

Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

[a] Includes fatigue and asthenia.

[b] Includes anemia, decreased hemoglobin, iron deficiency, and iron deficiency anemia.

[c] Includes rash, rash maculopapular, rash macular, rash erythematous, rash papular, erythema, toxic skin eruption, and pemphigoid.

[d] Includes increased alanine aminotransferase, increased aspartate aminotransferase, increased transaminases, and hypertransaminasemia.

Clinically relevant adverse reactions in <10% of patients who received JEMPERLI included:

Endocrine Disorders: Hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, autoimmune thyroiditis.

Eye Disorders: Uveitis.

Gastrointestinal Disorders: Colitis, enterocolitis, enterocolitis hemorrhage, pancreatitis, acute pancreatitis.

General Disorders and Administration Site Conditions: Chills.

Injury, Poisoning, and Procedural Complications: Infusion related reaction.

Hepatobiliary Disorders: Hepatocellular injury.

Musculoskeletal and Connective Tissue Disorders: Myalgia.

Renal and Urinary Disorders: Nephritis, tubulointerstitial nephritis.

Respiratory, Thoracic, and Mediastinal Disorders: Pneumonitis, interstitial lung disease.

Table 8 summarizes laboratory abnormalities worsening from baseline to Grade 3 or 4 in ≥1% of patients with dMMR recurrent or advanced solid tumors in GARNET.

Table 8. Laboratory Abnormalities that Worsened from Baseline to Grade 3 or 4 Occurring in ≥1% of Patients with dMMR Recurrent or Advanced Solid Tumors in GARNET

Laboratory Test	JEMPERLI N = 267	
	All Grades[a] %	Grade 3 or 4[a] %
Hematology		
Decreased lymphocytes	33	7
Decreased leukocytes	18	1.1
Decreased neutrophils	12	1.5
Chemistry		
Decreased albumin	26	2.2
Increased alkaline phosphatase	26	3.4
Increased aspartate aminotransferase	26	1.5
Increased alanine aminotransferase	22	1.9
Increased creatinine	21	1.1
Increased total bilirubin	7	1.5
Electrolytes		
Decreased sodium	21	4.9
Decreased magnesium	16	1.1
Decreased potassium	14	1.1
Increased potassium	14	1.1
Increased calcium	6	1.1
Increased magnesium	4.1	1.5
Decreased calcium	2.6	1.5

dMMR = Mismatch Repair Deficient.

[a] Consists of new onset of laboratory abnormality or worsening of baseline laboratory abnormality.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, JEMPERLI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data on the use of JEMPERLI in pregnant women. Animal studies have demonstrated that inhibition of the PD-1/PD-L1 pathway can lead to increased risk of immune-mediated rejection of the developing fetus resulting in fetal death *(see Data)*. Human IgG4 immunoglobulins (IgG4) are known to

cross the placental barrier; therefore, dostarlimab-gxly has the potential to be transmitted from the mother to the developing fetus. Advise women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: Animal reproduction studies have not been conducted with JEMPERLI to evaluate its effect on reproduction and fetal development. A central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining maternal immune tolerance to the fetus. In murine models of pregnancy, blockade of PD-L1 signaling has been shown to disrupt tolerance to the fetus and to result in an increase in fetal loss; therefore, potential risks of administering JEMPERLI during pregnancy include increased rates of abortion or stillbirth. As reported in the literature, there were no malformations related to the blockade of PD-1/PD-L1 signaling in the offspring of these animals; however, immune-mediated disorders occurred in PD-1 and PD-L1 knockout mice. Based on its mechanism of action, fetal exposure to dostarlimab-gxly may increase the risk of developing immune-mediated disorders or altering the normal immune response.

8.2 Lactation

Risk Summary

There is no information regarding the presence of dostarlimab-gxly in human milk or its effects on the breastfed child or on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to JEMPERLI are unknown. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 4 months after the last dose of JEMPERLI.

8.3 Females and Males of Reproductive Potential

JEMPERLI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating JEMPERLI *[see Use in Specific Populations (8.1)]*.

Contraception

Females: Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after the last dose.

8.4 Pediatric Use

The safety and efficacy of JEMPERLI have not been established in pediatric patients.

8.5 Geriatric Use

In Combination with Carboplatin and Paclitaxel

Of the 241 patients treated with JEMPERLI in RUBY, 52.3% were younger than 65 years, 36.5% were aged 65 through 75 years, and 11.2% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

As a Single Agent

Of the 605 patients treated with JEMPERLI in GARNET, 51.6% were younger than 65 years, 36.9% were aged 65 through 75 years, and 11.5% were 75 years or older. No overall differences in safety or effectiveness were observed between these patients and younger patients.

11 DESCRIPTION

Dostarlimab-gxly is a programmed death receptor-1 (PD-1)–blocking IgG_4 humanized monoclonal antibody. Dostarlimab-gxly is produced in Chinese hamster ovary cells and has a calculated molecular weight of about 144 kDa.

JEMPERLI (dostarlimab-gxly) injection is a sterile, clear to slightly opalescent, colorless to yellow solution essentially free from visible particles. It is supplied as single-dose vials.

Each vial contains 500 mg of JEMPERLI in 10 mL of solution with a pH of 6. Each mL of solution contains 50 mg of dostarlimab-gxly, citric acid monohydrate (0.48 mg), L-arginine hydrochloride (21.07 mg), polysorbate 80 (0.2 mg), sodium chloride (1.81 mg), trisodium citrate dihydrate (6.68 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors, and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Dostarlimab-gxly is a humanized monoclonal antibody of the IgG4 isotype that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

12.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for safety and effectiveness of dostarlimab-gxly have not been fully characterized.

Dostarlimab-gxly provides sustained target engagement as measured by direct PD-1 binding and stimulation of IL-2 production throughout the dosing interval at the recommended dose.

12.3 Pharmacokinetics

The pharmacokinetics of dostarlimab-gxly as a single agent and in combination with carboplatin and paclitaxel were evaluated using population PK analysis in patients with various solid tumors, including 546 patients with EC. Mean C_{max}, $AUC_{0\text{-}inf}$, and $AUC_{0\text{-}tau}$ increased proportionally over the dose range of 1 to 10 mg/kg. The Cycle 1 mean (coefficient of variation [%CV]) C_{max} and $AUC_{0\text{-}tau}$ of dostarlimab-gxly as a single agent were 171 mcg/mL (20%) and 35,730 mcg*h/mL (20%) at the dosage of 500 mg once every 3 weeks and 309 mcg/mL (31%) and 95,820 mcg*h/mL (29%) at the dosage of 1,000 mg every 6 weeks, respectively. The exposures of dostarlimab-gxly administered in combination with carboplatin and paclitaxel and as a single agent were comparable.

Distribution

The mean (%CV) volume of distribution of dostarlimab-gxly at steady state is approximately 5.8 L (15%).

Elimination

The mean terminal elimination half-life of dostarlimab-gxly at steady state is 23.5 days and its mean (%CV) clearance is 0.007 L/h (30%) at steady state.

Metabolism: Dostarlimab-gxly is expected to be metabolized into small peptides and amino acids by catabolic pathways.

Specific Populations

No clinically significant differences in the pharmacokinetics of dostarlimab-gxly were observed based on age (24 to 86 years), sex, race/ethnicity (75% White, 2% Asian, and 5% African American), tumor type, and renal impairment based on the estimated creatinine clearance and mild [total bilirubin (TB) > ULN to 1.5 times ULN or aspartate aminotransferase (AST) > ULN] to moderate (TB > 1.5 to 3 times ULN and any AST) hepatic impairment.

Drug Interaction Studies

Dostarlimab exposure when administered in combination with carboplatin and paclitaxel was comparable to single agent exposure and there was no evidence to suggest a clinically relevant change of dostarlimab-gxly clearance over time in patients with recurrent or advanced endometrial cancer.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of JEMPERLI or of other dostarlimab-gxly products.

The immunogenicity of dostarlimab-gxly was evaluated in RUBY at a dose of 500 mg every 3 weeks for 6 doses followed by 1,000 mg every 6 weeks thereafter; there was no formation of treatment-emergent anti-drug antibodies and treatment-emergent neutralizing antibodies in 225 patients receiving JEMPERLI at the recommended dosage.

The immunogenicity of dostarlimab-gxly was evaluated in GARNET at a dose of 500 mg every 3 weeks for 4 doses followed by 1,000 mg every 6 weeks thereafter. Treatment-emergent anti-drug antibodies against dostarlimab-gxly were detected in 2.1% (8/384) of patients who received JEMPERLI at the recommended dosage. Neutralizing antibodies were detected in 1% (4/384) of patients.

Because of the small number of patients who developed ADAs, the effect of immunogenicity on the efficacy and safety of dostarlimab-gxly is inconclusive.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of dostarlimab-gxly for carcinogenicity or genotoxicity.

Fertility studies have not been conducted with dostarlimab-gxly. In 1- and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, many animals in these studies were not sexually mature.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-L1/PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. *Mycobacterium tuberculosis*-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 blockade using a primate anti-PD-1 antibody was also shown to exacerbate *M. tuberculosis* infection in rhesus macaques. PD-L1 and PD-1 knockout mice and mice receiving PD-L1–blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

14 CLINICAL STUDIES

14.1 Endometrial Cancer

<u>In Combination with Carboplatin and Paclitaxel for the Treatment of dMMR or MSI-H Primary Advanced or Recurrent Endometrial Cancer</u>

The efficacy of JEMPERLI in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent, was evaluated in RUBY (NCT03981796), a randomized, multicenter, double-blind, placebo-controlled trial. Efficacy was assessed in a pre-specified subgroup of 122 patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer.

The identification of dMMR/MSI-H tumor status was prospectively determined based on local testing assays (IHC, PCR or NGS), or central testing (IHC) using the VENTANA MMR RxDx Panel when no local result was available.

The trial enrolled patients with primary Stage III or Stage IV disease (per FIGO Staging Classification), including Stage IIIA to IIIC1 patients with evaluable or measurable disease, Stage IIIC1 patients with carcinosarcoma, clear cell, serous, or mixed histology regardless of presence of measurable disease, Stage IIIC2 or Stage IV disease regardless of presence of measurable disease. The trial also enrolled patients with first recurrent disease with a low potential for cure by radiation therapy or surgery alone or in combination, including patients who were naïve to systemic anticancer therapy or who had received prior neo-adjuvant/adjuvant systemic anticancer therapy and had a recurrence or disease progression ≥6 months after completing treatment.

Patients were randomized (1:1) to one of the following treatments arms:

- JEMPERLI 500 mg, carboplatin AUC 5 mg/mL/min, paclitaxel 175 mg/m^2 intravenously on Day 1 of each 21-day cycle for 6 doses followed by JEMPERLI 1,000 mg intravenously every 6 weeks. JEMPERLI was administered prior to chemotherapy on Day 1.
- Placebo, carboplatin AUC 5 mg/mL/min, paclitaxel 175 mg/m^2 intravenously on Day 1 of each 21-day cycle for 6 doses followed by placebo intravenously every 6 weeks.

Randomization was stratified by MMR/MSI status, prior external pelvic radiotherapy, and disease status (recurrent, primary Stage III, or primary Stage IV). Treatment with JEMPERLI continued until disease progression, unacceptable toxicity, or a maximum of 3 years. Administration of JEMPERLI was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator.

Assessment of tumor status was performed every 6 weeks through Week 25, every 9 weeks through Week 52 and every 12 weeks thereafter. In the dMMR/MSI-H subgroup, the major efficacy outcome was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST v 1.1). Additional efficacy outcome measures included overall survival (OS), Objective Response Rate (ORR), and Duration of Response (DOR). The major efficacy outcomes for the overall population were investigator-assessed PFS using RECIST v 1.1 and OS, with additional efficacy outcome measures of ORR and DOR.

Among the 122 patients evaluated, the baseline characteristics were: median age 65 years (50% aged 65 years or older); 83% White, 9% Black, 3% Asian; Eastern Cooperative Oncology Group (ECOG) Performance Status 0 (57%) or 1 (43%); and primary stage III (22%); primary stage IV (28%) and recurrent EC (50%).

Efficacy results are presented in Table 9 and Figure 1. Overall survival data in this subpopulation were immature with 27% deaths.

Table 9. Efficacy Results of dMMR/MSI-H Endometrial Cancer Population in RUBY

Endpoint	JEMPERLI with Carboplatin and Paclitaxel N = 60	Placebo with Carboplatin and Paclitaxel N = 62
Progression-Free Survival (PFS)		
Number (%) of patients with event	23 (38.3)	47 (75.8)
Median in months (95% CI)[a]	30.3 (11.8, NR)	7.7 (5.6, 9.7)
Hazard ratio (95% CI)[b]	0.29 (0.17, 0.50)	
p-value[a]	<0.0001	
Objective Response Rate (ORR)[c]		
Number of participants with measurable disease at baseline (n)	42	45
ORR, n (%) (95% CI)	31 (73.8) (58.0, 86.1)	28 (62.2) (46.5, 76.2)
Complete response rate, n (%)	11 (26.2)	5 (11.1)
Partial response rate, n (%)	20 (47.6)	23 (51.1)
Duration of Response (DOR)[c, d]		
Number of Responders	31	28
Median in months (range)	NR (3.4, 28.3+)	5.4 (2.7, 27.2+)
Patients with duration >12 months, n (%)	19 (61.3)	4 (14.3)

dMMR = Mismatch Repair Deficient; MSI = Microsatellite Instability-High; NR = Not Reached; + = ongoing at last assessment.

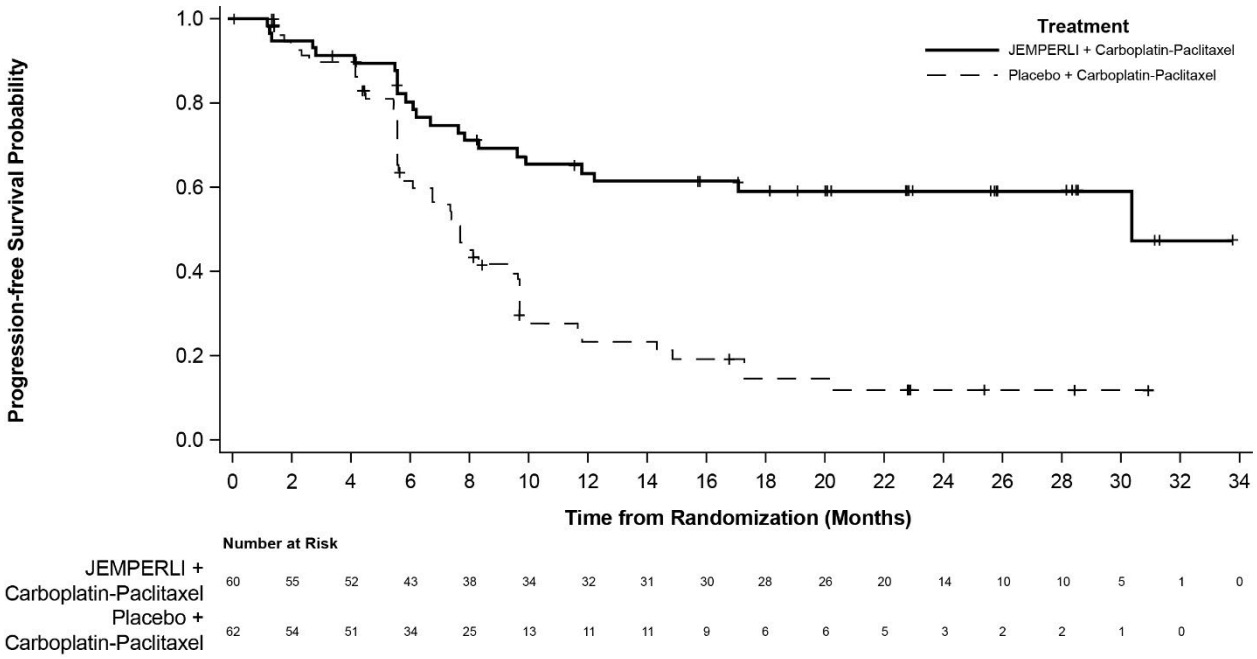
[a] One-sided p-value based on stratified log-rank test was statistically significant.

[b] Based on stratified Cox regression model.

[c] Confirmed responses as assessed by investigator according to RECIST v1.1.

[d] For patients with a partial or complete response.

Figure 1. Kaplan-Meier Curve for Progression-free Survival in patients with dMMR/MSI-H Endometrial Cancer in RUBY



As a Single Agent for the Treatment of dMMR Recurrent or Advanced Endometrial Cancer

The efficacy of JEMPERLI as a single agent was evaluated in the GARNET trial (NCT02715284), a multicenter, multicohort, open-label trial conducted in patients with advanced solid tumors. The efficacy population consisted of a cohort of 141 patients with dMMR recurrent or advanced EC who had progressed on or after treatment with a platinum-containing regimen. Patients with prior treatment with PD-1/PD-L1–blocking antibodies or other immune checkpoint inhibitor therapy and patients with autoimmune disease that required systemic therapy with immunosuppressant agents within 2 years were excluded from the trial.

Patients received JEMPERLI 500 mg intravenously every 3 weeks for 4 doses followed by 1,000 mg intravenously every 6 weeks. Treatment continued until disease progression or unacceptable toxicity. The major efficacy outcome measures were ORR and DOR as assessed by BICR according to the RECIST v 1.1.

The baseline characteristics were: median age 65 years (53% aged 65 years or older); 77% White, 4% Asian, 3% Black, 4% Hispanic or Latino; and Eastern Cooperative Oncology Group Performance Status 0 (38%) or 1 (62%).

The most common histology seen was endometrioid carcinoma type 1 (65%), Grade 3 endometrioid (15%), followed by serous (5%), mixed (5%) and undifferentiated (2.8%).

All patients with dMMR EC had received prior anticancer treatment, with 89% of patients receiving prior anticancer surgery and 71% receiving prior anticancer radiotherapy. Sixty-three

percent of patients had one prior line of anticancer treatment and 37% had two or more prior lines. Forty-eight patients (34%) received treatment only in the neoadjuvant or adjuvant setting before participating in the study.

The dMMR tumor status was retrospectively confirmed using the VENTANA MMR RxDx Panel assay.

Efficacy results are presented in Table 10.

Table 10. Efficacy Results of dMMR Endometrial Cancer Population in GARNET

Endpoint	JEMPERLI N = 141
Overall response rate[a]	
ORR (95% CI)	45.4% (37.0, 54.0)
Complete response rate	15.6%
Partial response rate	29.8%
Duration of response[b]	
Median in months	Not reached
(range)	(1.2+, 52.8+)
Patients with duration ≥12 months	85.9%
Patients with duration >24 months	54.7%

dMMR = Mismatch Repair Deficient; + = ongoing at last assessment.

[a] Based on confirmed response by blinded independent central review.

[b] Median follow up for duration of response was 27.9 months measured from time of first response.

14.2 Mismatch Repair Deficient Recurrent or Advanced Solid Tumors

The efficacy of JEMPERLI as a single agent was evaluated in GARNET (NCT02715284), a non-randomized, multicenter, open-label, multicohort trial. The efficacy population consisted of a cohort of 209 patients with dMMR recurrent or advanced solid tumors who progressed following systemic therapy and had no satisfactory alternative treatment options. Patients with dMMR endometrial cancer must have progressed on or after treatment with a platinum-containing regimen. Patients with dMMR colorectal cancer must have progressed after or been intolerant to a fluoropyrimidine, oxaliplatin, and irinotecan.

Patients with prior treatment with PD-1/PD-L1–blocking antibodies or other immune checkpoint inhibitor therapy and patients with autoimmune disease that required systemic therapy with immunosuppressant agents within 2 years were excluded from the trial.

Patients received JEMPERLI 500 mg intravenously every 3 weeks for 4 doses followed by 1,000 mg intravenously every 6 weeks. Treatment continued until disease progression or unacceptable toxicity.

The major efficacy outcome measures were ORR and DOR as determined by a BICR according to RECIST v 1.1.

The baseline characteristics were female (77%); median age 63 years (47% aged 65 years or older); 63% White, 3% Asian, 2% Black; and Eastern Cooperative Oncology Group Performance Status 0 (39%) or 1 (61%).

At time of trial entry, 97.2% of patients (103/106) with non-endometrial dMMR solid tumors had Stage IV disease, and 68.0% (70/103) of patients with dMMR endometrial tumors had FIGO Stage IV disease.

Approximately 43% of patients had received 1 prior line of systemic anticancer treatment, 36% had received 2 prior lines, and 21% had received 3 or more prior lines.

The dMMR tumor status was retrospectively confirmed using the VENTANA MMR RxDx Panel assay.

Efficacy results are presented in Tables 11 and 12.

Table 11. Efficacy Results of dMMR Recurrent or Advanced Solid Tumors in GARNET

Endpoint	JEMPERLI N = 209
Overall response rate[a]	
ORR (95% CI)	41.6% (34.9, 48.6)
Complete response rate	9.1%
Partial response rate	32.5%
Duration of response[b]	
Median in months	34.7
(range)	2.6, 35.8+
Patients with duration ≥6 months	95.4%

dMMR = Mismatch Repair Deficient; + = ongoing at last assessment.

[a] Based on confirmed response by blinded independent central review.

[b] Median follow-up for duration of response was 17.5 months measured from time of first response.

Table 12. Efficacy Results of dMMR Tumor Types in GARNET

Tumor Type	Patients N	ORR (per RECIST v 1.1) n (%)	ORR (per RECIST v 1.1) 95% CI[a]	DOR Range (months)
EC	103	46 (44.7)	(34.9, 54.8)	2.6, 35.8+
non-EC	106	41 (38.7)	(29.4, 48.6)	5.6, 30.1+
CRC	69	25 (36.2)	(25.0, 48.7)	5.6, 30.1+
Small intestinal cancer	12	4 (33.3)	(9.9, 65.1)	11.1+, 28.0+
Gastric cancers	8	3 (37.5)	(8.5, 75.5)	8.4+, 17.5
Pancreatic carcinoma	4	0 (0.0)	(0.0, 60.2)	NA
Biliary neoplasm	2	CR, CR	NA	8.4+, 13.5+
Liver cancer	2	PR, PD	NA	13.8+
Ovarian cancer	2	PR, SD	NA	25.1+
Adrenal cortical	1	PR	NA	19.5+
Breast cancer	1	CR	NA	16.8+
Esophageal cancer	1	PD	NA	NA
Genital neoplasm malignant female	1	PR	NA	22.2+
Pleural	1	PR	NA	15.2+
Renal cell carcinoma	1	SD	NA	NA
Unknown origin	1	PR	NA	20.4+

dMMR = Mismatch Repair Deficient; ORR = Overall Response Rate; DOR = Duration of Response; EC = endometrial cancer; CRC = colorectal cancer; PR = partial response; PD = progressive disease; CR = complete response; SD = stable disease; + = ongoing at last assessment.

[a] Exact, 2-sided 95% CI for binomial proportion.

16 HOW SUPPLIED/STORAGE AND HANDLING

JEMPERLI (dostarlimab-gxly) injection is a clear to slightly opalescent, colorless to yellow solution supplied in a carton containing one 500 mg/10 mL (50 mg/mL), single-dose vial (NDC 0173-0898-03).

Store vial refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions

Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid or other treatment and interruption or discontinuation of JEMPERLI. These reactions may include:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.1)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.1)]*.
- Immune-mediated endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypothyroidism, hyperthyroidism, thyroiditis, adrenal insufficiency, hypophysitis, or type 1 diabetes mellitus *[see Warnings and Precautions (5.1)]*.
- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.1)]*.
- Severe skin reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS, TEN, or DRESS *[see Warnings and Precautions (5.1)]*.
- Other immune-mediated adverse reactions:
  - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new signs or symptoms *[see Warnings and Precautions (5.1)]*.
  - Advise patients of the risk of solid organ transplant rejection and to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection [*see Warnings and Precautions (5.1)*].

Infusion-Related Reactions

- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT

- Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications *[see Warnings and Precautions (5.3)]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.
- Advise females of reproductive potential to use effective contraception during treatment with JEMPERLI and for 4 months after the last dose *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1, 8.3)]*.

Lactation

- Advise women not to breastfeed during treatment with JEMPERLI and for 4 months after the last dose *[see Use in Specific Populations (8.2)]*.

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GSK
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JMP:XPI

PHARMACIST DETACH HERE AND GIVE LEAFLET TO PATIENT

MEDICATION GUIDE

JEMPERLI (jem-PER-lee)

(dostarlimab-gxly)

injection

What is the most important information I should know about JEMPERLI?

JEMPERLI is a medicine that may treat certain cancers by working with your immune system. JEMPERLI can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or life-threatening and can lead to death. You can have more than one of these problems at the same time. These problems may happen anytime during treatment or even after your treatment has ended.

Call or see your healthcare provider right away if you develop any new or worsening signs or symptoms, including:

Lung problems.

- cough
- shortness of breath
- chest pain

Intestinal problems.

- diarrhea or more bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdomen) pain or tenderness

Liver problems.

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- dark urine (tea colored)
- bleeding or bruising more easily than usual

Hormone gland problems.

- headaches that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heartbeat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems.

- change in the amount or color of your urine
- blood in your urine
- swelling in your ankles
- loss of appetite

Skin problems.

- rash
- itching
- skin blistering or peeling
- swollen lymph nodes
- painful sores or ulcers in your mouth or in your nose, throat, or genital area
- fever or flu-like symptoms

Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with JEMPERLI. Call or see your healthcare provider right away for any new or worse signs or symptoms.

- chest pain, irregular heartbeat, shortness of breath, swelling of ankles
- confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- persistent or severe muscle pain or weakness, muscle cramps
- low red blood cells, bruising

Infusion reactions that can sometimes be severe or life-threatening. Signs and symptoms of infusion reactions may include:

- chills or shaking
- itching or rash
- flushing
- shortness of breath or wheezing
- dizziness
- feel like passing out
- fever
- back or neck pain

Rejection of a transplanted organ. Your healthcare provider should tell you what signs and symptoms you should report and monitor you, depending on the type of organ transplant that you have had.

Complications, including graft-versus-host-disease (GVHD), in people who have received a bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be serious and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with JEMPERLI. Your healthcare provider will monitor you for these complications.

Getting medical treatment right away may help keep these problems from becoming more serious.

Your healthcare provider will check you for these problems during treatment with JEMPERLI. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with JEMPERLI, if you have severe side effects.

What is JEMPERLI?

JEMPERLI is a prescription medicine used to treat adults with:

- a kind of uterine cancer called endometrial cancer (EC)
  - JEMPERLI may be used in combination with the chemotherapy medicines, carboplatin and paclitaxel, and then after that JEMPERLI may be used alone:
    - when a laboratory test shows that your tumor is mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H), **and**
    - your cancer has spread outside your uterus (advanced) **or**,
    - your cancer has returned.
  - JEMPERLI may be used alone:
    - when a laboratory test shows that your tumor is mismatch repair deficient (dMMR), **and**
    - your cancer has returned, or it has spread (advanced EC), **and**

- you have received chemotherapy that contains platinum and it did not work or is no longer working, **and**
- your cancer cannot be treated by surgery or radiation.

- a kind of cancer that is shown by laboratory test to be mismatch repair deficient (dMMR) solid tumor. JEMPERLI may be used to treat:
  - cancer that has returned or has spread (advanced cancer) **and**,
  - has progressed during treatment or after treatment, and you have no satisfactory treatment options.

It is not known if JEMPERLI is safe and effective in children.

Before receiving JEMPERLI, tell your healthcare provider about all of your medical conditions, including if you:

- have immune system problems, such as Crohn's disease, ulcerative colitis, or lupus.
- have received an organ transplant.
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic).
- have received radiation treatment to your chest area.
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome.
- are pregnant or plan to become pregnant. JEMPERLI can harm your unborn baby.
  Females who are able to become pregnant:
  - Your healthcare provider will do a pregnancy test before you start treatment with JEMPERLI.
  - You should use an effective method of birth control during your treatment and for 4 months after your last dose of JEMPERLI. Talk to your healthcare provider about birth control methods that you can use during this time.
  - Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with JEMPERLI.
- are breastfeeding or plan to breastfeed. It is not known if JEMPERLI passes into your breast milk. Do not breastfeed during treatment and for 4 months after your last dose of JEMPERLI.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive JEMPERLI?

- Your healthcare provider will give you JEMPERLI into your vein through an intravenous (IV) line over 30 minutes.
- When JEMPERLI is used in combination with carboplatin and paclitaxel, JEMPERLI is usually given every 3 weeks for the first 6 doses. Beginning 3 weeks later, it is usually given alone every 6 weeks.
- When JEMPERLI is used alone to treat dMMR recurrent or advanced EC and dMMR recurrent or advanced solid tumors, it is usually given every 3 weeks for the first 4 doses. Beginning 3 weeks later, it is usually given every 6 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for side effects.

- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of JEMPERLI?

JEMPERLI can cause serious side effects.

- **See "What is the most important information I should know about JEMPERLI?"**

The most common side effects of JEMPERLI when given with carboplatin and paclitaxel in people with dMMR/MSI-H endometrial cancer include:

- rash
- diarrhea
- decreased thyroid function
- high blood pressure

The most common side effects of JEMPERLI in people with dMMR solid tumors (including endometrial cancer) when used alone include:

- tiredness and weakness
- low red blood cell count (anemia)
- diarrhea
- nausea
- constipation
- vomiting

These are not all of the possible side effects of JEMPERLI. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of JEMPERLI.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about JEMPERLI, talk with your healthcare provider. You can ask your healthcare provider for information about JEMPERLI that is written for healthcare professionals.

What are the ingredients in JEMPERLI?

Active ingredient: dostarlimab-gxly

Inactive ingredients: citric acid monohydrate, L-arginine hydrochloride, polysorbate 80, sodium chloride, trisodium citrate dihydrate, and Water for Injection.

Manufactured by:
GlaxoSmithKline LLC, Philadelphia, PA 19104, U.S. License No. 1727
Distributed by:
GSK
GlaxoSmithKline, Durham, NC 27701

JMP:XMG
For more information, call 1-888-825-5249 or go to www.gsk.com.
This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: July 2023

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761174Orig1s006

MULTI-DISCIPLINE REVIEW(S)

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical
Non-Clinical
Statistical
Clinical Pharmacology
Clinical Microbiology/Virology

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. FDA collaborated with Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Switzerland's Swissmedic (SMC), and United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA). While the conclusions and recommendations expressed herein reflect FDA's completed review of the application, the applications may still be under review at the other regulatory agencies.

In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	BLA
Application Number(s)	761174 S-006
Priority or Standard	Priority
Submit Date(s)	March 23, 2023
Received Date(s)	March 23, 2023
PDUFA Goal Date	September 23, 2023
Division/Office	Division of Oncology 1 /Office of Oncologic Diseases
Review Completion Date	*Electronic Stamp Date*
Established Name	Dostarlimab-gxly
(Proposed) Trade Name	JEMPERLI
Pharmacologic Class	Programmed death-1 (PD-1) Blocking Antibody
Applicant	GlaxoSmithKline LLC
Formulation(s)	500 mg/10 mL, single-dose vial
Dosing Regimen	500 mg administered via intravenous infusion over 30 minutes every 3 weeks for 6 doses followed by 1,000 mg monotherapy every 6 weeks
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Regular Approval

Recommended Indication(s)/Population(s) (if applicable)	JEMPERLI, in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H).

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Reviewers of Multi-Disciplinary Review and Evaluation

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Dostarlimab-gxly is a humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that binds to programmed cell death protein 1 (PD-1), and inhibits the binding of PD-1 to both programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2).

Dostarlimab-gxly is currently approved for the following indications by the FDA:

- As a single agent for the treatment of adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation.
- As a single agent for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options (Approved under accelerated review).

In the current supplemental Biological Licensing Application (sBLA), the Applicant proposed the following indication:

(b) (4)

The recommended indication for regular approval is:

JEMPERLI, in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H).

The recommended dose for dostarlimab-gxly is 500mg IV every 3 weeks for 6 doses in combination with carboplatin and paclitaxel, followed by 1000 mg IV as monotherapy every 6 weeks until disease progression or unacceptable toxicity, or up to 3 years.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The FDA review team recommends regular approval of this sBLA for dostarlimab-gxly, according

to 21 Code of Federal Regulations (CFR) Part 601.20, Subpart C of the Biological Licensing Regulations.

The basis for this approval is a favorable benefit: risk profile of dostarlimab in combination with carboplatin and paclitaxel followed by dostarlimab in primary advanced or recurrent dMMR/MSI-H EC in Part 1 of the RUBY study. The RUBY study is an ongoing, multicenter, Phase 3, randomized, double-blind, placebo-controlled trial. Part 1 of the clinical study is to evaluate the efficacy and safety of treatment with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab vs. treatment with placebo plus carboplatin-paclitaxel followed by placebo in participants with primary advanced (Stage III or IV) or recurrent EC.

The trial enrolled patients with primary Stage III or Stage IV EC (per FIGO Staging Classification), including Stage IIIA to IIIC1 patients with evaluable or measurable disease, Stage IIIC1 with carcinosarcoma, clear cell, serous, or mixed histology regardless of presence of measurable disease, Stage IIIC2 or Stage IV disease regardless of presence of measurable disease. The trial also enrolled patients with first recurrent disease with a low potential for cure by radiation therapy or surgery alone or in combination, including patients who had not received systemic anticancer therapy or who had received prior neo-adjuvant/adjuvant systemic anticancer therapy and had a recurrence or disease progression ≥6 months after completing treatment. Prior neoadjuvant/adjuvant systemic anticancer therapy for primary Stage III or IV disease or prior immunotherapy was not allowed in the study. MMR/MSI tumor status was prospectively determined by local IHC, PCR, or NGS test or by central IHC testing with the Ventana MMR RxDx Panel when no local result was available.

A total of 494 patients were randomized 1:1 to dostarlimab plus carboplatin and paclitaxel, followed by dostarlimab vs. placebo plus carboplatin and paclitaxel, followed by placebo. Dostarlimab was dosed at 500 mg intravenously (IV) over 30 minutes every 3 weeks for 6 doses followed by 1,000 mg monotherapy IV every 6 weeks and continued until disease progression, unacceptable toxicity, or a maximum of 3 years. Randomization was stratified by MMR/MSI status (dMMR/MSI-H or MMRp/MSS), prior external pelvic radiotherapy (yes or no), and disease status (recurrent, primary Stage III, or primary Stage IV). In the dMMR/MSI-H subgroup, the major efficacy outcome was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST v 1.1). Additional efficacy outcome measures included overall survival (OS), objective Response Rate (ORR), and duration of Response (DOR). The major efficacy outcomes for the overall population were investigator-assessed PFS using RECIST v 1.1 and OS, with additional efficacy outcome measures of ORR and DOR.

Efficacy was assessed in a pre-specified subgroup of 122 patients (n=60 in the dostarlimab arm, n=62 in the control arm) with dMMR/MSI-H primary advanced or recurrent EC. At the prespecified interim analysis of PFS (77% information fraction) with a data cut off (DCO) of September 28, 2022, RUBY Part 1 showed a statistically significant and clinically meaningful

improvement in the primary endpoint of PFS by investigator in the dMMR/MSI-H subpopulation. The hazard ratio was 0.29 (95% CI 0.172, 0.497, p<0.0001), with median PFS of 30.3 months in the dostarlimab plus carboplatin-paclitaxel arm vs 7.7 months in the placebo plus carboplatin-paclitaxel arm. In the dMMR/MSI-H population, the one-sided p-value for investigator-assessed PFS is <0.0001, which crossed the pre-specified stopping boundary of 0.0081 (1-sided) for statistical significance. OS was a secondary endpoint for the dMMR/MSI-H population and was immature with 27% deaths at the time of the DCO, but there was no trend in detriment noted. ORR in the dMMR/MSI-H population was 73.8% (95% CI 58.0, 86.1) in the dostarlimab plus carboplatin-paclitaxel arm vs 62.2% (95% CI 46.5, 76.2) in the placebo plus carboplatin-paclitaxel arm. DOR in months was not reached (3.4, 28.3+) in the dostarlimab plus carboplatin-paclitaxel arm vs 5.4 months (2.7, 27.2+) in the placebo plus carboplatin-paclitaxel arm.

PFS was also statistically significant in the total population. However, improvement in PFS in the all-comer population was primarily attributed to results from patients in the dMMR/MSI-H subgroup. OS was immature in the all-commer population as well. In the total population, final OS analysis is planned to be conducted when 321 OS events have been observed. The second and third interim analyses of OS are planned to be conducted when 221 (69% information fraction) and 273 (85% information fraction) OS events have been observed, respectively.

Overall, the toxicity of dostarlimab plus carboplatin and paclitaxel was determined to be acceptable for the intended population with a serious and life-threatening condition. The most common adverse events (≥20%) with dostarlimab in combination with carboplatin and paclitaxel were rash, diarrhea, hypothyroidism, and hypertension. Immune related adverse events (irAEs) were noted with the addition of dostarlimab and included pneumonitis, colitis, hepatitis, endocrinopathies, nephritis with renal dysfunction, and skin adverse reactions. The rates of certain irAEs were higher in the overall population of the RUBY study when combining dostarlimab with carboplatin and paclitaxel compared to other trial with monotherapy dostarlimab including hypothyroidism (12%), hyperthyroidism (3.3%), and type 1 diabetes mellitus (0.4%) and these were updated in product labeling.

RUBY Part 1 demonstrated a statistically significant and clinically meaningful improvement in PFS with no newly identified safety signals. The FDA review team recommends regular approval for this sBLA for the following indication:

> *JEMPERLI, in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H).*

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Dostarlimab-gxly is a humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that binds to programmed cell death protein 1 (PD-1), and inhibits the binding of PD-1 to both programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2).

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States. The estimated number of new cases in 2023 is 66,200 representing 3.4% of all new cancers, with an estimated 13,030 deaths. EC can be classified as dMMR or mismatch repair proficient (MMRp) based on the presence or absence of proteins that are involved in the mismatch repair (MMR) process. Deficiencies in MMR result in genetic hypermutability known as microsatellite instability (MSI) with EC estimated to have a prevalence of dMMR/microsatellite instability-high (MSI-H) at approximately 25% to 30%.

There is no approved treatment for primary advanced or metastatic Stage III or IV first-line endometrial cancer; however, platinum-containing chemotherapy is considered a standard of care, with the most common regimen being carboplatin-paclitaxel in the first line setting (including dMMR/MSI-H) after local therapy, with response rates ranging from 40-62% and an overall survival ranging from 13 to 29 months.

The efficacy and safety assessment of dostarlimab plus carboplatin and paclitaxel is based on data from RUBY Part 1, a randomized, multicenter, double-blind, placebo-controlled trial in primary advanced (Stage III or IV) or recurrent EC. Efficacy was assessed in a pre-specified subgroup of 122 patients with dMMR/MSI-H primary advanced or recurrent EC. Randomization was stratified by MMR/MSI status (dMMR/MSI-H or MMRp/MSS), prior external pelvic radiotherapy (yes or no), and disease status (recurrent, primary Stage III, or primary Stage IV). In the dMMR/MSI-H subgroup, the major efficacy outcome was investigator-assessed PFS using RECIST v 1.1. Additional efficacy outcome measures in the dMMR/MSI-H population included OS, ORR, and DOR.

FDA's efficacy evaluation is based on the dMMR/MSI-H population with MMR/MSI status used for randomization. The protocol and SAP for RUBY study also specified that the primary efficacy analyses were planned to be based on the stratum assigned at randomization. RUBY Part 1 showed a statistically significant and clinically meaningful improvement in the primary endpoint of PFS by investigator in the dMMR/MSI-H subpopulation. The hazard ratio was 0.29 (95% CI 0.172, 0.497, p<0.0001), with median PFS of 30.3 months in the dostarlimab plus carboplatin-paclitaxel arm vs 7.7 months in the placebo plus carboplatin-paclitaxel arm. OS was a secondary endpoint for the dMMR/MSI-H population and

was immature with 27% deaths at the time of the DCO, but there was no trend in detriment noted. ORR in the dMMR/MSI-H population was 73.8% (95% CI 58.0, 86.1) in the dostarlimab plus carboplatin-paclitaxel arm vs 62.2% (95% CI 46.5, 76.2) in the placebo plus carboplatin-paclitaxel arm. DOR in months was not reached (3.4, 28.3+) in the dostarlimab plus carboplatin-paclitaxel arm vs 5.4 months (2.7, 27.2+) in the placebo plus carboplatin-paclitaxel arm.

The most common adverse reactions (≥20%) with dostarlimab in combination with carboplatin and paclitaxel were rash, diarrhea, hypothyroidism, and hypertension. Immune related adverse events (irAEs) were noted with the addition of dostarlimab and included pneumonitis, colitis, hepatitis, endocrinopathies, such as hypothyroidism, nephritis with renal dysfunction, and skin adverse reactions. The incidence rate and severity of irAEs observed with dostarlimab-gxly are generally consistent with those reported for other approved anti-PD-1 agents in combination with chemotherapy. Serious adverse reactions occurred in 13% of patients receiving dostarlimab in combination with carboplatin and paclitaxel; the most common serious adverse reaction was sepsis, including urosepsis (6%). Fatal adverse reactions occurred in 6% of patients receiving dostarlimab including septic shock (3.8%), and myelosuppression (1.9%).

Advanced or recurrent Stage III and IV EC is a serious and life-threatening disease with a significant unmet medical need for more effective therapies in the first-line setting. The review team concludes that the statistically significant and clinically meaningful PFS result in the dMMR/MSI-H population and acceptable safety profile for the intended population with a serious and life-threatening condition demonstrates a favorable benefit-risk profile. Therefore, the recommended indication by the FDA review team for regular approval for this supplemental BLA is:

JEMPERLI, in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H).

FDA has issued two postmarketing commitments with this approval for the prespecified interim and final OS results from the RUBY Part 1 study, as well as a commitment to develop a nucleic acid based in vitro diagnostic device that is essential to support the safe and effective use of dostarlimab, in combination with carboplatin and paclitaxel, for patients with EC that are MSI-H.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Endometrial cancer (EC) is the most common gynecologic malignancy in the United States. The estimated number of new cases in 2023 is 66,200 representing 3.4% of all new cancers, with an estimated 13,030 deaths. • EC is estimated to have a prevalence of dMMR/MSI-H at approximately 25% to 30%.	**Advanced or recurrent Stage III and IV EC is a serious and life-threatening disease with a significant unmet medical need for more effective therapies.**
Current Treatment Options	• Advanced or recurrent EC is not curable. Treatment goals are to reduce cancer-related symptoms, delay progression and prolong survival. • There is no approved treatment for primary advanced or metastatic Stage III or IV first-line endometrial cancer; however, platinum-containing chemotherapy is considered a standard of care, with the most common regimen being carboplatin-paclitaxel with response rates ranging from 40-62% and an overall survival ranging from 13 to 29 months.	**All treatment options are palliative. There remains an unmet need to improve outcomes for patients with primary advanced or recurrent dMMR/MSI-H EC.**
Benefit	• RUBY Part 1 enrolled 494 patients with primary advanced or recurrent Stage III or IV EC, 122 of which with dMMR/MSI-H EC. • RUBY Part 1 showed a statistically significant and clinically meaningful improvement in the primary endpoint of PFS by investigator in the dMMR/MSI-H subpopulation. The hazard ratio was 0.29 (95% CI 0.172, 0.497, p<0.0001), with median PFS of 30.3 months in the dostarlimab plus carboplatin-paclitaxel arm vs 7.7 months in the placebo plus carboplatin-paclitaxel arm. • OS was a secondary endpoint for the dMMR/MSI-H population and was immature with 27% deaths at the time of the DCO, but there was no trend in detriment noted. • ORR in the dMMR/MSI-H population was 73.8% (95% CI 58.0, 86.1) in	**The submitted evidence meets the statutory evidentiary efficacy standard for approval.** **Study RUBY Part 1, a well-controlled randomized trial, met its primary endpoint of PFS by investigator, and while OS is immature and a secondary endpoint in the dMMR/MSI-H population, did not show evidence of detriment for the addition of dostarlimab to carboplatin and paclitaxel.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the dostarlimab plus carboplatin-paclitaxel arm vs 62.2% (95% CI 46.5, 76.2) in the placebo plus carboplatin-paclitaxel arm. • DOR in months was not reached (3.4, 28.3+) in the dostarlimab plus carboplatin-paclitaxel arm vs 5.4 months (2.7, 27.2+) in the placebo plus carboplatin-paclitaxel arm.	
Risk and Risk Management	• The most common adverse reactions (≥20%) with dostarlimab in combination with carboplatin and paclitaxel were rash, diarrhea, hypothyroidism, and hypertension. • The most common Grade 3 or 4 laboratory abnormalities (≥10%) are decreased neutrophils, decreased hemoglobin, decreased white blood cell count, decreased lymphocytes, increased glucose, decreased sodium, and decreased platelets. • Immune-mediated adverse reactions occurred with dostarlimab, including pneumonitis, colitis, hepatitis, endocrinopathies, such as hypothyroidism, nephritis with renal dysfunction, and skin adverse reactions.	**The safety of dostarlimab plus carboplatin and paclitaxel is acceptable for the intended population and is manageable with current labeling.** **No REMS is indicated**

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

					Section where discussed, if applicable
☐	The patient experience data that was submitted as part of the application, include:				
	X	Clinical outcome assessment (COA) data, such as			Section 8.1.2
			X	Patient reported outcome (PRO)	Section 8.1.2
			☐	Observer reported outcome (ObsRO)	

			□ Clinician reported outcome (ClinRO)	
			□ Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that was not submitted in the application, but was considered in this review.			

X _____

Preeti Narayan, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Endometrial cancer accounted for 4.5% of all new cancer cases in women diagnosed in 2020, making it the second most common gynecological cancer after cervical cancer and the sixth most common type of malignancy diagnosed in women worldwide [Sung, 2021]. The annual ASIR in the US was 21.4 per 100,000, with a total of 61,738 new cases [GLOBOCAN, 2020]. The median age at diagnosis is 63 years [SEER, 2022]. The ASIR among women ages 15 to 19 years was 0.45 per 100,000 and for those >60 years, was 102.2 per 100,000 [GLOBOCAN, 2020]. The 5-year partial prevalence estimates indicate 241,265 cases, and there were 11,460 deaths [GLOBOCAN, 2020]. Despite improvements in cancer mortality for many cancer types, the mortality rates for EC have been increasing over the past 20 years. This is mainly attributed to the increasing incidence of obesity, a known risk factor for EC, with EC mortality rates approaching ovarian cancer mortality rates, this is therefore an area of high unmet need [Koskas et al, 2021; Oaknin et al, 2022; Dalmartello et al, 2022; Giaquinto et al, 2022; Siegel 2021].

Patients with early stage disease have excellent outcomes with 5 year OS >95% for patients with stage I tumors. However, outcomes in women with primary advanced (Stage III or IV) or recurrent EC remain poor with 5-year OS rates of 20% to 25%, highlighting the urgent need for new therapeutic strategies that prevent EC recurrence and prolong survival [Koskas 2021; Oaknin et al, 2022]. The majority of patients with EC are diagnosed in early stages (Stage I or II) and receive surgery with curative intent; however, approximately 20% of patients are diagnosed with high-risk primary advanced or metastatic disease (Stage III or IV) for which a surgical cure is not possible [Siegel et al, 2021]. For these patients, there is no approved anticancer therapy and optimal therapy following surgical resection and staging remains an area of active investigation [NCCN 2022; Oaknin et al, 2022]. The prognosis for patients with advanced or recurrent EC depends upon site and extent of the recurrence, tumor size, whether the patient had received prior radiotherapy, the relapse-free interval, and histology [Oaknin et al, 2022]. Approximately 40% of EC are diagnosed as locally advanced tumors, and most recurrences occur within 3 years of primary treatment [Koskas et al, 2021].

The Cancer Genome Atlas has identified 4 molecular subgroups that more accurately reflect the underlying tumor [Kandoth et al, 2013]. These include POLE-mut/ultramutated, MSI-H, copy number low, and copy number high. These subgroups have been replicated by using surrogate markers to allow increased reproducibility between laboratories, and include p53-abn, POLE-mut, dMMR and no specific molecular profile. Approximately 25% to 30% of ECs are

dMMR/MSI-H [Nagle 2018; Oaknin et al, 2022] and have biological features that result in increased antitumor activity with an anti- PD-1 antibody therapy [Oakinin et al, 2022].

Studies have demonstrated the clinical efficiacy of immune checkpoint inhibition as monotherapy in dMMR/MSI-H EC in the second-line setting. Therefore, the addition of immune checkpoint inhibition therapy to SOC chemotherapy could improve patient outcomes in the first-line setting in patients with primary advanced or recurrent EC, an area of considerable unmet need.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of primary advanced or recurrent dMMR/MSI-H endometrial cancer.

2.2. Analysis of Current Treatment Options

A total abdominal hysterectomy and bilateral salpingo-oophorectomy is recommended for all patients with EC eligible for surgery [NCCN 2022] [Concin et al, 2021] [Oaknin et al., 2022] and lymph node staging is performed to complete surgical staging by FIGO. The European guidelines include molecular classification into risk assessment for patients with early-stage disease to escalate or de-escalate adjuvant therapy depending on molecular features.

There is a consensus that patients with primary advanced Stage III or IV EC with extrauterine disease are at increased risk of recurrence and there is a need for adjuvant therapy, although the optimal therapy is yet to be determined [NCCN 2022; Oaknin et al, 2022]. The recommended treatment options include systemic chemotherapy and/or external beam radiotherapy with or without brachytherapy. For patients with recurrent tumors, treatment options include surgery, radiotherapy and systemic therapy [NCCN guidelines, 2022; Oaknin et al, 2022].

There is no approved treatment in the first-line setting for primary advanced and recurrent EC, but platinum-based chemotherapy is considered as standard of care, the most common regimen being carboplatin-paclitaxel [NCCN 2022; Colombo et al, 2016]. Although cisplatin-paclitaxel in combination with doxorubicin has a similar efficacy to carboplatin-paclitaxel, it is not commonly used due to the higher toxicity observed with this regimen [Miller et al, 2020; Sorbe et al, 2008]. Based on the results of the landmark GOG 209 study, carboplatin-paclitaxel is the preferred regimen in the first-line setting for patients with primary advanced or recurrent EC [Miller et al, 2020]. This study enrolled a high proportion of participants with previously untreated Stage III or nonmeasurable– Stage III (41.7%) or IV EC (31%) and a lower proportion of participants with recurrent EC (27.3%). Participants received paclitaxel-doxorubicin-cisplatin or carboplatin plus paclitaxel demonstrated non-inferiority of carboplatin plus paclitaxel to paclitaxel-doxorubicin-cisplatin, with a median OS of 37 months and a median PFS of 13 months with this regimen [Miller et al, 2020].

Given that approximately 25% to 30% of ECs are dMMR/MSI-H, ICIs have been investigated as potential options in EC. Thus far, dostarlimab and pembrolizumab have been approved by the

FDA and EMA as monotherapy in second-line dMMR or dMMR/MSI-H EC. Dostarlimab received accelerated approval in the US with subsequent conversion to full approval for the treatment of patients with dMMR recurrent or advanced EC, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation, with an ORR of 45.4% in 141 participants with dMMR EC [JEMPERLI USPI, 2023]. The PD–1 inhibitor pembrolizumab received full approval in March 2022 as second-line therapy for advanced dMMR or MSI-H EC after prior systemic therapy, with an ORR of 46% in 90 patients with dMMR/MSI-H EC [KEYTRUDA USPI, 2022].

Additional therapies for primary advanced disease, and alternative treatments for primary advanced or recurrent disease in certain circumstances are included in Applicant - Table 1, though none approved.

Applicant - Table 1. Summary of Treatment Armamentarium Relevant to Proposed Indication

Agent	Population	Characteristics	Design	Endpoint	Summary of Results	Reference
Therapies approved for the first-line treatment of endometrial cancer						
No therapies are approved						
Other therapies used for the first-line treatment of endometrial cancer, primary advanced (not approved)						
Carboplatin-paclitaxel (CT)	Stage I-II (high risk), III-IVA		P3 N=813	RFS	58% 5y RFS (v. 59% in chemoRT/CT) Noninferior to concurrent chemoRT/CT	Matei et al, 2019
Concurrent cisplatin RT followed by carboplatin-paclitaxel (chemoRT/CT)	Stage I-II (high risk), III- IVA		P3 N=813	RFS	59% 5y RFS (v. 58% in CT) Noninferior to CT	Matei et al, 2019
	Stage I-II (high risk), III		P3 N =686	FFS OS	76% v5y RFS (v. 69% RT alone) 82% 5y OS (v. 77% with RT alone)	de Boer, et al 2018
Other therapies used for the first-line treatment of endometrial cancer, primary advanced and recurrent (not approved)						
Carboplatin-paclitaxel (CT)	Stage III, IV, recurrent		P3 N=1381	OS	37 mo (v. 41 mo in TAP arm) Noninferior to TAP, global SOC	Miller et al, 2020
Cisplatin-doxorubicin-paclitaxel (TAP)	Stage III, IV, recurrent		P3 N=1381	OS	41 mo (v. 37 mo in CT) Noninferior to CT, increased toxicities	Miller et al, 2020
Cisplatin-doxorubicin (AP)	Stage III, IV, recurrent		P3 N=273	OS	12 mo (v. 15 mo for TAP)	Fleming et al, 2004
Carboplatin-paclitaxel-bevacizumab	Stage III, IV, recurrent		P2 N=108	PFS (OS 2ndary)	13.7 mo (v. 10.5 mo for CT) – PFS 40 mo (v. 29.7 mo for CT) - OS	Lorusso, et al, 2019

Agent	Population	Characteristics	Design	Endpoint	Summary of Results	Reference
Carboplatin-paclitaxel-trastuzumab	Stage III-IV recurrent	HER2+ uterine serous carcinoma (USC) / carcinosarcoma (CS)	P2 61 HER2+ USC	PFS (OS 2ndary)	12.9 mo (v. 8.0 for CT) – PFS 29.6 mo (v 24.4) - OS	Fader et al, 2020
paclitaxel/ifosfamide	Stage I-IV, recurrent	Carcinosarcoma (CS)	P3 536 Uterine CS	OS	29 mo (v 37 mo in CT) noninferior to CT for CS	Powell et al, 2022

The FDA's Assessment:
FDA agrees with the Applicant's assessment of current treatment options for primary advanced or recurrent dMMR/MSI-H endometrial cancer. Platinum-containing chemotherapy is considered standard of care in the first-line setting for the treatment of patients with primary advanced or recurrent EC after local therapy, that is not amenable to curative surgery and/or radiation, inclusive of patients with dMMR/MSI-H disease. GOG0209 Study (Miller, 2020) demonstrated noninferiority of carboplatin-paclitaxel to paclitaxel-doxorubicin-cisplatin, with a favorable toxicity profile. As a result, carboplatin-paclitaxel is currently the standard chemotherapy regimen used for patients with primary advanced or recurrent EC.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Dostarlimab was granted accelerated approval by the FDA on 22 April 2021 and full approval on 09 February 2023 for the treatment of adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation (BLA 761,174). Dostarlimab was also granted accelerated approval by the FDA on 17 August 2021 for the treatment of patients with recurrent or advanced dMMR solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options (BLA 761,223).

The Ventana MMR RxDx Panel was approved for selection of patients for treatment with dostarlimab in endometrial cancer (P200019) and solid tumor (P210001) indications on 22 April 2021 and 17 August 2021, respectively. The Applicant also agreed to a post-marketing

commitment to develop a CDx for selection of patients with solid tumors based on MSI-H status (PMR 4124-1).

A summary of the relevant regulatory interactions related to RUBY and activities for the development of dostarlimab in endometrial cancer are summarized in Applicant - Table 2.

The FDA's Assessment:
FDA agrees with the Applicant's summary of the approvals for dostarlimab.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Applicant - Table 2. Relevant Regulatory Interactions Related to Development of Dostarlimab in Primary Advanced or Recurrent Endometrial Cancer

Type	Date	Description
Type B meeting	September 2018	Type B, Pre-Phase 3 meeting to discuss the pivotal Phase 3 study design of dostarlimab in combination with chemotherapy in 1L EC (RUBY).
BLA 761174 Submission	December 2019	BLA submitted for the indication of recurrent or advanced dMMR EC that has progressed on or following prior treatment with a platinum-containing regimen. Note: PMR agreement (June 2020) with the Agency to utilize data from either RUBY or GARNET to convert an accelerated approval to full approval.
Type B Meeting	March 2021	Type B interaction on the proposed amendment to add Part 2 to the RUBY study (evaluation of the addition of niraparib to dostarlimab as maintenance therapy following initial therapy with dostarlimab plus carboplatin-paclitaxel in 1L EC).
Dostarlimab received Accelerated Approval	April 2021, under BLA 761,174	Accelerated approval (AA) for the treatment of adult patients with dMMR recurrent or advanced EC, as determined by an FDA approved test, that has progressed on or following prior treatment with a platinum containing regimen. AA received based on objective response rate (ORR) and supportive duration of response (DoR) data in 71 patients treated in cohort A1 of the GARNET trial.
Type C Meeting	July 2021	Type C WRO to obtain agreement on the content and format for the planned sBLA from Part 1 of the RUBY study.
sBLA Submission to BLA 761,174	May 2022	sBLA submitted to support the conversion of the accelerated approval for the indication of recurrent or advanced dMMR EC that has progressed on or following prior treatment with a platinum-containing regimen to regular approval. This submission contained updated data from the GARNET study and seeks to fulfil Accelerated Approval Requirement 3090-1.
Type B Meeting	November 2022	Type B interaction regarding the study design and statistical analysis plan for the ongoing phase 3, randomized trial (DOMENICA) of dostarlimab versus carboplatin-paclitaxel for the first-line treatment of patients with dMMR/MSI-H advanced or recurrent endometrial cancer.
RUBY Informal Teleconference	December 2022	Discussion of RUBY Part 1 Topline data and proposed submission strategy.
Dostarlimab received Full Approval	February 2023, under BLA 761,174	Full approval for the treatment of adult patients with dMMR recurrent or advanced EC, as determined by an FDA approved test, that has progressed on or following prior treatment with a platinum containing regimen in any setting and are not candidates for curative surgery or radiation.
Type B Meeting	February 2023	Type B pre-sBLA meeting to discuss headline efficacy and safety data from RUBY Part 1, seek advice on the filing strategy, and discuss plans for future analyses of overall survival.

Type	Date	Description

Abbreviations: BLA=Biologics License Application; dMMR=mismatch repair-deficient; DoR=duration of response; EC=Endometrial Cancer; FDA=United States Food and Drug Administration; MSI-H=Microsatellite Instability-High; ORR=Objective Response Rate; PMR=Post-Marketing requirements; sBLA=Supplemental Biologics License Application; WRO=Written Response Only.

The FDA's Assessment:
FDA agrees with the pre-submission regulatory activity for dostarlimab, as stated by the Applicant above.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical sites were not inspected as part of this supplemental BLA based on discussion with OSI, as there were no concerning outlier sites from the BIMO on FDA review. In addition, the Applicant was recently inspected.

4.2. Product Quality

The Applicant did not submit new CMC information or data in this sBLA.

4.3. Clinical Microbiology

The Applicant did not submit clinical microbiology data in this sBLA.

4.4. Devices and Companion Diagnostic Issues

In RUBY Study Part 1, MMR/MSI status was determined by local immunohistochemistry (IHC), next-generation sequencing (NGS), and polymerase chain reaction (PCR) test, or by central IHC testing using the Ventana MMR RxDx Panel when local testing was not available.

On April 22, 2021, the VENTANA MMR RxDx Panel of antibodies as a companion diagnostic (CDx) to select patients with dMMR endometrial cancer eligible for treatment with dostarlimab was contemporaneously approved by CDRH with the accelerated approval of dostarlimab in this disease. In the current sBLA submitted on 3/23/2023, the Applicant has submitted the results of the clinical bridging study using samples enrolled into the Part 1 of RUBY Study. Among the 199 participants who were enrolled based on a local MMR/MSI test, 192 (96.5%) participants had an evaluable MMR result from retrospective central test with the Ventana

MMR RxDx Panel, therefore, 192 participants were used as concordance analysis set for the concordance analysis. The overall percent agreement (OPA) for MMR status between the central Ventana MMR RxDx Panel and local MMR/MSI tests was 95.8% (95% CI: 92.0%, 98.2%). PPA was 91.8% (95% CI: 80.4%, 97.7%) with 4 discordant results and NPA was 97.2% (95% CI: 93.0%, 99.2%) with 4 discordant results. The clinical bridging study report and data were reviewed by CDRH and appear acceptable. See CDRH review for further information.

A Post Marketing Commitment (PMC 4124-2) was issued on August 9, 2021 under BLA 761223 to establish and support the availability of a nucleic acid based in vitro diagnostic device that is essential to support the safe and effective use of dostarlimab in patients with solid tumors that are MSI-H. PMC 4481-2 will be issued with this sBLA approval for the Applicant to make available a nucleic acid based in vitro diagnostic device that is essential to support the safe and effective use of dostarlimab, for patients with endometrial cancer that is MSI-H. The Applicant may re-test specimens from EC patients enrolled in RUBY clinical trial using the CDx device that will be validated for selecting MSI-H patients and used for fulfillment of the PMC 4124-2 issued under BLA 761223 and provide the bridging data for FDA review in the future. See section 13 of this review document for information regarding PMC 4481-2.

5 Nonclinical Pharmacology/Toxicology

Non-clinical pharmacology and toxicology is not a component of this submission. As of the data-cut off date, no new studies on non-clinical pharmacology and toxicology have been performed.

6 Clinical Pharmacology

6.1. Executive Summary

<u>The FDA's Assessment:</u>
The Applicant submitted efficacy supplement 6 to support approval of the following new indication for JEMPERLI (dostarlimab-gxly): in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial cancer (EC) that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H). Efficacy and safety data to support this new indication were derived from Phase 3 Study 213361 (RUBY) (see Sections 7 and 8 for details and results on this clinical trial). The proposed recommended dosage of dostarlimab-gxly is 500 mg Q3W for 6 doses in combination with carboplatin and paclitaxel followed by 1000 mg Q6W as monotherapy.

The proposed recommended dosage of dostarlimab-gxly is acceptable, as the doses are

currently approved doses for dostarlimab-gxly and based on clinically significant improvements in PFS from the RUBY Part 1 trial, which evaluated the proposed recommended dosage. Overall, the safety profile of dostarlimab-gxly in combination with carboplatin-paclitaxel was relatively consistent with dostarlimab monotherapy.

The population PK modeling did not show a clinically meaningful change in the PK of dostarlimab-gxly when it was administered in combination with carboplatin-paclitaxel vs. when it was administered as monotherapy. There was a lack of clinically meaningful exposure-response relationships between dostarlimab-gxly exposures and measurements of efficacy and safety.

The immunogenicity data of dostarlimab-gxly from the RUBY trial showed no formation of treatment-emergent anti-drug antibodies or treatment-emergent neutralizing antibodies in 225 patients who received JEMPERLI at the recommended dosage.

RECOMMENDATION
The Office of Clinical Pharmacology has reviewed the information and data submitted in this efficacy supplement for BLA 761174 (S-6). This BLA efficacy supplement is approvable from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The clinical pharmacology of dostarlimab was described in the previously submitted reports in BLA 761174 (sequence 0004) and BLA 761223 (sequence 0001). The new clinical pharmacology information includes an evaluation of dostarlimab pharmacokinetic (PK), exposure-response (E-R; efficacy and safety) relationships, and immunogenicity using data from participants with primary advanced or recurrent EC including the dMMR/MSI-H population from Part 1 of the RUBY study.

General clinical pharmacology and PK characteristics of dostarlimab are unchanged from previous studies. Clinical pharmacokinetics in RUBY were consistent with that observed in GARNET and known PK characteristics of dostarlimab.

The previously developed model (Melhem et al., 2022) was externally validated and updated using pooled data RUBY and GARNET studies. Based on the pooled analysis, no adjustment in dosing regimen is deemed necessary based on any covariates, including age, body weight, race, sex, ethnicity, or coadministration with platinum-containing chemotherapy in participants receiving dostarlimab.

The E-R analyses using Cox (proportional hazards) regression did not demonstrate a meaningful relationship between exposure and response (PFS/DOR) in dostarlimab treated participants in RUBY Part 1 including those in the dMMR/MSI-H population and support the dosing regimen. Exploratory Kaplan-Meier plots of overall survival (OS) by exposure quartiles showed high degree of overlap between dostarlimab exposure, suggesting no E-R relationship.

Exposure-safety analyses were performed for the top five adverse events (AEs) related to dostarlimab alone or in combination with platinum-containing chemotherapy of any grade as assessed by investigators, which included arthralgia, diarrhoea, fatigue, nausea and rash. No statistically significant E-R relationship was found for diarrhoea, fatigue or nausea. Arthralgia showed significant relationships with area under the concentration-time curve during the first 21 days (AUC) and minimum concentration at Day 21 (Cmin) in the time period Cycle 7 and beyond when only dostarlimab participants were included in the analysis. The relationships were not significant when the placebo arm was included in the analysis, supporting the fact that the addition of dostarlimab to the SOC does not increase the risk of arthralgia. Rash showed significant yet flat E-R relationships for all 3 exposure metrics (AUC, maximum concentration during the first 21 days (Cmax), Cmin), in all 3 time periods when all participants were included in the analysis. The increase in predicted probability for rash was limited; between 5.2% and 10% for participants with high exposure (90th percentile) compared to low exposure (10th percentile), depending on exposure metric and time period. dMMR/MSI-H status was not a significant covariate in any of the exposure-safety analyses.

The overall immunogenicity risk for dostarlimab is low. The current clinical data from RUBY Part 1 are consistent with this assessment; the incidence of treatment-emergent positive anti-drug antibody (ADA) samples was 0% and there was no evidence of a clinically-meaningful impact of pre-existing ADA or ADA formation on pharmacokinetics, safety or efficacy of dostarlimab.

Collectively, these analyses support the use of dostarlimab 500 mg Q3W in combination with platinum-containing chemotherapy for 6 cycles followed by 1000 mg Q6W for subsequent cycles in patients with dMMR/MSI-H primary advanced or recurrent EC. No dose adjustment based on any covariate is warranted.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

The dosing regimen of dostarlimab in patients with dMMR/MSI-H primary advanced or recurrent EC is 500 mg Q3W for the first 6 cycles followed by 1000 mg Q6W for all subsequent

cycles administered as an IV infusion over approximately 30 minutes, and in combination with platinum-containing chemotherapy for the first 6 cycles.

Based on findings in RUBY Part 1, the dosing regimen is expected to result in full receptor occupancy (RO) for the duration of treatment based on previous pharmacodynamic analysis in the GARNET study (Section 2.1.1.4 of m2.7.2 BLA 761174 sequence 0004). Although only one dose regimen was evaluated in the intended target population in RUBY, the flat E-R relationship for efficacy and safety do not suggest any necessary changes of the dosing regimen in the intended treatment population to improve safety or efficacy. This, combined with meaningful efficacy responses in the participants and overall limited additional toxicity with the addition of dostarlimab to chemotherapy in the dosing regimen, supports the choice of the therapeutic dose and regimen.

The FDA's Assessment:
FDA agrees with the Applicant's position that the proposed dosing regimen is supported by available data.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

Therapeutic individualization of dose is not required for subpopulations based on intrinsic factors based on the results of PopPK and E-R analyses.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.2.2.3. Outstanding Issues

The Applicant's Position:

None

The FDA's Assessment:
FDA agrees that there are no outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

The clinical pharmacology portion of the submission characterizes the pharmacokinetics (PK), immunogenicity, and exposure-response (E-R) relationship of dostarlimab in patients with primary advanced or recurrent endometrial cancer (EC). Population PK (PopPK) modeling was conducted combining all dostarlimab PK data available from Part 1 of the study 213361 (RUBY), and available monotherapy PK data from study 213346 (GARNET). In addition, the E-R

relationship for efficacy (PFS and DOR) and safety endpoints (top 5 dostarlimab-related AEs, any grade) in part 1 of RUBY study were investigated.

The PopPK analysis included pooled data from GARNET and RUBY studies, including effect of co-administered chemotherapy, other comedications, patient and disease-related characteristics as deemed necessary.

The overall dostarlimab PK profile was well described by a two-compartment model, with time-dependent linear elimination with body weight (WT) as an allometric covariate on clearance (CL), volume of distribution of central compartment (Vc), and volume of distribution of peripheral compartment (Vp). Applicant - Table 3 presents a summary of PK parameters based on the updated population pharmacokinetic analysis using GARNET and RUBY data.

Applicant - Table 3: Dostarlimab PK Parameters in Patients with Solid Tumors

Parameter	Estimate (CV%)
Clearance at Steady-State (CL_{ss})	0.00681 L/hour (30.2%)
Volume of Distribution at Steady-State (V_{ss})[a]	5.81 L (14.9%)
Terminal elimination half-life ($t_{1/2}$)	23.2 days (20.8%)

Source: m5.3.5.3, Population PK and Exposure-Response Analysis Report, Table A.7.1
Abbreviations: CV%=percentage coefficient of variation; PK=pharmacokinetics
[a] V_{ss} calculated as central volume of distribution (V_c) + peripheral volume of distribution (V_p).

Dostarlimab PK was approximately dose-proportional over the dose and dosing regimens studied, with an approximate two-fold accumulation.

The maximum change in CL over time was estimated to be 10.7%. Baseline age, sex, time-varying albumin (ALB), time-varying alanine aminotransferase (ALT), and coadministration with platinum-containing chemotherapy were statistically significant covariates on CL. Time-varying ALB and sex were statistically significant covariates on Vc. However, none of the significant covariates were found to be clinically relevant. No adjustment in dosing regimen is deemed necessary based on any covariates, including age, body weight, race, sex, ethnicity, or coadministration with platinum-containing chemotherapy in participants receiving dostarlimab. No statistically significant effects of mild to moderate renal impairment and mild hepatic impairment were found on dostarlimab PK. Therefore, no dose adjustment is warranted for patients with mild or moderate renal impairment or with mild hepatic impairment. There were limited data in participants with severe renal impairment, end-stage renal disease undergoing dialysis, and moderate hepatic impairment. There was no participant with severe hepatic impairment.

Based on PopPK simulations, the lower bounds of the 90% PI of the $C_{min,ss}$ for the 500 mg Q3W and 1000 mg Q6W regimens were approximately 2.80-fold and 1.89-fold higher respectively, as compared to the target C_{min} needed for maintenance of 90% of maximal peripheral PD-1 suppression [Austin et al., 2023]. Hence the dose and regimen of 500 mg Q3W for 6 cycles

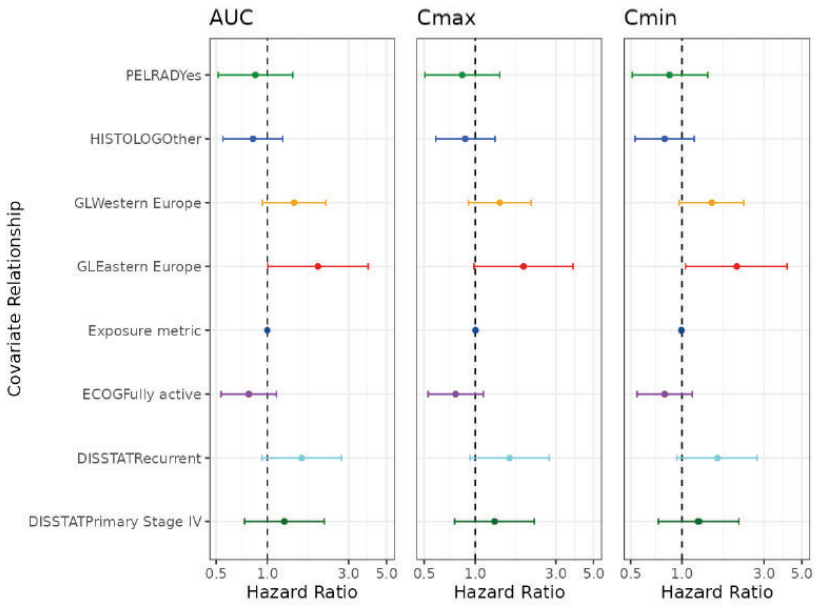
followed by 1000 mg Q6W is expected to result in full target engagement for the duration of treatment in RUBY study.

E-R for Safety and Efficacy Endpoints: An E-R analysis explored the relationship of model-predicted dostarlimab exposure with both safety and efficacy variables. PK data from RUBY Part 1 were included through the data cutoff date of 08 August 2022 as appropriate for each analysis.

Efficacy: The main focus of the E-R analyses of efficacy was the primary efficacy endpoint PFS, as assessed by the investigator per RECIST v.1.1. For the E-R analysis of efficacy, Cycle 1 (day 21) predictions of AUC, C_{max}, and C_{min} were generated based on planned dose and individual post-hoc PopPK parameters. Due to the time-varying nature of dostarlimab CL, Cycle 1 exposure was used in the E-R analyses to avoid potential bias as described by Dai et al. [Dai et al., 2020]. As a first step, a univariate analysis with exposure as the independent predictor was performed. Subsequently, covariates were explored via a full model approach. Since the hazards within the MMR/MSI status were non-proportional, Cox (proportional hazards) regression stratified by MMR/MSI was performed for the three exposure metrics (AUC, Cmax and Cmin) with the additional covariates such as MMR/MSI status in EC, prior external pelvic radiotherapy (yes or no), baseline ECOG performance, histology (endometrioid carcinoma or other) and geographic location (North America/Western Europe/Eastern Europe). Covariate effects were considered significant if the 95% confidence interval (CI) for the hazard ratio did not include a value of 1.

During univariate analysis, none of the tested exposure metrics had a statistically significant relationship with PFS ($\alpha = 0.05$) with p-values of 0.90, 0.28 and 0.40 for AUC, C_{max} and C_{min}, respectively. The hazard ratios of the tested covariates can be seen in Applicant - Figure 1.

Applicant - Figure 1: Hazard Ratio Multivariate Analysis, PFS



Source: m5.3.5.3, Population PK and ExposureResponse Analysis Report, Figure 35

AUC=area under the concentrationtime curve; CI=confidence interval; C_{max}=maximum observed concentration; C_{min}=minimum observed concentration; DISSTAT=disease status in EC (reference primary Stage III); ECOG=Eastern Cooperative Oncology Group; GL=geographic location; HISTOLOG=histology (reference EC); PELRAD=prior external pelvic radiotherapy (reference No); PFS=progressionfree survival

Note: Circles represent hazard ratios. Lines represent 95% CIs. The 95% CI of geographic location for Eastern Europe does not include 1 when tested with the exposure metrics AUC and C_{min}, while the other tested covariates include 1. The 95% CIs for geographic location, Eastern Europe, were 1.008 to 3.91 and 1.052 to 4.105 for AUC and C_{min}, respectively

The only significant covariate during multivariate analyses was geographic location (Eastern Europe) analyzed under AUC and C_{min}. Eastern European patients had an increased risk of tumor progression or death compared to North American patients (hazard ratio about 2). However, given the small sample size (n=13), the results should be interpreted with caution. In conclusion, E-R analyses of PFS demonstrated that the exposure-efficacy relationship achieved a plateau over the range of exposures achieved with the recommended therapeutic dose. This supports the use of dostarlimab in combination with platinum-containing chemotherapy in patients with primary advanced or recurrent EC using the dosing regimen of 500 mg Q3W for the first 6 cycles and followed by 1000 mg Q6W for all subsequent cycles.

Additionally, the potential relationship between dostarlimab exposure to the key secondary endpoint duration of response (DOR) was analyzed using Cox (proportional hazards) regression, which showed no significant E-R relationship for DOR. Overall survival was only explored graphically using exploratory plots, and no formal analysis was performed as data had only 33% maturity in the intent to treat (ITT) population, and was deemed immature for exposure response analysis.

Safety: Binary data for the top five AEs of any grade related to dostarlimab when administered alone or in combination with platinum-containing chemotherapy (arthralgia, diarrhoea, fatigue, nausea and rash) in the study were analyzed using univariate logistic regression. Cycle 1 exposures were used for all three periods above, to represent an early exposure metric given that the first AEs are expected to occur early rather than late following dostarlimab administration.

Arthralgia showed significant relationships with AUC and C_{min} in the time period cycle 7 and beyond, when only dostarlimab patients were included in the analysis. The relationships were not significant when the placebo arm was included in the analysis and thereby increasing the intercept. This indicates that the prevalence of arthralgia in the placebo arm is high enough to render the ER relationship non significant (prevalence 5.6% and 1.2% for the dostarlimab treated and placebo patients respectively in the time period cycle 7 and beyond), and the addition of dostarlimab to the platinum-containing chemotherapy does not increase the risk of arthralgia.

When all patients were included, significant E-R relationships for rash was seen for all exposure metrics (AUC, C_{max} and C_{min}) in all periods. However, when only dostarlimab-treated

participants were included in the analysis the E-R relationships were no longer significant, since the relationships were less supported in the lower range of exposures. This indicates a relatively flat E-R relationship.

No other significant relationships were seen for any of the other AEs (diarrhea, fatigue or nausea) in any of the tested time periods. Overall there was no clinically relevant impact of dostarlimab exposure on the top 5 dostarlimab-related AEs.

Immunogenicity:

Overall, none of the 225 participants evaluable for treatment-emergent ADA had treatment-induced or treatment-boosted ADAs, for an overall incidence of treatment-emergent ADAs of 0%. (Applicant - Table 4). Thirty-four participants (15.1%) had treatment-unaffected ADAs (i.e., pre-existing reactive antibodies to dostarlimab at baseline with no meaningful increase in titer postdose). One hundred eighty-five participants (82.2%) were classified as ADA-negative, and 6 participants (2.7%) were classified as inconclusive with respect to treatment-emergent ADAs.

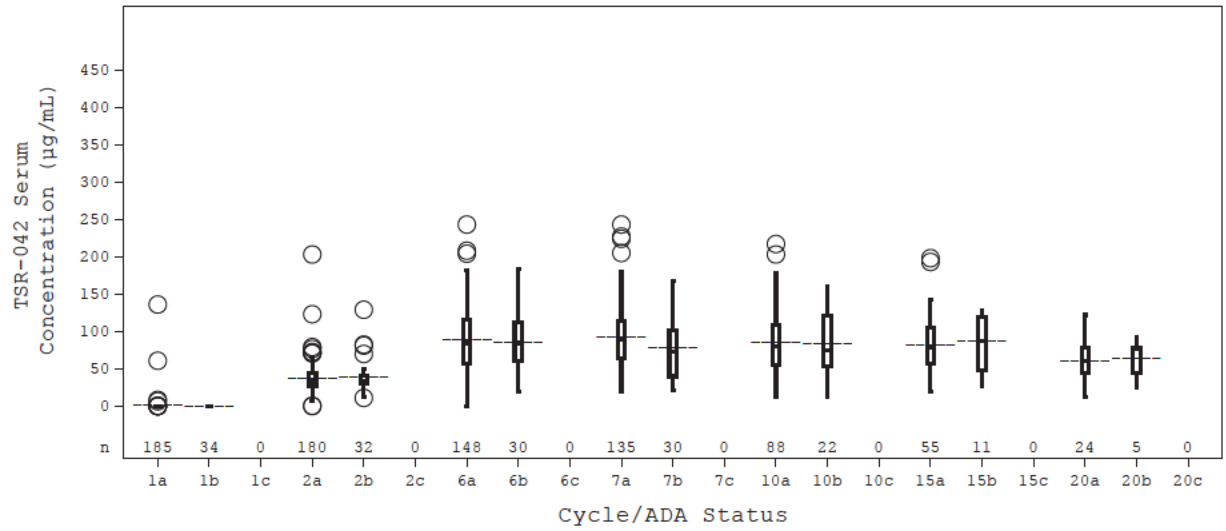
Applicant - Table 4: Incidence of Subjects with and without Treatment-Emergent Anti-Dostarlimab Antibodies Postbaseline, Overall and by MMR Status (ADA Population)

		Treatment-Emergent ADA [a]		Treatment-Unaffected ADA [b]		Negative for ADA [b]		Inconclusive ADA Status [b]	
Population	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Overall Population	225	0	0.0	34	15.1	185	82.2	6	2.7
dMMR/MSI-H	50	0	0.0	8	16.0	41	82.0	1	2.0
MMRp/MSS	175	0	0.0	26	14.9	144	82.3	5	2.9

Source: m5.3.5.1, study 213361 CSR; Table 66
ADA=antidrug antibody.
[a]Treatment-induced or -boosted
[b]Using drug tolerance limit of 250 µg/mL

Immunogenicity results were similar in participants with dMMR/MSIH or MMRp/MSS status. Observed serum dostarlimab concentrations were also similar in participants with ADA-positive samples at baseline (treatment unaffected ADA) and those who were negative for ADAs at all time points (Applicant - Figure 2) indicating no impact of preexisting ADAs on the PK of dostarlimab.

Applicant - Figure 2: Boxplots of Dostarlimab Serum Predose Concentrations for Part 1 Across Cycles Stratified by ADA Status on Linear Scale (Pharmacokinetic Analysis Set)



Source (m5.3.5.1, study 213361 CSR; Figure 27); Note: Boxes present median, 25% quartile, and 75% quartile. Whiskers are minimum and maximum excluding outliers (i.e values outside of 1.5 x of interquartile range). Outliers are presented by symbols and mean is shown as dashed line. 'n' is the number of observations with matched predose and immunogenicity results in each category.
ADA Status: a = ADA -ve subjects*;
b = Treatment-unaffected ADA subjects;
c = ADA+ve subjects who are treatment-boosted and induced.
*ADA -ve subjects include subjects who tested -ve at baseline as well as post dose.

In addition, based on the updated PopPK analysis, the development of ADAs was not found to have a significant effect on dostarlimab CL.

The efficacy and safety results were similar between participants with treatment-unaffected ADA and participants who tested negative at all time points. Furthermore, at this point in time there is no evidence of a clinically meaningful impact of preexisting ADA or NAb on any safety or efficacy measures. In summary, there were no treatment-emergent ADAs in Part 1 of the RUBY study and no observed impact of dostarlimab immunogenicity on safety, efficacy, or PK endpoints. These data are consistent with the immunogenicity results from the GARNET study, and confirm that the overall immunogenicity risk for dostarlimab is low.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Based on PK-PD analysis in the GARNET study, a target dostarlimab Cmin concentration of 18 µg/mL is needed to maintain 90% of maximal peripheral PD-1 suppression (Austin et al., 2023). The dosing regimen in RUBY is expected to result in Cmin,ss approximately 2-3 fold higher than the threshold required for 90% maximal peripheral PD-1 suppression, thus providing appropriate receptor occupancy.

Study 4010-03-001 (RUBY) met its primary endpoint of investigator-assessed PFS, by prolonging PFS in all participants with primary advanced or recurrent endometrial cancer (EC) and in participants with dMMR/MSI-H primary advanced or recurrent EC treated with dostarlimab in combination with carboplatin-paclitaxel versus placebo in combination with carboplatin-paclitaxel (details in section 8.1.2). The median OS was not reached for either treatment arm as of the data cutoff date of 28 September 2022. However, the interim OS data (33% maturity) support a strong numerical trend in favor of the dostarlimab plus carboplatin-paclitaxel arm compared to carboplatin-paclitaxel alone in the overall population.

The Applicant's Position:

The clinical pharmacology program provides supportive evidence of effectiveness and dosing regimen.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

The proposed dosing regimen for dostarlimab in combination with platinum-containing chemotherapy in the treatment of patients with primary advanced or recurrent endometrial cancer is 500 mg Q3W for 6 cycles and 1000 mg Q6W thereafter as an IV infusion over approximately 30 minutes. This dosing regimen was selected based on PopPK modeling and RO data and confirmed based on the clinical results of dMMR/MSI-H patients in RUBY Part 1 as well as PK/PD and E-R analyses for efficacy and safety endpoints (Module 2.7.2 Section 3.5 sequence 0004).

RUBY Part 1 was not designed to assess efficacy or safety at different dose levels, however, the findings from the population PK, and E-R analyses (Section 6.3.1) do not suggest that the dose regimen should be adjusted in the relevant patient population. This combined with meaningful efficacy responses in dMMR/MSI-H EC patients and overall acceptable safety profile of dostarlimab in combination with platinum-containing chemotherapy in RUBY Part 1 supports the choice of the therapeutic dose and regimen.

No clinically relevant E-R relationship was found for any of the investigated top 5 AEs related to dostarlimab when administered in combination with platinum-containing chemotherapy (arthralgia, diarrhea, fatigue, nausea and rash). The collective evidence from the clinical

efficacy, safety, population PK, and E-R analyses of efficacy/safety provide supportive evidence of the use of dostarlimab as a single agent at the dosing regimen of 500 mg Q3W for 6 cycles followed by 1000 mg Q6W for subsequent cycles.

The Applicant's Position:

The proposed dosing regimen of 500 mg Q3W for the first 6 cycles and 1000 mg Q6W thereafter administered as an IV infusion over approximately 30 minutes in combination with platinum-containing chemptherapy (first 6 cycles) is appropriate in the primary advanced or recurrent EC population.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:

In population PK analyses, potential covariates influencing the PK of dostarlimab have been evaluated (Section 6.3.1). Statistically significant covariates included: WT, time-varying ALB, time-varying ALT, sex, age, and coadministration with platinum-containing chemotherapy on CL and time-varying ALB, WT, and sex as covariates on Vc. The impact of these covariates on dostarlimab exposure was not clinically relevant. Therefore, no adjustment in dose or dosing regimen is required based on these covariates in patients receiving dostarlimab in combination with platinum-containing chemotherapy.

No statistically significant effects of mild to moderate renal impairment and mild hepatic impairment were found. There are limited data in participants with severe renal impairment, end-stage renal disease undergoing dialysis and moderate hepatic impairment and no data in the severe hepatic impairment category. Further, there was no effect of dMMR/MSI-H status, ECOG status, race, ethnicity, and geographic location on dostarlimab PK.

The Applicant's Position:

Dose adjustment is not required for subpopulations based on intrinsic and extrinsic patient factors based on the results of PopPK analyses.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

As dostarlimab is administered intravenously, no clinical assessment of potential food-drug interactions has been performed. No specific clinical studies to assess potential drug-drug interactions (DDIs) have been performed. However, dostarlimab is a mAb isotype IgG4. Nonspecific CL of mAbs through lysosome degradation disqualifies dostarlimab as a victim drug or a perpetrator in combination with small molecule drugs (Silva et al., 2015; Wang et al., 2014; Varga et al., 2015). In addition, there is no evidence of DDIs mediated by nonspecific CL of lysosome degradation for antibodies and comedicated biologic(s) (Silva et al., 2015). Dostarlimab is not a substrate for cytochrome P450 (CYP) or drug transporters and is not a cytokine. Dostarlimab did not stimulate cytokine release from peripheral blood mononuclear cells (Section 2.1.1.4 of m2.7.2 sequence 0004), suggesting that dostarlimab is unlikely to independently induce cytokine release during in vivo exposure and to change the expression of either CYP or drug transporters. Thus, dostarlimab is not deemed a perpetrator in DDIs with standard treatments, in this specific case, carboplatin (metabolized mainly through renal clearance as parent) in combination with paclitaxel (metabolized by CYP 2C8 and 3A4).

During the PopPK analysis, immune suppressors, immune stimulators, and systemic use of corticosteroids were planned to be evaluated as covariates. While there were not enough patients in each category of immune suppressors or stimulators for evaluation as covariates, the systemic use of corticosteroids as a separate covariate was evaluated. No impact of systemic use of corticosteroids on dostarlimab PK was found. Prior lines of therapy (1^{st} vs. 2^{nd}) in EC, and prior external pelvic radiotherapy were evaluated as possible covariates in E-R analyses and were not found to be significant. Dostarlimab in combination with platinum-containing chemotherapy resulted in slightly higher exposure (1.08 fold higher AUC) compared to dostarlimab alone. Nevertheless, the impact of coadministration with platinum-containing chemotherapy on dostarlimab exposure was limited and not of clinical relevance.

The Applicant's Position:

As dostarlimab is administered intravenously, no food-drug interactions are anticipated. As summarized above, the current assessment is that the risk for clinically relevant DDIs is low.

The FDA's Assessment:
FDA agrees with the Applicant's position.

X X

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Applicant - Table 5: Listing of Clinical Trials Relevant to This BLA

Trial Identity, NCT Number	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/ Follow Up	Number of Patients	Study Population	Number of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
213361 (also RUBY, 4010-03-001; ENGOT EN-6; GOG-3031) **NCT03981796** Part 1	Multicenter, randomized; double-blind; placebo controlled; parallel group	Dostarlimab 500 mg Q3W for first 6 cycles, and then 1000 mg Q6W for all subsequent cycles or placebo Q3W for first 6 cycles, and then Q6W for all subsequent cycles plus carboplatin AUC of 5 and paclitaxel 175 mg/m^2 Q3W for 6 cycles	Primary: PFS based on investigator assessment per RECIST v1.1, OS Secondary: PFS per BICR, ORR, DCR, DOR, PFS2, PROs, safety	Up to 3 years or until progressive disease, withdrawal of consent, investigator's decision, or death	245 dostarlimab, 249 placebo/	Primary advanced or recurrent EC and dMMR/MSI-H primary advanced or recurrent EC	Part 1: 158 centers in 19 countries
Uncontrolled Studies to Support Pharmacokinetics of Dostarlimab							
4010-01-001 (GARNET), NCT 02715284	Multicenter open-label, first-in-human, 2-part, dose escalating and expansion study	Part 1 (dose escalation): Dostarlimab 1, 3, or 10 mg/kg Q2W IV Part 2A (fixed-dose): Q6W Cohort - Dostarlimab 1000 mg Q6W IV; Q3W Cohort - Dostarlimab 500 mg Q3W IV Part 2B (expansion): Dostarlimab 500 mg Q3W IV for first 4 cycles, dostarlimab 1000 mg Q6W IV for all subsequent cycles (all cohorts)	Primary: Cohorts A1, A2, F: ORR and DOR by BICR Cohort E: irORR by Investigators' assessment Secondary: PK, immunogenicity, safety, ORR, irORR, DCR, irDCR, DOR, irDOR, PFS, irPFS, and OS	Up to 2 years, or until the subject meets protocol specific discontinuation criteria	Part 1: 21 Part 2A: 13 Part 2B: Cohort A1: 153, Cohort A2: 161, Cohort E: 67, Cohort F: 210; Cohort G: 14	Parts 1/2A: Advanced solid tumors Part 2B: Cohort A1: dMMR/MSI-H EC Cohort A2: MMRp/MSS EC Cohort E: NSCLC Cohort F: dMMR/MSI-H or POLE-mut solid tumors Cohort G: Recurrent high-grade serous, endometrioid, or clear cell ovarian, fallopian tube, or primary peritoneal cancer	Part 1/2A: 3 sites across 1 country Part 2B: Cohorts A1 and A2 - 84 sites across 8 countries Cohort E: 22 across 6 countries Cohort F: 49 sites across 8 countries Cohort G: 11 sites across 3 countries

ADA=anti-drug antibody; AUC=area under the concentration time curve; BICR=blinded independent central review; DCR=disease control rate; DLT=dose-limiting toxicity; dMMR=mismatch repair-deficient; DOR=duration of response; EC=endometrial cancer; irDCR=immune-related disease control rate; irDOR=immune-related duration of response; irORR=immune-related objective response rate; irPFS=immune-related progression-free survival; irRECIST=immune-related response evaluation criteria in solid tumors; IV=intravenous; MMRp=mismatch repair proficient; MSI-H=microsatellite instability-high; MSS=microsatellite stable; NCT=national clinical trial; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PK=pharmacokinetic; PO=by mouth; POLE-mut=DNA polymerase epsilon mutation; QD=daily; QxW=every x weeks; RECIST=response evaluation criteria in solid tumors; RP2D=recommended phase II dose

The FDA's Assessment:

For this sBLA application, the clinical data for the FDA's analysis of efficacy and safety were based on the data from RUBY Part 1 in support of the combination of dostarlimab with carboplatin-paclitaxel in patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer. The FDA's evaluation of the Applicant's PPK analysis is based on the data from GARNET trial and RUBY Part 1.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Dostarlimab Study 213361, RUBY

Trial Design

The Applicant's Description:

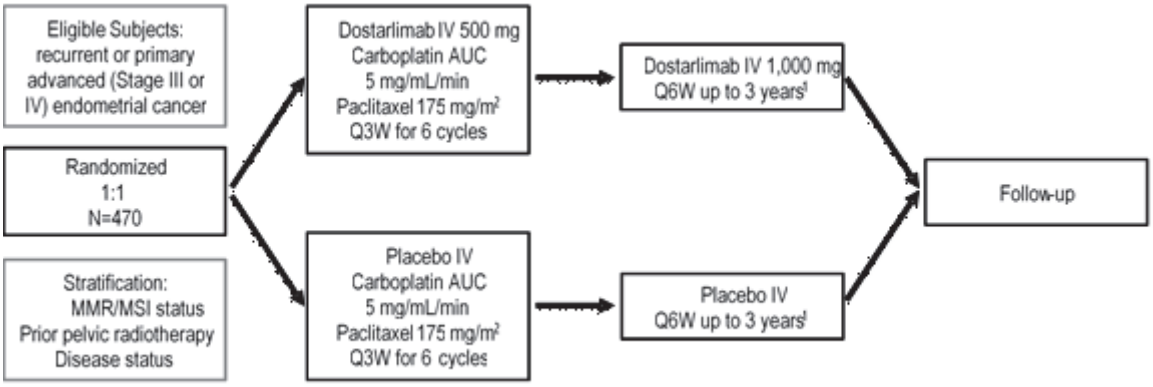
RUBY is a Phase 3, randomized, double-blind, multicenter study. Part 1 of the study is to evaluate the efficacy and safety of treatment with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab versus treatment with placebo plus carboplatin-paclitaxel followed by placebo in participants with primary advanced (Stage III or IV) or recurrent EC.

The RUBY study consists of a Screening Period (Day -28 to -1), Treatment Period, End of Treatment Visit, Safety Follow-up Visit, and Survival Assessment Period (Applicant - Figure 3). Following informed consent, eligible participants were randomized 1:1:

- Arm 1: Participants received dostarlimab IV plus carboplatin-paclitaxel followed by dostarlimab IV.
- Arm 2: Participants received placebo IV plus carboplatin-paclitaxel followed by placebo IV.

Randomization for each arm was stratified by MMR/MSI status (dMMR/MSI-H or MMR-proficient [MMRp]/MSS), prior external pelvic radiotherapy (yes or no), and disease status (recurrent, primary Stage III, or primary Stage IV). Approximately 470 participants were planned for enrollment in Part 1.

Applicant - Figure 3. Study 213361 Part 1 design



Abbreviations: AUC=area under the plasma or serum concentration-time curve; IV=intravenous; MMR=mismatch repair of DNA; MSI=microsatellite instability; QxW=every x weeks.

[1] Treatment ends after 3 years, progression of disease, toxicity, withdrawal of consent, Investigator's decision, or death, whichever occurs first. Continued treatment with dostarlimab or placebo IV beyond 3 years may be considered following discussion between the sponsor and the Investigator.

Following randomization, eligible participants began Cycle 1 treatment in the assigned treatment arm. Study intervention administration occurred in 3-week cycles for the first 6 cycles and in 6-week cycles for all following cycles starting with Cycle 7. Assessments were performed as illustrated in the Schedule of Events provided in the Protocol. Study intervention continued up to 3 years or until progressive disease (PD), unacceptable toxicity, withdrawal of consent, Investigator's decision, or death. Treatment beyond 3 years could be considered following discussion between the Investigator and Sponsor. Participants with PD who were clinically stable could continue treatment at the Investigator's discretion after discussion with the Sponsor, until the Investigator determined that the participant was no longer experiencing clinical benefit or until study treatment was no longer tolerated by the participant.

The FDA's Assessment:
FDA agrees with the Applicant's summary of the trial design for RUBY Part 1.

Eligibility Criteria

The Applicant's Description:

Inclusion criteria

1. Female, ≥18 years of age, able to understand the study procedures, and agrees to participate in the study by providing written informed consent.
2. Histologically or cytologically proven EC with advanced or recurrent disease.
3. Adequate tumor tissue sample at Screening for MMR/MSI status testing.
4. Primary Stage III or Stage IV disease or first recurrent EC with a low potential for cure by radiation therapy or surgery alone or in combination and at least 1 of the following:
    a. Primary Stage IIIA to IIIC1 disease with presence of evaluable or measurable disease per RECIST v.1.1 based on Investigator's assessment. Lesions that are equivocal or can be representative of post-operative change should be biopsied and confirmed for the presence of tumor.
    b. Primary Stage IIIC1 disease with carcinosarcoma, clear cell, serous, or mixed histology (containing ≥10% carcinosarcoma, clear cell, or serous histology), regardless of presence of evaluable or measurable disease on imaging.
    c. Primary Stage IIIC2 or Stage IV disease, regardless of presence of evaluable or measurable disease.
    d. First recurrent disease and is naïve to systemic anticancer therapy.
    e. Received prior neoadjuvant/adjuvant systemic anticancer therapy and had a recurrence or PD ≥6 months after completing treatment (first recurrence only).

    Note: Participants with uterine sarcoma are not allowed.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Participant has adequate organ function.

Exclusion criteria

1. Received neoadjuvant/adjuvant systemic anticancer therapy for primary Stage III or IV disease and 1 of the following:
   a. Has not had a recurrence or PD prior to first dose on the study, or
   b. Has had a recurrence or PD within 6 months of completing systemic anticancer therapy treatment prior to first dose on the study

   Note: Low-dose cisplatin given as a radiation sensitizer or hormonal therapies do not exclude participants from study participation.
2. Had >1 recurrence of EC.
3. Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
4. Received prior anticancer therapy within 21 days or <5 times the halflife of the most recent therapy prior to Study Day 1, whichever is shorter. Note: Palliative radiation therapy to a small field of ≥1 week prior to Day 1 of study intervention is allowed.
5. Concomitant malignancy, prior nonendometrial invasive malignancy but has been disease free for <3 years, or received any active treatment in the last 3 years for that malignancy. Nonmelanoma skin cancer is allowed.
6. Known uncontrolled central nervous system metastases, carcinomatosis meningitis, or both. Note: Participants with previously treated brain metastases may participate provided they are stable (without evidence of PD by imaging [using the identical imaging modality for each assessment, either magnetic resonance imaging {MRI} or computed tomography {CT} scan] for at least 4 weeks prior to the first dose of study intervention and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and have not been using steroids for at least 7 days prior to study intervention. Carcinomatous meningitis precludes a participant from study participation regardless of clinical stability.

The FDA's Assessment:
FDA agrees with the Applicant's summary of the RUBY Part 1 eligibility criteria.

Study Endpoints

Applicant - Table 6: Summary of Objectives and Endpoints

	Objectives	Endpoints
Primary	To compare the PFS of participants treated with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab to participants treated with placebo plus carboplatin-paclitaxel followed by placebo, as assessed by Investigator per RECIST v.1.1, in the following: • Participants with dMMR/MSI-H primary advanced or recurrent EC • All participants with primary advanced or recurrent EC	The primary efficacy endpoint is PFS based on Investigator assessment, which is defined as the time from the date of randomization to the earliest date of radiographic assessment of progressive disease (PD) or death by any cause in the absence of PD, whichever occurs first.

	Objectives	Endpoints
	To compare the OS of participants treated with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab to participants treated with placebo plus carboplatin-paclitaxel followed by placebo • All participants with primary advanced or recurrent EC.	**Assessments:** Tumor Response, Radiographic Evaluation
Secondary	To evaluate the following measures of clinical benefit of treatment with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab to treatment with placebo plus carboplatin-paclitaxel followed by placebo in dMMR/MSI-H and all participants with primary advanced or recurrent EC: • PFS based on BICR assessment • ORR based on BICR and Investigator assessment • DOR based on BICR and Investigator assessment • DCR based on BICR and Investigator assessment • PROs: European Quality of Life scale, 5 Dimensions, 5-Levels (EQ-5D-5L) and European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (C30 [Core; QLQ-C30] and EC Module [QLQ-EN24]) • Progression-free survival 2 (PFS2), defined as the time from treatment randomization to the date of assessment of progression on the first subsequent anticancer therapy following study intervention or death by any cause, whichever is earlier.	OS, PFS, ORR, DOR, DCR, PFS2, PRO, safety, PK and Immunogenicity of dostarlimab
	To evaluate the safety and tolerability of dostarlimab plus carboplatin-paclitaxel followed by dostarlimab compared to placebo plus carboplatin-paclitaxel followed by placebo (all-comers)	
	To assess the PK and immunogenicity of dostarlimab when given in combination with carboplatin and paclitaxel	

The FDA's Assessment:

FDA agrees with the Applicant's summary of primary and secondary objectives and endpoints. In the dMMR/MSI-H population, investigator-assessed PFS is the primary endpoint and OS is a secondary endpoint. In the all-comers population, both investigator-assessed PFS and OS are primary endpoints.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The original statistical analysis plan was issued 9 October 2019 and amended once on 06 October 2022 prior to the unblinding of RUBY Part 1 on 23 November 2022. The analyses presented in this report are based on data contained in the reporting database as of the cutoff date of 28 September 2022.

Sample Size Considerations

The sample size calculation was driven by the primary efficacy endpoint of PFS, as assessed by the Investigator using RECIST v.1.1. The following assumptions were made for the sample size calculation:

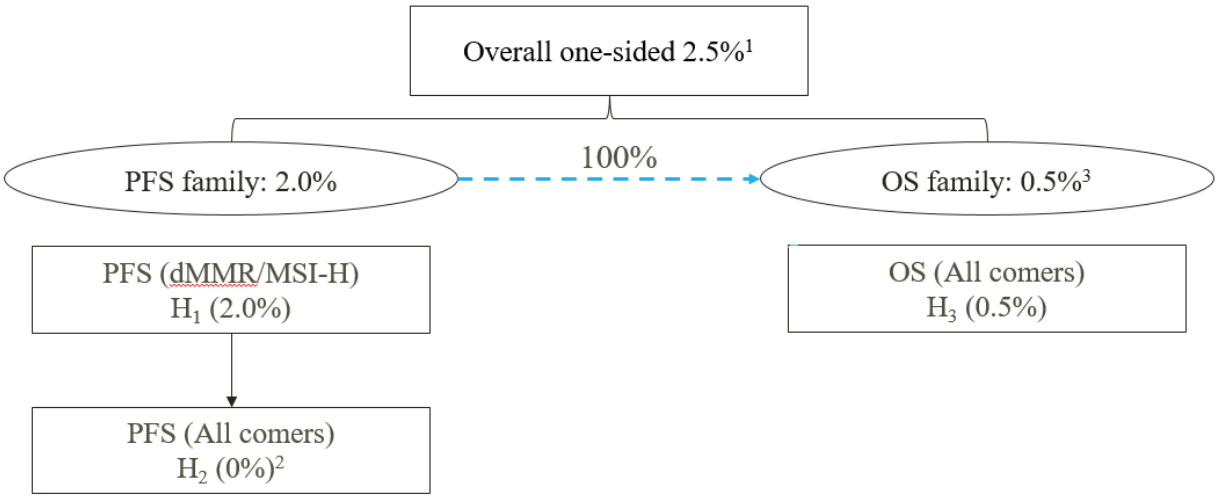
- dMMR/MSI Status Independent Participant Population (all-comers): HR of 0.67, corresponding to an increase in median PFS from 10 months in the placebo plus carboplatin-paclitaxel arm to 15 months in the dostarlimab plus carboplatinpaclitaxel arm
- dMMR/MSI-H Participant Population: HR of 0.50, corresponding to an increase in median PFS from 10 months in the placebo plus carboplatin-paclitaxel arm to 20 months in the dostarlimab plus carboplatin-paclitaxel arm
- Participant distribution by tumor MMR/MSI status: 25% with dMMR/MSI-H and 75% with MMRp/MSS
- 1:1 randomization
- Alpha=0.02 (1-sided)
- Power=approximately 89% for testing of H1
- Accrual over a period of 22 months
- Assuming an annual dropout rate of 5%
- Exponential distribution of PFS

With the assumptions above, and a group sequential log-rank test design with 2 analyses was planned: 1 IA at approximately 84.6% information and 1 FA, based on a LanDeMets (O'Brien-Fleming) alpha spending function [Lan, 1983] a total sample size of 470 participants was planned, and approximately 118 participants were expected to be dMMR/MSI-H. To maintain the natural distribution of dMMR/MSI-H (25%) and MMRp/MSS (75%) participants in the overall EC population in this study, the number of participants enrolled with dMMR/MSI-H or MMRp/MSS EC would be capped at approximately 120 or 350, respectively. In addition, the total number of participants with carcinosarcoma was capped at 50 (approximately 10%) to prevent overrepresentation of this patient population.

Multiplicity Adjustment

Part 1 of the study used the graphical method [Maurer, 2013] to provide strong multiplicity control for multiple hypotheses as well as interim analyses. The family-wise type I error for this study is strongly controlled at 2.5% (one-sided). The initial one-sided alpha-allocation for PFS and OS is presented graphically in Applicant - Figure 4. Hypotheses presented as nodes in squares are divided into 2 subfamilies presented in ellipsoids. The weights for re-allocation from each subfamily/hypothesis to the others are represented on the lines connecting hypotheses.

Applicant - Figure 4: Multiplicity Control Strategy for Comparisons Between Dostarlimab plus Carboplatin-Paclitaxel Followed by Dostarlimab and Placebo plus Carboplatin-Paclitaxel Followed by Placebo



1. The alpha level assigned to a subfamily will be rolled over only if the hypotheses within the subfamily are all significant based on the weight for re-allocation presented on the dashed lines connecting subfamilies. Within each subfamily, the weights for re-allocation from each hypothesis to the others are represented on the solid lines connecting hypotheses.
2. Hypothesis testing for PFS in all-comers will only be performed if null hypothesis of PFS has been rejected in dMMR/MSI-H.
3. Hypothesis testing for OS will start at the time when the hypothesis testing for PFS has completed (i.e., no further hypothesis testing could be performed for PFS), at re-allocated alpha level (2.5%) if both null hypotheses have been rejected for H1 and H2; otherwise, OS will be tested at initial alpha level (0.5%).

Interim Analyses

To test hypothesis 1 (H1) (PFS in dMMR/MSI-H), a stratified group sequential log-rank test with one IA and one FA was planned. The IA was planned at approximately 77 events, and the FA was planned at 91 events. The boundary for declaring superiority of Arm 1 over Arm 2 is based on a Lan-DeMets (O'Brien-Fleming) alpha spending function [Lan, 1983] with overall alpha=0.02, 1-tailed. The IA of PFS in dMMR/MSI-H was based on the data cutoff date of 28 September 2022, when 66 PFS events were observed in the dMMR/MSI-H population. The stopping boundary was adjusted based on the actual observed number of PFS events with a p-value stopping boundary=0.00630.

To test hypothesis 3 (H3) (OS in all-comers), a stratified group sequential log-rank test based on a Lan-DeMets (O'Brien-Fleming) alpha spending function [Lan, 1983] was planned. Based on the positive testing results of PFS in both the dMMR/MSI-H (H1) and all-comers (H2) populations at the IA of PFS in dMMR/MSI-H population, the alpha level and number of planned analyses for OS followed scenario 1 in Table 13 of Protocol Section 13.3 (i.e., OS was tested at one-sided alpha level of 0.025 with 3 planned IAs and 1 FA at 321 OS events).

The first IA of OS was conducted at the same time as the IA of PFS in the dMMR/MSI-H population, when 165 deaths were observed. The stopping boundary for this first IA of OS was adjusted based on the actual observed number of deaths with a p-value stopping boundary of 0.00177.

The IA to assess superiority was performed by an IDMC. The stopping rules described in the IDMC charter and Protocol Section 13.3 were guidelines for decision-making and the totality of the data was considered when making a decision.

Full details of the interim analyses are provided in the IDMC charter and the Protocol Section 13.3.

The planned interim analyses were performed after the completion of the following sequential steps:

1. All required database cleaning activities were completed, database release and database freeze were declared by Data Management
2. All criteria for unblinding the randomization codes/kit numbers were met
3. Randomization codes/kit Numbers were distributed according to RUBY Study Unblinding Plan for Planned Analyses.

The FDA's Assessment:

The MMR/MSI status (dMMR/MSI-H or MMR-proficient [MMRp]/MSS) is one of three stratification factors for RUBY Part 1. There are two sources of the data for stratification factors: one is from the randomization list, and the other one is from eCRF. In general, when biomarker status is a stratification factor, formally tested subgroup analyses for biomarker subgroups should be based on biomarker status used for randomization since this impacts how patients were randomized. The protocol and SAP for RUBY study also stated that the primary efficacy analyses were planned to be based on the stratum assigned at randomization, and efficacy analyses by using the actual values from the eCRF for the stratification factors were sensitivity analyses.

In RUBY Part 1 Clinical Study Report and the original Assessment Aid, the Applicant provided efficacy analyses for the dMMR/MSI-H population and MMRp/MSS population based on MMR/MSI status collected from eCRF. The FDA sent an Information Request and required the Applicant to revise the Assessment Aid with efficacy results based on MMR/MSI status used for randomization. The current version of Assessment Aid summarizes efficacy results based on MMR/MSI status used for randomization.

In the Subsection of INTERIM ANALYSIS, the number of events and efficacy stopping boundaries for PFS reported by the Applicant are based on the dMMR/MSI-H population determined by MMR/MSI status collected from eCRF. FDA's efficacy evaluation is based on the dMMR/MSI-H

population with MMR/MSI status used for randomization. At the DCO date of September 28, 2022, in the dMMR/MSI-H population with MMR/MSI status used for randomization, the number of investigator-assessed PFS events should be 70 (77% information fraction), and the one-sided p-value stopping boundary should be 0.0081.

In the all-comers population, final OS analysis is planned to be conducted when 321 OS events have been observed. Second and third interim analyses of OS are planned to be conducted when 221 (69% information fraction) and 273 (85% information fraction) OS events have been observed, respectively.

No multiplicity adjustment was planned for the analysis of OS in the dMMR/MSI-H population.

Protocol Amendments

The Applicant's Description:

The original protocol was issued on 13 March 2019. Three global amendments to the study protocol were implemented prior to the time of the data cutoff.

High-level summaries of key changes for each amendment are presented below. Full descriptions of each amendment are provided in the Protocol.

Protocol amendment 1 (Version 2.0, Dated 11 November 2020)

- The addition of Part 2 to the RUBY study to evaluate the efficacy and safety of treatment with dostarlimab plus carboplatin-paclitaxel followed by dostarlimab plus niraparib (Arm 3) versus treatment with placebo plus carboplatin-paclitaxel followed by placebo (Arm 4) in subjects with recurrent or primary advanced (Stage III or IV) endometrial cancer.
- The primary endpoint was changed from PFS per Investigator Assessment to PFS per BICR. This was to mitigate the potential risk of bias associated with some investigators requesting to unblind treatment allocation when participants entered the treatment maintenance phase, to keep those that were assigned to the placebo arm from visiting the study site during the COVID-19 pandemic.

Protocol amendment 2 (Version 3.0, Dated 23 September 2021)

- To revise the RUBY Part 1 statistical design to include both PFS and OS as dual primary endpoints with alpha splitting (one-sided 0.02 for PFS and one-sided 0.005 for OS), which also allows alpha recycling from PFS to OS.
- Within PFS, the original Hochberg procedure for multiplicity control of hypothesis testing was revised to a hierarchical testing strategy for PFS in the dMMR/MSI-H followed by the overall population.

Protocol amendment 3 (Version 4.0, Dated 31 March 2022)

- The primary endpoint was reverted to PFS assessed by the investigator, as was initially proposed with the original protocol. Accordingly, PFS assessed by BICR was changed to a secondary endpoint. The potential risk of bias that drove the initial amendment in the primary objective did not materialize as only 4 participants were eventually unblinded in one site in the United States. Therefore, the primary endpoint was reverted to the original design of PFS per Investigator assessment (RECIST v1.1).
- The statistical design for RUBY Part 2 was updated. Per regulator feedback, the interim PFS analysis was removed. Additionally, the nominal power of PFS was increased to mitigate the impact of potential non-proportional hazards. Hypothesis testing for key secondary endpoint OS was added.

The FDA's Assessment:
FDA agrees with the Applicant's summary of the protocol amendments regarding Part 1 of RUBY trial.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

The study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board, in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) and applicable country-specific requirements, including US 21 Code of Federal Regulations 312.3(b) for constitution of independent ethics committees. Ethics committee or institutional review board approvals are maintained in the sponsor's study file.

Investigators were trained to conduct the study in accordance with GCPs and the study protocol, as defined in ICH E3, Section 9.6. Written commitments were obtained from Investigators to conduct the study in accordance with ICH GCP and all applicable participant privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2013, and to conduct the study in accordance with the protocol.

The study was monitored in accordance with ICH E6, Section 5.18. If significant findings (e.g., potential serious misconduct or noncompliance with GCP, including potential Serious Breaches) were identified during monitoring or auditing of a site, these are presented in Section 5.2, Protocol Deviations, of the Clinical Study Report.

Written informed consent was obtained from each participant prior to the performance of any study-specific procedures. The participant was given as much time as necessary to review the document, to inquire about details of the trial, before they decided whether or

not to participate in the study. The informed consent was signed and dated by the study participant and by the person who conducted the informed consent discussion. Each participant's data were recorded in case report forms.

The FDA's Assessment:
FDA agrees with the Applicant's position that there is no evidence that compliance with good clinical practices was violated during conduct of RUBY Part 1.

Financial Disclosure

The Applicant's Position:

In accordance with 21 CFR 54, the Sponsor submitted a financial disclosure certification document. The financial disclosure document contain all Investigators who participated in the covered clinical study (RUBY, 213361): those with disclosable financial interests, no disclosable interests, and those whose financial disclosure information is missing or incomplete.

Of 819 total investigators who participated in Study 213361, there were 10 investigators who received varying amounts of compensation from GSK for activities such as grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.

The Sponsor provided a list of all Investigators and sub investigators from Study 213361 who had no disclosable interests and a copy of the certification (Option 1 on Form FDA 3454, List A) for these participants. For the Investigators and sub investigators with missing financial disclosure information, the Sponsor submitted certification that TESARO/GlaxoSmithKline acted with due diligence but was unable to obtain the missing information (Option 3 on Form FDA 3454, List B).

The FDA's Assessment:
FDA agrees with the Applicant's assessment. Refer also to Section 19.2 of this Assessment Aid.

Patient Disposition

The Applicant's Position:

As of the data cutoff date, 494 participants were included and randomized in the overall ITT population: 245 participants randomized to dostarlimab plus carboplatin-paclitaxel followed by dostarlimab (Arm 1), and 249 participants randomized to placebo plus carboplatin-paclitaxel followed by placebo (Arm 2). Overall, 241 participants received at least 1 dose of dostarlimab in the dostarlimab plus carboplatin-paclitaxel arm, and 246 patients received at least 1 dose of placebo but did not receive any dostarlimab in the placebo plus carboplatin-paclitaxel arm. The pre-specified primary analysis for efficacy based on dMMR/MSI-H classification as randomized included 60 participants in the dostarlimab plus carboplatin-paclitaxel arm and 62 participants in the placebo plus carboplatin-paclitaxel arm.The dMMR/MSI-H Safety Analysis Set, based on source verified dMMR/MSI-H classfication, included 52 participants in the dostarlimab plus carboplatin-paclitaxel arm and 65 participants in the placebo plus carboplatin-paclitaxel arm.

In the overall population, twenty-six participants in the dostarlimab plus carboplatin-paclitaxel arm and 17 participants in the placebo plus carboplatin-paclitaxel arm discontinued study due to withdrawal of consent. The most common reason for withdrawal of consent in both groups was that they were no longer willing to participate in study treatment or procedures (17 dostarlimab arm, 11 placebo arm), primarily following treatment discontinuation due to disease/clinical progression (3 dostarlimab plus carboplatin-paclitaxel arm; 6 placebo plus carboplatin-paclitaxel arm) or adverse events (3 in each arm), or no reason provided (9 dostarlimab plus carboplatin-paclitaxel arm, 1 placebo plus carboplatin-paclitaxel arm).

In both treatment arms, the most common reason for dostarlimab or placebo discontinuation was PD according to RECIST v.1.1 criteria per Investigator assessment. The most common reason for discontinuation of carboplatin or paclitaxel was AE. One participant who died and discontinued from study, is still being counted under "ongoing on paclitaxel" due to unavailability of end of treatment data for paclitaxel in the database.

Key patient disposition data is summarized in Applicant - Table 7 and participant treatment status is summarized in Applicant - Table 8.

Applicant - Table 7: Patient Disposition (ITT Population)

Variable Reason [n (%)]	dMMR/MSI-H		All Participants	
	Dostar + carbo/pac (N=60)	Placebo + carbo/pac (N=62)	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)
Participant Status				
Discontinued from Study	16 (26.7%)	32 (51.6%)	100 (40.8%)	124 (49.8%)
Ongoing	44 (73.3%)	30 (48.4%)	145 (59.2%)	125 (50.2%)
On Study Treatment	24 (40.0%)	6 (9.7%)	52 (21.2%)	36 (14.5%)
In Follow-up	20 (33.3%)	24 (38.7%)	93 (38.0%)	89 (35.7%)
Reasons for Discontinuation from Study				
Withdrawal of consent	4 (6.7%)	3 (4.8%)	26 (10.6%)	17 (6.8%)
Lost to follow up	3 (5.0%)	3 (4.8%)	5 (2.0%)	5 (2.0%)
Death from any cause	8 (13.3%)	25 (40.3%)	65 (26.5%)	100 (40.2%)
Sponsors decision to terminate study	0	0	0	0
Other	1 (1.7%)	1 (1.6%)	4 (1.6%)	2 (0.8%)
Main Cause of Death				
Disease Progression	6 (10.0%)	20 (32.3%)	57 (23.3%)	87 (34.9%)
Adverse Event	2 (3.3%)	0	6 (2.4%)	2 (0.8%)
Unknown	0	5 (8.1%)	2 (0.8%)	11 (4.4%)
Other	0	0	0	0

Applicant - Table 8: Subject Treatment Status (Safety Population)

Variable Reason [n (%)]	dMMR/MSI-H		All Participants	
	Dostar + carbo/pac (N=52)	Placebo + carbo/pac (N=65)	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)
Participants Treatment Status				
Discontinued Dostarlimab/ Placebo	29 (55.8%)	57 (87.7%)	189 (78.4%)	210 (85.4%)
Discontinued Paclitaxel	52 (100%)	64 (98.5%)	241 (100%)	245 (99.6%)
Discontinued Carboplatin	52 (100%)	65 (100%)	241 (100%)	246 (100%)
Reasons for Discontinuing Treatment with Dostarlimab/Placebo				
PD per RECIST 1.1 by IA	13 (25.0%)	40 (61.5%)	107 (44.4%)	160 (65.0%)
AE	9 (17.3%)	7 (10.8%)	45 (18.7%)	24 (9.8%)
Clinical Progression	1 (1.9%)	0	3 (1.2%)	8 (3.3%)
Lost to follow-up	1 (1.9%)	1 (1.5%)	1 (0.4%)	1 (0.4%)
Death from any cause	1 (1.9%)	0	2 (0.8%)	1 (0.4%)
Risk to subject as judged by Investigator/Sponsor, or both	1 (1.9%)	2 (3.1%)	4 (1.7%)	2 (0.8%)
Withdrawal by Subject	1 (1.9%)	3 (4.6%)	20 (8.3%)	7 (2.8%)
Severe noncompliance with the protocol	0	1 (1.5%)	1 (0.4%)	1 (0.4%)
Other	2 (3.8%)	3 (4.6%)	6 (2.5%)	6 (2.4%)

The FDA's Assessment:

FDA's review of patient disposition is based on review of the dMMR/MSI-H subpopulation data submitted with this sBLA. The FDA generally agrees with the Applicant's assessment in Table 7. See Section 8.2.4 for FDA's review of the Applicant's assessment of safety provided in Table 8.

Protocol Violations/Deviations

The Applicant's Position:

In May 2020, the clinical study transitioned from TESARO protocol deviation definitions and methodologies to those of GSK. Discussion of protocol deviations focused on significant protocol deviations (according to the TESARO definition) and important protocol deviations (according to the TESARO and GSK definitions) as these align protocol deviation categories with potential impact on study integrity or participant safety. It was noted that the SAP definition did not include significant protocol deviations (TESARO definition), therefore a posthoc analysis was performed to include these in the summary of the protocol deviation data. The relatively high frequency of resulting protocol deviations is likely due to the variation in the definitions in the two methodologies, since the TESARO definitions included categories with a broader scope. None of these significant (according to the TESARO definition) or important (according to the TESARO and GSK definition) protocol deviations were ultimately considered to affect the participants' safety or well-being or the overall integrity of the study.

In the dostarlimab plus carboplatin-paclitaxel arm, 219 important protocol deviations (which includes TESARO significant, TESARO important, and GSK important definition) were recorded for 105 participants, with 69 important protocol deviations in 30 participants in the dMMR/MSI-H population. In the placebo plus carboplatin-paclitaxel arm, 211 important protocol deviations were recorded for 87 participants, with 65 important protocol deviations in 21 participants in the dMMR/MSI-H population.

The most frequently reported protocol deviation category was assessment or time point completion in both treatment arms. Most deviations in this category, 41 participants (50 events) in the dostarlimab plus carboplatin-paclitaxel arm and 25 participants (31 events) in the placebo plus carboplatin-paclitaxel arm, were out of window efficacy assessments. Other noteworthy protocol deviation categories included wrong study treatment/administration/dose, failure to report safety events per protocol, and eligibility criteria not met.

The FDA's Assessment:
There were 69 important protocol deviations in 30 patients in the dMMR/MSI-H population identified by the Applicant. FDA agrees that the protocol deviations described did not compromise the overall efficacy and safety outcomes of the trial.

Table of Demographic Characteristics

The Applicant's Position:

Most participants were white (>70%) with a median age of 65 years and baseline ECOG status of 0 (Applicant - Table 9). There were no significant differences in participant baseline demographics between treatment arms in the overall and dMMR/MSI-H populations (Applicant - Table 8). The placebo plus carboplatin/paclitaxel arm had a slightly higher proportion of participants in the ≥65 years age group (58.1% versus 41.7%). Mean weight and BMI were slightly higher in the placebo plus carboplatin-paclitaxel arm compared with the dostarlimab plus carboplatin-paclitaxel arm (92.11 kg and 34.94 kg/m^2 versus 83.1 kg and 31.36 kg/m^2, respectively). ECOG status was worse in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm (44.1% with ECOG status of 1 compared with 41.9%).

Applicant - Table 9: Summary of demographic characteristics (ITT analysis set)

Variable Reason [n (%)]	dMMR/MSI-H		All Participants	
	Dostar + carbo/pac (N=60)	Placebo + carbo/pac (N=62)	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)
Age				
n	60	62	245	249
Median	61.0	66.0	64	65
Min, Max	45, 81	39, 85	41, 81	28, 85
≥65	25 (41.7%)	36 (58.1%)	118 (48.2%)	135 (54.2%)
ECOG Score				
n	59	62	241	246
0	33 (55.9%)	36 (58.1%)	145 (60.2%)	160 (65.0%)
1	26 (44.1%)	26 (41.9%)	96 (39.8%)	86 (35.0%)
BMI				
n	59	62	240	246
Median	29.60	35.35	30.80	32.75
Min, Max	20.1, 54.4	17.9, 58.1	17.6, 60.6	17.7, 68.0
Prior Anticancer Treatment				
n	60	62	245	249
Prior Surgery	56 (93.3%)	57 (91.9%)	224 (91.4%)	224 (90.0%)
Any Prior Anticancer Treatment	10 (16.7%)	12 (19.4%)	48 (19.6%)	52 (20.9%)

The FDA's Assessment:

FDA agrees with the Applicant's assessment regarding demographics characteristics, except that less patients were ≥65 years old in the dostarlimab plus carboplatin-paclitaxel arm compared to patients in the placebo plus carboplatin-paclitaxel arm in the dMMR/MSI-H population. A sensitivity analysis of PFS per investigator assessment adjusting for age group in the dMMR/MSI-H population was conducted by the FDA. More details are included in the EFFICACY RESULTS subsection of this review document. There were no noteworthy differences in ECOG score and prior anticancer treatment between the two treatment arms in both dMMR/MSI-H population and all-comers population. Race and region are also balanced between treatment arms.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

With regard to histology at diagnosis, the distribution was reflective of what would be expected for participants with primary advanced or recurrent EC. Of the overall study population, approximately 25% were participants with dMMR/MSI-H EC. The proportion of participants with dMMR/MSI-H EC enrolled in the study was capped at approximately 25% to reflect the known prevalence of these tumors in the EC population.

As expected, there was a higher proportion of the more aggressive histological sub-types, including carcinosarcoma, serous and clear cell in the overall population compared with the dMMR/MSI-H population (Applicant - Table 10). These were balanced between the arms. There were 6 participants with carcinosarcoma in the dMMR/MSI-H population, with the majority (5 participants) in the dostarlimab plus carboplatin-paclitaxel arm vs 1 participant in the placebo plus carboplatin-paclitaxel arm. The frequency of endometrioid tumors was higher in the dMMR/MSI-H population, with 81.1% having endometrioid histology.

These distributions are expected based on the known association of MMR status with histology and are representative of the population with primary advanced or recurrent EC.

Based on stratrification, the majority of participants had no prior external pelvic radiotherapy in the dMMR/MSI-H population (83.9%and the overall population (72%). The majority of participants with dMMR/MSI-H primary advanced or recurrent EC enrolled in RUBY Part 1 were in the recurrent setting (50.0%), with approximately a third having metastatic disease (primary Stage IV 22.1%) and the remaining were primary Stage III (27.9%).

Applicant - Table 10: Summary of disease history (ITT analysis set)

Variable Reason [n (%)]	dMMR/MSI-H		All Participants	
	Dostar + carbo/pac (N=60)	Placebo + carbo/pac (N=62)	Dostar + carbo/pac (N=245)	Placebo + carbo/pac (N=249)
FIGO Stage at Diagnosis				
Stage I	18 (30.0%)	21 (33.9%)	65 (26.5%)	71 (28.5%)
Stage II	4 (6.7%)	5 (8.1%)	13 (5.3%)	13 (5.2%)
Stage III	20 (33.3%)	20 (32.3%)	75 (30.6%)	65 (26.1%)
Stage IV	14 (23.3%)	13 (21.0%)	72 (29.4%)	84 (33.7%)
Unknown	4 (6.7%)	3 (4.8%)	20 (8.2%)	16 (6.4%)
Histology at Diagnosis				
Endometroid	48 (80.0%)	51 (82.3%)	134 (54.7%)	136 (54.6%)
Carcinosarcoma	5 (8.3%)	1 (1.6%)	25 (10.2%)	19 (7.6%)
Mixed Carcinoma ≥10% of carcinosarcoma, clear cell or serous histology	2 (3.3%)	3 (4.8%)	10 (4.1%)	9 (3.6%)
Serous adenocarcinoma	3 (5.0%)	3 (4.8%)	50 (20.4%)	52 (20.9%)
Clear cell adenocarcinoma	0	1 (1.6%)	8 (3.3%)	9 (3.6%)
Mucinous adenocarcinoma	0	0	0	1 (0.4%)
Undifferentiated carcinoma	0	0	1 (0.4%)	2 (0.8%)
Other	2 (3.3%)	3 (4.8%)	17 (6.9%)	21 (8.4%)

The FDA's Assessment:

FDA agrees with the Applicant's assessment of baseline disease characteristics. The most frequent histology type was endometrioid histology (80%), followed by carcinosarcoma (8%), and serous carcinoma (5%) in the dMMR/MSI-H subpopulation. The majority of patients had no prior external pelvic radiotherapy. Fifty percent of the patients were in the recurrent setting, and approximately 22% had metastatic disease (primary Stage IV) and 28% with primary Stage

III disease. Overall, the baseline characteristics were well balanced between the treatment arms.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

The study drug was administered by qualified study staff members at the study centers. The Investigator or designee was responsible for maintaining accurate dispensing records of the study treatments throughout the clinical study.

The most frequent (>50% of total participants) concomitant medications were dexamethasone, paracetamol, ondansetron, and famotidine, and were similar to those for the dMMR/MSI-H population. No noteworthy differences (>10%) between the dostarlimab plus carboplatin-paclitaxel and the placebo plus carboplatin-paclitaxel arms were observed, except for prednisone (18.7% versus 6.9%). Increased use of glucocorticoids as a concomitant medication was expected in the dostarlimab plus carboplatin-paclitaxel arm, based on the known side effect profile of immune checkpoint inhibitors. In the dMMR/MSI-H Safety population, the reported use of ondansetron, prednisone, and ascorbic acid was >10% higher in the dostarlimab plus carboplatin-paclitaxel arm, whereas reported use of lisinopril, palonosetron, aprepitant, metformin, and potassium was higher in the placebo plus carboplatin-paclitaxel arm.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Progression-free survival (Investigator assessed)

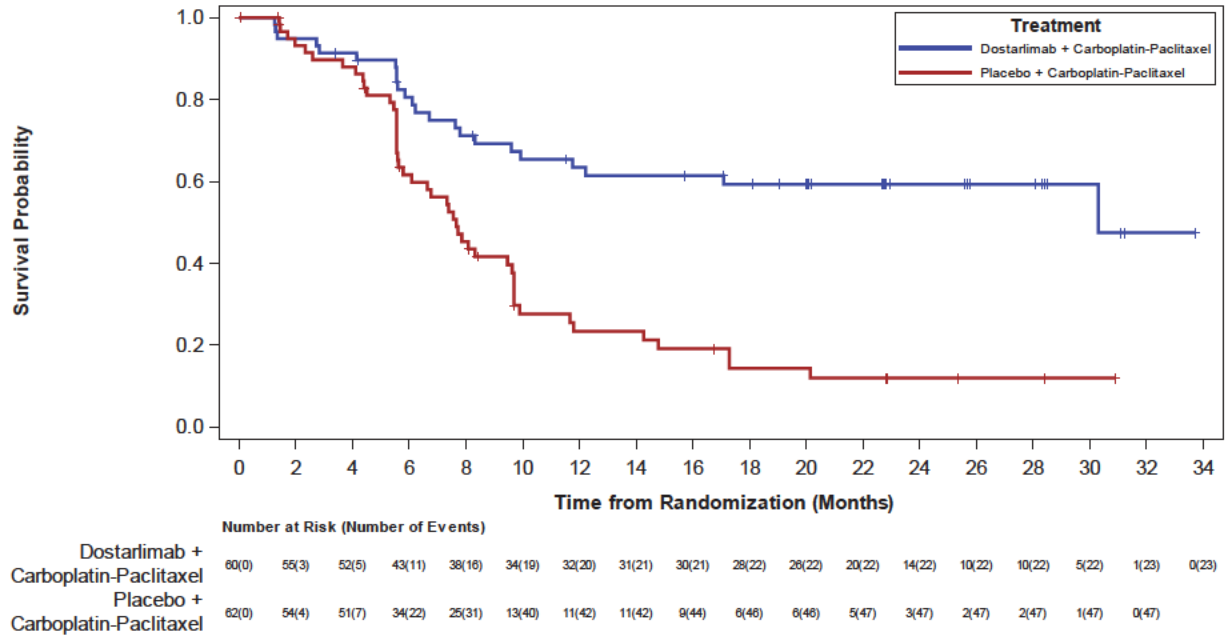
dMMR/MSI-H Population

The primary endpoint analysis of PFS based on dMMR/MSI-H classification as randomized included 60 participants in the dostarlimab plus carboplatin-paclitaxel arm and 62 participants in the placebo plus carboplatin-paclitaxel arm (Applicant - Table 4). At the time of data cutoff (57% PFS maturity), dostarlimab plus carboplatin-paclitaxel reduced the risk of progression or death by 71%, with an HR of 0.29 (95% CI 0.172, 0.497, p<0.0001; median PFS was 30.3 months vs 7.7 months, respectively). The estimated Kaplan-Meier probability of progression-free survival at 24 months were 59.3% and 11.9% in the dostarlimab plus carboplatin-paclitaxel and placebo plus carboplatin-paclitaxel arms, respectively (Applicant - Figure 5, Applicant - Table 11).

Overall Population

At the time of data cutoff (63% PFS maturity), dostarlimab plus carboplatin-paclitaxel reduced the risk of progression or death by 36% with an HR of 0.64 (95% CI 0.507, 0.800; p<0.0001; median PFS 11.8 months vs 7.9 months) in participants with primary advanced or recurrent EC (Applicant - Figure 6). The estimated Kaplan-Meier probability of progression-free survival at 24 months were 36.1% and 18.1% in the dostarlimab plus carboplatin-paclitaxel and placebo plus carboplatin-paclitaxel arms, respectively.

Applicant - Figure 5: Kaplan-Meier curves of progression-free survival - RECIST v.1.1 by Investigator assessment (Primary Analysis) (dMMR/MSI-H population, ITT analysis set)



Source: Figure 15.1.14

Applicant - Figure 6. Kaplan-Meier curves of progression-free survival – RECIST v.1.1 by Investigator assessment (Primary Analysis) (Overall population, ITT analysis set)

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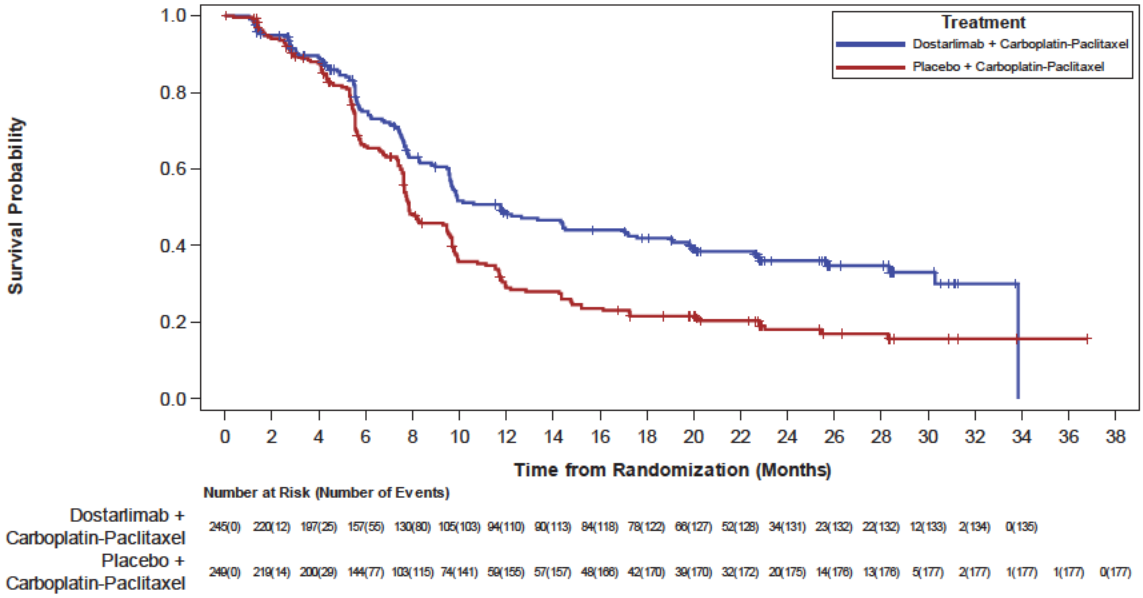


Source: Figure 15.1.1

Applicant - Table 11: Kaplan-Meier analysis of progression-free survival - RECIST v.1.1 by Investigator assessment (Primary analysis) (dMMR/MSI-H population, ITT analysis set)

Category subcategory	Dostar + carbo/pac (N=60)	Placebo + carbo/pac (N=62)
PFS status, n (%)		
Events observed	23 (38.3%)	47 (75.8%)
Disease progression	20 (33.3%)	44 (71.0%)
Death	3 (5.0%)	3 (4.8%)
Censored	37 (61.7%)	15 (24.2%)
PFS Quartile, months (95% CI) [a]		
25%	6.7 (5.6, 11.8)	5.6 (4.1, 5.6)
50%	30.3 (11.8, NE)	7.7 (5.6, 9.7)
75%	NE (30.3, NE)	11.8 (9.7, 20.1)
PFS distribution function (95% CI)		
Month 6	80.5% (67.5%, 88.7%)	61.6% (47.7%, 72.8%)
Month 12	63.4% (49.1%, 74.7%)	23.3% (13.0%, 35.5%)
Month 18	59.3% (44.9%, 71.1%)	14.3% (6.2%, 25.7%)
Month 24	59.3% (44.9%, 71.1%)	11.9% (4.6%, 22.9%)
Hazard ratio (95% CI) [b]	0.29 (0.172, 0.497)	
p-value of 1-sided stratified logrank test	<0.0001	

carbo=carboplatin; Dostar=dostarlimab; ITT=intent-to-treat; NR=not reached; pac=paclitaxel; PFS=progression-free survival.
a. 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).
b. Stratified Cox regression
Source: Table 14.2.1.20

Overall survival

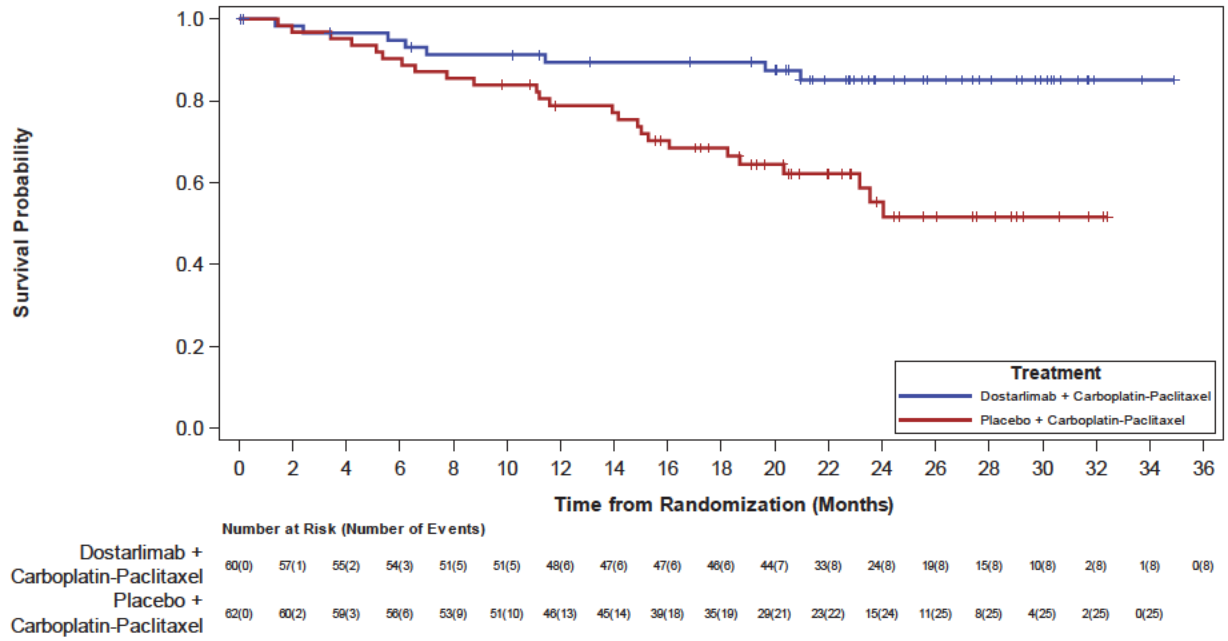
dMMR/MSI-H Population

The OS analysis based on dMMR/MSI-H classification as randomized included 60 participants in the dostarlimab plus carboplatin-paclitaxel arm and 62 participants in the placebo plus carboplatin-paclitaxel arm (Applicant - Table 12). Although OS in the dMMR/MSI-H population is not a primary endpoint, a prespecified analysis in this population was performed. At 27% OS maturity, there was a strong trend in favor of dostarlimab plus carboplatin-paclitaxel reducing the risk of death by 71%, with an HR of 0.29 (95% CI: 0.129, 0.644; nominal p=0.0006; median OS not reached for either arm). The Kaplan-Meier probability of survival at 24 months was 85.1% and 55.3% in the dostarlimab plus carboplatin-paclitaxel and placebo plus carboplatin-paclitaxel arms, respectively (Applicant - Figure 6, Applicant - Table 12).

Overall Population

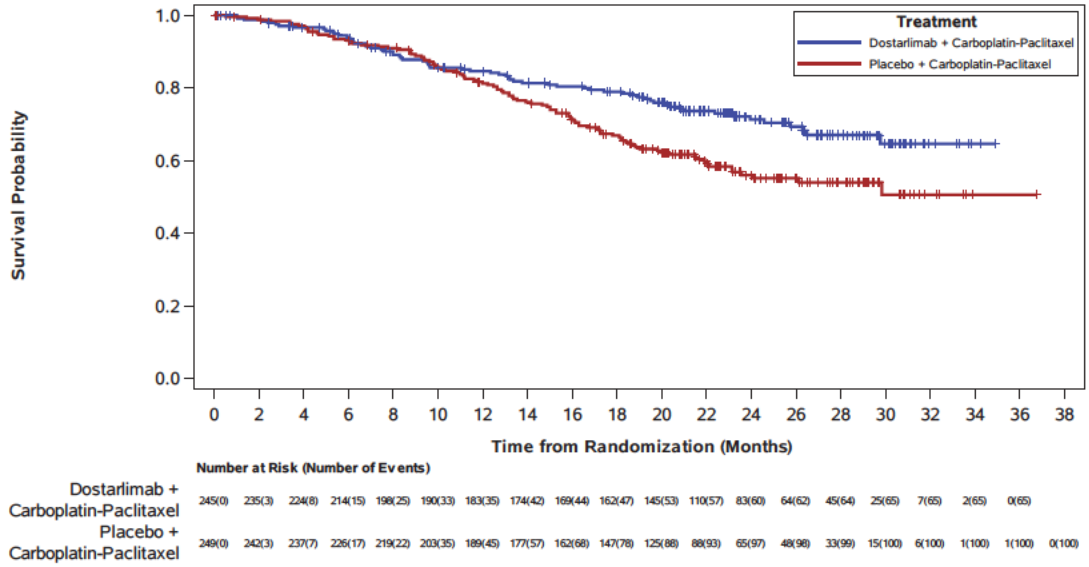
At this OS interim analysis with 33% OS maturity, there was a trend in favor of the dostarlimab plus carboplatin-paclitaxel arm reducing the risk of death by 36%, with an HR of 0.64 (95% CI 0.464, 0.870; p=0.0021; [P-value stopping boundary for significance was 0.00177]) (Applicant - Figure 7). Median OS was not reached for either arm, and the Kaplan-Meier probability of survival at 24 months was 71.3% and 56.0% in the dostarlimab plus carboplatin-paclitaxel and placebo plus carboplatin-paclitaxel arms, respectively.

Applicant - Figure 7: Kaplan-Meier analysis overall survival (dMMR/MSI-H population, ITT analysis set)



Source: Figure 15.1.21

Applicant - Figure 8. Kaplan-Meier analysis overall survival (Overall population, ITT analysis set)



Source: Figure 15.1.8

Applicant - Table 12: KaplanMeier analysis of overall survival (dMMR/MSI-H population, ITT analysis set)

Category subcategory	Dostar + carbo/pac (N=60)	Placebo + carbo/pac (N=62)
OS status, n (%)		
Events observed	8 (13.3%)	25 (40.3%)
Censored	52 (86.7%)	37 (59.7%)
OS Quartile, months (95% CI) [a]		
25%	NE (21.0, NE)	14.9 (7.8, 20.3)
50%	NE (NE, NE)	NE (20.3, NE)
75%	NE (NE, NE)	NE (NE, NE)
OS probability (95% CI)		
Month 12	89.4% (77.9%, 95.1%)	78.8% (66.3%, 87.1%)
Month 18	89.4% (77.9%, 95.1%)	68.5% (55.1%, 78.6%)
Month 24	85.1% (72.3%, 92.3%)	55.3% (39.8%, 68.3%)
Month 30	85.1% (72.3%, 92.3%)	51.6% (35.6%, 65.4%)
Hazard ratio (95% CI) [b]	0.29 (0.129, 0.644)	
Nominal p-value of 1-sided stratified log-rank test	0.0006	

carbo=carboplatin; Dostar=dostarlimab; ITT=intent-to-treat; NR=not reached; OS=overall survival; pac=paclitaxel.
a. 95% Confidence intervals generated using the method of Brookmeyer and Crowley (1982).
b. Stratified Cox regression
Source: Table 14.2.1.27

The FDA's Assessment:
This supplemental BLA application is based on the results of interim analysis of PFS. All p-values

and efficacy boundaries presented in this review are 1-sided. The proposed indication for the current submission is the dMMR/MSI-H subpopulation. This review is focused on the benefit/risk assessment in this subpopulation only.

FDA agrees with the Applicant's description of PFS as assessed by the investigator in the dMMR/MSI-H subpopulation and all-comers population and OS results in the dMMR/MSI-H subpopulation. The study showed a statistically significant and clinically meaningful improvement in the primary endpoint of PFS by investigator in the dMMR/MSI-H subpopulation. The hazard ratio was 0.29 (95% CI 0.172, 0.497, p<0.0001), with median PFS of 30.3 months in the dostarlimab plus carboplatin-paclitaxel arm vs 7.7 months in the placebo plus carboplatin-paclitaxel arm. In the dMMR/MSI-H population, the one-sided p-value for investigator-assessed PFS is <0.0001, which crossed the pre-specified stopping boundary of 0.0081 (1-sided) for statistical significance. In all-comers population, the one-sided p-value for investigator-assessed PFS is <0.0001, which also crossed the pre-specified efficacy boundary of 0.02 (1-sided) for statistical significance. In all-comers population, the p-value (1-sided) for OS is 0.0021, which didn't cross the pre-specified efficacy boundary of 0.00177 for statistical significance. No multiplicity adjustment was planned for the analysis of OS in the dMMR/MSI-H population, the p-value for this analysis is considered nominal.

Analyses of investigator-assessed PFS and OS in the dMMR/MSI-H population based on MMR/MSI status collected from eCRF were conducted by the Applicant. FDA considers these analyses as sensitivity analyses. In the dMMR/MSI-H population based on MMR/MSI status collected from eCRF the HR for PFS was 0.28 (95% CI: 0.16, 0.49). The observed median PFS was not reached in the dostarlimab plus carboplatin-paclitaxel arm and 7.7 months in the placebo plus carboplatin-paclitaxel arm. The HR for OS was 0.30 (95% CI: 0.13, 0.70). The observed median OS was not reached in either arm. The sensitivity analyses results of PFS and OS in the dMMR/MSI-H population based on MMR/MSI status collected from eCRF are consistent with the primary findings of PFS and OS in the dMMR/MSI-H population based on MMR/MSI status used for randomization.

The Applicant conducted sensitivity analyses of PFS per investigator assessment in the dMMR/MSI-H population based on MMR/MSI status collected from eCRF. Sensitivity analyses 1 and 2 used alternate censoring rules for PFS, sensitivity analysis 3 used BICR assessment instead of investigator assessment, and sensitivity analysis 4 was performed using stratification factors based on the source verified values from eCRF in the stratified log-rank test and stratified Cox model. FDA reconducted sensitivity analyses of PFS per investigator assessment in the dMMR/MSI-H population based on MMR/MSI status used for randomization. The sensitivity analyses results of PFS are generally consistent with the primary findings as noted in the Table below.

FDA– Table 1: Sensitivity Analyses of PFS (dMMR/MSI-H Population)

	Applicant analyses based on MMR/MSI status collected from eCRF Hazard ratio (95% CI)	FDA analyses based on MMR/MSI status collected for randomization Hazard ratio (95% CI)
S1: patients who had PD/death after ≥2 missed disease assessments will be counted as having an event at the date of PD/death	0.27 (0.16, 0.47)	0.28 (0.17, 0.48)
S2: patients without documented PD or death who discontinued treatment or initiated new anticancer therapy, whichever occurs later, were considered as having events	0.38 (0.24, 0.62)	0.44 (0.28, 0.68)
S3: PFS BICR primary censoring rules	0.29 (0.16, 0.54)	0.33 (0.18, 0.59)
S4: PFS INV primary censoring rules, stratification factors determined by eCRF	0.30 (0.17, 0.51)	0.30 (0.18, 0.51)

Since less patients were ≥65 years old in the dostarlimab plus carboplatin-paclitaxel arm compared to patients in the placebo plus carboplatin-paclitaxel arm in the dMMR/MSI-H population, FDA conducted a sensitivity analysis of PFS per investigator assessment by adjusting age group. The adjusted HR is 0.29 (95% CI: 0.17, 0.51). The results are consistent with the primary findings.

There were 372 patients in the MMRp/MSS subpopulation with classification as randomized: 185 patients in the dostarlimab plus carboplatin-paclitaxel arm and 187 patients in the placebo plus carboplatin-paclitaxel arm. At the time of data cutoff date of September 28, 2022, the HR for the investigator-assessed PFS was 0.78 (95% CI: 0.60, 1.00). The observed median PFS was 9.8 months in the dostarlimab plus carboplatin-paclitaxel arm and 7.9 months in the placebo plus carboplatin-paclitaxel arm. The HR for the OS was 0.76 (95% CI: 0.54, 1.07). The observed median OS was not reached in either arm. Analyses of PFS and OS in this subpopulation were not pre-specified, are considered descriptive and must be interpreted with caution. However, differential results with respect to PFS and OS were observed in this MMRp/MSS subpopulation compared to patients with dMMR/MSI-H.

Although dostarlimab in combination with carboplatin-paclitaxel was also associated with a statistically significant improvements in PFS in the all-comers population, patients with dMMR/MSI-H may derive greater PFS benefit from dostarlimab + carboplatin/paclitaxel compared to patients with MMRp/MSS.

Data Quality and Integrity

The Applicant's Position:

The case report forms and clinical source data has not yet been audited by any government authority.

The FDA's Assessment:
There were no concerns regarding the quality and integrity of the submitted data and datasets during the review of this sBLA.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:
The analysis of secondary efficacy endpoints for the dMMR/MSI-H population based on dMMR/MSI-H classification as randomized included 60 participants in the dostarlimab plus carboplatin-pactliaxel arm and 62 participants in the placebo plus carboplatin-paclitaxel arm

Progression-free Survival by BICR

PFS results based on BICR per RECIST v1.1 were consistent with PFS results by investigator assessment per RECIST v1.1 (primary analysis) for all populations.

In the dMMR/MSI-H population, dostarlimab plus carboplatin-paclitaxel reduced the risk of progression or death by 67% with an HR of 0.33 (95% CI 0.181, 0.587, nominal p<0.0001; median PFS not reached vs 9.4 months). Similar to the PFS primary analysis, the Kaplan Meier curve of PFS showed separation in favor of the dostarlimab plus carboplatin-paclitaxel treatment arm in the dMMR/MSI-H population and in the overall population.

There was a high rate of concordance between BICR-assessed PFS and investigator-assessed PFS. Agreement on the comparison of PFS per Investigator assessment and through BICR on determination of event/censoring for PFS was achieved for 83.3% and 75.8% of participants in the dMMR/MSI-H population, and 83.3% and 81.9% of participants in the overall population, respectively.

Progression-free Survival 2

The observed PFS2 results further depict the efficacy of dostarlimab beyond first progression in primary advanced or recurrent EC and support the observed OS trend favoring dostarlimab plus carboplatin-paclitaxel in participants with dMMR/MSI-H primary advanced or recurrent EC . At the time of data cutoff, dostarlimab plus carboplatin-paclitaxel reduced the risk of progression

following first subsequent anti-cancer therapy or death in the dMMR/MSI-H population by 58% with an HR of 0.42 (95% CI: 0.229, 0.789; NR vs 22.0 months).

Similar to the PFS primary analysis, the Kaplan-Meier curve of PFS2 showed separation in favor of the dostarlimab plus carboplatin-paclitaxel treatment arm in the dMMR/MSI-H and the overall populations.

Objective Response and Disease Control Rate

The ORR based on confirmed response by investigator assessment per RECIST v1.1 in participants with measurable disease at baseline was higher in the dostarlimab plus carboplatin-paclitaxel arm, driven predominantly by a higher percentage of CRs compared with the placebo plus carboplatin-paclitaxel arm in the dMMR/MSI-H population (73.8% vs 62.2%) and the overall population (70.3% vs 64.8%).

Very high disease control rates (approximately 90%) were observed in both the active arm and control arm.

The FDA's Assessment:
FDA generally agrees with the Applicant's assessment of PFS as assessed by BICR in the dMMR/MSI-H subpopulation. In the dMMR/MSI-H population, the results of PFS per BICR are consistent with the primary findings of PFS per investigator.

In the dMMR/MSI-H population, there are 87 patients with measurable disease at baseline per investigator assessment: 42 in the dostarlimab plus carboplatin-paclitaxel arm and 45 in the placebo plus carboplatin-paclitaxel arm. Confirmed ORR per investigator assessment in dMMR/MSI-H patients with measurable disease at baseline is numerically higher in the dostarlimab plus carboplatin-paclitaxel arm than the placebo plus carboplatin-paclitaxel arm. Among 93 dMMR/MSI-H patients with measurable disease at baseline per BICR assessment (43 in the dostarlimab plus carboplatin-paclitaxel arm and 50 in the placebo plus carboplatin-paclitaxel arm), confirmed ORR per BICR assessment is 79.1% in the dostarlimab plus carboplatin-paclitaxel arm and 62.0% in the placebo plus carboplatin-paclitaxel arm.

PFS2 and disease control rate are not endpoints that FDA considers as regulatory endpoints.

Dose/Dose Response

Data:

See results in Section 8.1.2.

The FDA's Assessment:
No additional analysis was performed by the FDA.

Durability of Response

Data:

The higher confirmed ORR observed in the dostarlimab plus carboplatin-paclitaxel arm in participants with measurable disease at baseline was accompanied by an increased Kaplan-Meier probability of DOR at 24 months with dostarlimab plus carboplatin-paclitaxel compared with placebo plus carboplatinpaclitaxel.

Increased durability of response from first confirmed response (PR or CR) was observed with dostarlimab plus carboplatin-paclitaxel compared with placebo plus carboplatinpaclitaxel in participants with measurable disease at baseline. The difference in probability of remaining in response at 6 months, which showed an early difference between the 2 arms of 77.4% vs 46.4% in the dMMR/MSI-H population and 73.6% vs 55.4% in the overall population, suggests that while the responses to chemotherapy are temporary, the addition of dostarlimab to chemotherapy augmented the tumor responses in participants who responded. The Kaplan-Meier probability of DOR at 24 months in the dMMR/MSI-H population was 60.5% vs 4.0% in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm, further supporting the durability of response to dostarlimab.

The assessment of DOR by BICR was generally similar to the investigator assessed DOR.

The FDA's Assessment:
FDA acknowledges the Applicant's description of duration of response. In the dMMR/MSI-H population, median DoR per investigator assessment was not reached in the dostarlimab plus carboplatin-paclitaxel arm and 5.4 months in the placebo plus carboplatin-paclitaxel arm. The percentage of responding patients in the dMMR/MSI-H population who had duration of response greater than 12 months are 61.3% vs 14.3% in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm.

Persistence of Effect

The Applicant's Position:

No analyses to assess the persistence of efficacy after treatment discontinuation have been conducted. There are no known tolerance effects of dostarlimab.

The FDA's Assessment:
No additional analysis was performed by the FDA.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
The Applicant's Position:

Assessment of quality-of-life measures indicated that participants in the dostarlimab plus carboplatin-paclitaxel arm had clinically similar quality of life (QoL) outcomes compared with those in the placebo plus carboplatin-paclitaxel arm in the dMMR/MSI-H population. While numerical improvements may be observed with some functional or symptom scores, they should be interpreted with caution as statistical testing and comparisons were not performed.

The results were consistent across all analyses as indicated by changes from baseline in EORTC-QLQ-C30. Furthermore, supportive and consistent results were observed as assessed by EORTC QLQ-EN24 domain scores and EQ-5D-5L VAS.

The FDA's Assessment:

In the RUBY trial, QoL outcomes were not statistically tested. FDA considers these QoL analyses to be exploratory and not interpretable from a statistical perspective.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Subgroup Analysis: Progression-free Survival

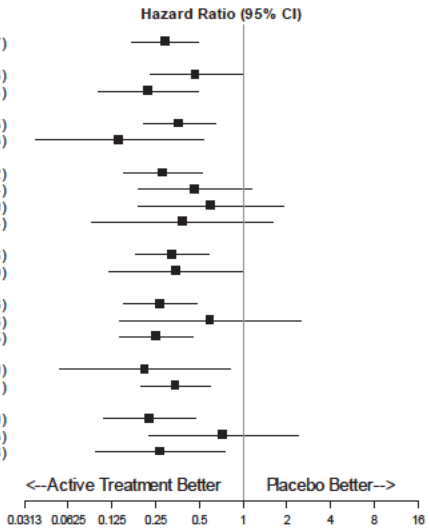
A forest plot of PFS in the dMMR/MSI-H population showed favorable HRs (<1) for all subgroups (Applicant - Figure 9) with generally similar trends as in the overall population. However, the individual subgroups in this population have small numbers of participants and the results should be interpreted with caution.

Patients with Stage III and those with no measurable disease are biologically expected to experience the same magnitude of benefit from treatment as stage IV and recurrent patients, however the low maturity in these subgroups suggests longer follow up may be needed to observe the strength of the treatment effect.

Applicant - Figure 9: Forest plot of progression-free survival and 95% confidence intervals by subgroup - RECIST v.1.1 by Investigator assessment (Primary Analysis) (dMMR/MSI-H population, ITT analysis set)

MMR/MSI Status=dMMR/MSI-H

Categories	Dostarlimab (No. of Subjects / No. of Events)	Placebo (No. of Subjects / No. of Events)	Dostarlimab (Median PFS - Months)	Placebo (Median PFS - Months)	HR(95% CI)
All Patients	60/23	62/47	30.3	7.7	0.29 (0.172, 0.497)
Age					
<65 yr	35/15	26/16	30.3	7.7	0.47 (0.229, 0.978)
>=65 yr	25/8	36/31	NE	7.7	0.22 (0.101, 0.494)
Race					
White	49/18	52/37	NE	8.3	0.36 (0.206, 0.645)
Other	11/5	10/10	30.3	5.6	0.14 (0.037, 0.533)
Region					
North America	40/15	47/35	NE	7.6	0.28 (0.150, 0.522)
Europe	20/8	15/12	NE	7.7	0.47 (0.190, 1.144)
Eastern Europe	9/5	7/7	8.3	7.7	0.61 (0.191, 1.920)
Western Europe	11/3	8/5	NE	7.7	0.38 (0.092, 1.614)
Histology category					
Endometrioid carcinoma	49/18	50/36	30.3	7.7	0.33 (0.183, 0.578)
Other	11/5	12/11	17.1	7.0	0.35 (0.119, 1.019)
MMR/MSI Status*					
dMMR/MSI-H	50/16	59/44	NE	7.6	0.27 (0.150, 0.483)
MMRp/MSS	10/7	3/3	9.6	8.1	0.59 (0.140, 2.526)
dMMR Status (Derived)	50/16	57/44	NE	7.6	0.25 (0.141, 0.455)
Prior External Pelvic Radiotherapy*					
Yes	10/4	13/9	30.3	7.4	0.21 (0.055, 0.820)
No	50/19	49/38	NE	7.7	0.34 (0.196, 0.601)
Disease Status*					
Recurrent	30/13	32/26	30.3	7.7	0.23 (0.109, 0.470)
Primary Stage III	14/5	12/6	NE	20.1	0.73 (0.224, 2.413)
Primary Stage IV	16/5	18/15	NE	5.6	0.27 (0.097, 0.758)
No Disease at Baseline	7/1	5/4	30.3	14.3	Not Applicable



Note: HRs presented are from unstratified Cox regression model.

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Source: Figure 15.2.3

The FDA's Assessment:
FDA generally agrees that the interpretation of the results of the subgroup analysis of PFS in the dMMR/MSI-H subpopulation is limited due to the small sample size. In addition, no multiplicity adjustments were planned for these subgroups analyses, these subgroup analyses are considered exploratory or hypothesis generating and no formal inference may be drawn. No apparent outliers were observed in the subgroup analyses.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:
Not applicable. The efficacy data submitted by the Applicant is based off a single trial (RUBY Part 1).

8.1.4. Assessment of Efficacy Across Trials

The data to support this BLA is from one single study, Study 2133561 RUBY, and thus an analysis of efficacy across trials is not applicable.

The FDA's Assessment:
FDA agrees.

Additional Efficacy Considerations

The FDA's Assessment:
Not applicable.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

- The study met its primary endpoint, demonstrating that dostarlimab in combination with carboplatin-paclitaxel improved PFS by investigator assessment in dMMR/MSI-H primary advanced or recurrent EC with a HR of 0.29 (95% CI 0.172, 0.497, p<0.0001), and in all participants with primary advanced or recurrent EC with a HR of 0.64 (95% CI 0.507, 0.800, p<0.0001), reducing the risk of progression or death by 71% and 36%, respectively.
- In the overall population, a numerical trend in OS was observed in favor of the dostarlimab plus carboplatin-paclitaxel arm compared to placebo plus carboplatin-paclitaxel (HR of 0.64; 95% CI 0.464,0.870; p = 0.0021) at the time of the data cutoff (33% maturity). The median OS was not reached for either treatment arm. A favorable trend in OS was also observed in the dMMR/MSI-H population (HR of 0.29; 95% CI 0.129,0.644).
- The benefit of dostarlimab plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel was consistently observed in all secondary efficacy endpoints including ORR,

DOR, and DCR by both BICR and investigator assessment, PFS2 by investigator assessment, and PFS by BICR assessment. Response rates in both arms were high; however, responses were more durable in the dostarlimab plus carboplatin-paclitaxel arm as demonstrated by increased DOR.

- PFS2 analysis demonstrated that the addition of dostarlimab to carboplatin-paclitaxel reduced the risk of progression on next-line treatment or death by 63% in the dMMR/MSI-H population of participants with primary advanced or recurrent EC, with HR of 0.37 (95% CI: 0.189, 0.727; NR vs 22.0 months), supportive of the OS results. Improved PFS2 was observed in the overall population.
- Participants treated with dostarlimab plus carboplatin-paclitaxel had clinically similar QoL outcomes in all populations compared with those who received placebo plus carboplatin-paclitaxel demonstrating that significant improvements in PFS due to the addition of dostarlimab to standard of care chemotherapy were not accompanied by any substantial deterioration in QoL.

The FDA's Assessment:

FDA's efficacy review and assessment for this BLA supplement is based on data from 122 patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer (EC) in RUBY Study Part 1. RUBY is a Phase 3, randomized, double-blind, multicenter study. Part 1 of the study evaluated the efficacy and safety of dostarlimab plus carboplatin-paclitaxel followed by dostarlimab as a single-agent versus placebo plus carboplatin-paclitaxel followed by placebo in patients with primary advanced (Stage III or IV) or recurrent EC in the dMMR/MSI-H subpopulation and all-comers population.

At the time of DCO (September 28, 2022) and interim analysis of PFS at 77% information fraction, the study showed a statistically significant and clinically meaningful improvement in the primary endpoint of PFS per investigator in the dMMR/MSI-H subpopulation. The hazard ratio was 0.29 (95% CI 0.172, 0.497, $p<0.0001$), with median PFS of 30.3 months in the dostarlimab plus carboplatin-paclitaxel arm vs 7.7 months in the placebo plus carboplatin-paclitaxel arm.

Overall survival data in this subpopulation were immature with 27% deaths at the time of DCO date. Confirmed ORR in dMMR/MSI-H patients with measurable disease at baseline is numerically higher in the dostarlimab plus carboplatin-paclitaxel arm as compared to the placebo plus carboplatin-paclitaxel arm. PFS2 is not an endpoint that FDA considers as a regulatory endpoint. In reference to the QoL outcomes presented above by the Applicant, no statistical testing and comparisons were performed for assessment of quality-of-life measures, therefore, FDA considers PRO observations to be exploratory and should be interpreted with caution.

8.2. Review of Safety

The Applicant's Position:

The Safety Analysis Set includes all participants enrolled in RUBY Part 1 who received any amount of study treatment regardless of randomization. All safety analyses were performed on the as-treated principle, where participants were allocated to the treatment that they actually received. Participants who received any amount of dostarlimab were assigned to the dostarlimab treatment arm, and participants who did not receive any amount of dostarlimab were assigned to the placebo treatment arm.

The safety analyses were based on the Safety Analysis Set. In the overall population, 241 participants had received treatment with dostarlimab in combination with carboplatin-paclitaxel and 246 participants had received treatment with placebo in combination with carboplatin-paclitaxel. In the dMMR/MSI-H Safety population, 52 participants had received treatment with dostarlimab in combination with carboplatin-paclitaxel and 65 participants had received treatment with placebo in combination with carboplatin-paclitaxel.

The safety assessments performed in Part 1 of the study included AE monitoring, physical examinations, vital sign measurements, ECOG performance status, ECGs, clinical laboratory tests, and recording of concomitant medication usage.

The FDA's Assessment:

In order to support the safety of dostarlimab for this sBLA, the Applicant submitted safety data from the RUBY Part 1, a phase 3, randomized, double-blind, multicenter trial of dostarlimab in combination with carboplatin and paclitaxel versus placebo in combination with carboplatin and paclitaxel in patients with recurrent or primary advanced endometrial cancer. The safety profile of dostarlimab was assessed in 241 patients with recurrent or primary advanced endometrial cancer who had received at least 1 dose of dostarlimab in combination with carboplatin-paclitaxel and 246 patients who had received at least one dose of placebo in combination with carboplatin-paclitaxel by the data cutoff date of September 28, 2022. Additionally, a subset analysis was performed in the dMMR/MSI-H population including 52 patients treated with dostarlimab in combination with carboplatin and paclitaxel and 65 patient treated with placebo in combination with carboplatin and paclitaxel.

8.2.1. Safety Review Approach

The Applicant's Position:

No statistical comparisons have been performed: all analyses are descriptive in nature. Full details of the statistical methods used are provided in the original SAP and SAP addendum for RUBY study Part 1.

AEs and concomitant medications were coded using standard dictionaries. Medical history and AEs were coded using MedDRA Version 25.0. Prior and concomitant medications were summarized by WHO drug dictionary preferred name. NCI-CTCAE Version 4.03 severity grades were applied to AEs and clinical laboratory parameters.

Safety data and analyses for dostarlimab are presented below. The primary safety concern for dostarlimab, similar to other drugs in the anti-PD-(L)1 class, is immune-related adverse events (irAEs) related to the mechanism of action of these agents. irAEs are managed with dose interruption, discontinuation and immunosuppressants including systemic steroids, and other immune suppressants, as well hormonal replacement therapy as clinically indicated.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

The overall median treatment duration was 43 weeks (range: 3.0 to 150.9 weeks) for participants in the dostarlimab plus carboplatin-paclitaxel arm and 36 weeks (range: 2.1 to 165.1 weeks) for participants in the placebo plus carboplatin-paclitaxel arm. As of the DCO date, 38.6% of participants in the dostarlimab plus carboplatin-paclitaxel arm and 26.4% of participants in the placebo plus carboplatin-paclitaxel arm received >54 weeks (>1 year) of treatment, while 17.8% and 12.6% received >102 weeks (>2 years) of treatment, respectively. There was only 1 participant in either treatment arm who received >156 weeks (>3 years) of treatment (placebo plus carboplatin-paclitaxel). The proportion of participants who had follow-up at 1 year, 2 years, and 3 years was as follows: 74.7% vs 75.9%, 62.0% vs 59.8%, 0.8% (2 participants) vs 1.2% (3 participant) in the dostarlimab plus carboplatin-paclitaxel arm vs placebo plus carboplatin-paclitaxel, respectively. Of the 4 participants who had the opportunity for 3 years of follow up and received less than 3 years of treatment, 2 discontinued treatment due to disease progression, 1 withdrew consent, and 1 withdrew consent and entered hospice care.

In the dMMR/MSI-H safety population, the median treatment duration was 76.50 weeks (range: 3.0 to 150.3 weeks) for participants in the dostarlimab plus carboplatin-paclitaxel arm and 31.86 weeks (range: 3.0 to 153.0 weeks) for participants in the placebo plus carboplatin-paclitaxel arm. As of the data cutoff date, 55.8% of participants in the dostarlimab plus carboplatin-paclitaxel arm received >54 weeks (>1 year) of treatment, while 30.8% received >102 weeks (>2 years) of treatment; no participants received >156 weeks (>3 years) of treatment. In the placebo plus carboplatin-paclitaxel arm 21.5% of participants received >54 weeks (>1 year) of treatment, while 12.3% received >102 weeks (>2 years) of treatment; no participants received >156 weeks (>3 years) of treatment. The proportion of participants who had follow-up at 18 to 21 months, 21 months, 24 months, and 36 months was as follows: 15.4% vs 15.4%, 84.6% vs 84.6%, 55.8% vs 55.4%, 1.9% (1 participant) vs 1.5% (1 participant) in the dostarlimab plus carboplatin-paclitaxel arm vs placebo plus carboplatin-paclitaxel, respectively.

The median RDI data indicate that most participants received all scheduled doses of dostarlimab/placebo or chemotherapy across both the overall and dMMR/MSI-H populations.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of treatment duration based on the nearest number of whole treatment cycles in a year (e.g., 18 cycles of dostarlimab over 54 weeks). The Applicant defined duration of follow up as time from randomization to cut off date. Since endometrial cancer is an incurable disease and deaths were frequent in RUBY, FDA defined duration of follow up as time from randomization to last date known alive. Based on FDA analysis, the follow-up duration at 1 year, 2 years, and 3 years in the overall and dMMR/MSI-H populations are as follows:

FDA – Table 2: FDA Analysis of Follow Up Duration[a]

Year	Overall Population		dMMR Population	
	Dostar + carbo/pac (n = 241)	Placebo + carbo/pac (n = 246)	Dostar + carbo/pac (n = 52)	Placebo + carbo/pac (n = 65)
1	76%	77%	83%	74%
2	34%	26%	35%	25%
3	0	0.04%	0	0

[a] adsl dataset assessed using FUDURM (ADSL.LSTALVDT – ADSL.RANDDT +1)/30.4375

FDA agrees that median RDI assessment is balanced across arms and demonstrates high exposures for dosarlimab/placebo and paclitaxel, with somewhat lower exposure for carboplatin.

Relevant characteristics of the safety population:

The Applicant's Position:

Participant demographics and baseline characteristics are provided in Section 8.1.2. The Safety Analysis and ITT Analysis Sets were similar for both the overall population and the dMMR/MSI-H population. In the Safety Analysis Set, overall population included 241 participants who received dostarlimab plus carboplatin-paclitaxel and 246 who received placebo plus carboplatin-paclitaxel; and the dMMR/MSI-H safety population included 52 participants who received dostarlimab plus carboplatin-paclitaxel and 65 who received placebo plus carboplatin-paclitaxel.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Adequacy of the safety database:

The Applicant's Position:

The size of the safety database from RUBY Part 1 (all participants who received at least one dose of study drug) is 487 participants, including 241 participants who received dostarlimab plus chemotherapy and 246 participants receiving placebo plus chemotherapy. Of these, the dMMR/MSI-H safety population includes 117 participants: 52 in the dostarlimab plus carboplatin-paclitaxel arm and 65 in the pladebo plus carboplatin-paclitaxel arm.

The size of the safety database is considered adequate to define the risks of treatment with dostarlimab plus platinum-containing chemotherapy, which will be managed via labeling.

Observed AEs included events that were in line with those expected in subjects with recurrent or primary advanced EC, as well as those consistent with the established safety profiles for each individual regimen.

As agreed upon by the Agency, the Applicant will submit an updated safety analysis with corresponding datasets to supplement the summary of clinical safety as part of a 90-day safety update.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. The 90-day safety update was reviewed by FDA and is consistent with the original safety data set.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety.

The FDA's Assessment:
FDA agrees that the quality and integrity of the submitted datasets and individual case narratives are generally sufficient for a thorough review of safety

Categorization of Adverse Event

The Applicant's Position:

The Investigator and site staff were responsible for detecting, documenting, and reporting events that met the definition of an AE or serious adverse event (SAE).

The following information on AEs was obtained:

- Duration (start and stop dates)
- Severity (according to the National Cancer Institute Common Toxicity Criteria for Adverse Events [CTCAE], version 4.03)
- Relationship (related, not related)

- Actions taken and outcome

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Routine Clinical Tests

The Applicant's Position:

Laboratory values were primarily based on International Standard (SI) units. Laboratory result toxicity grades were based on NCI-CTCAE v4.03. The laboratory parameters analyzed were:

1. Hematology (including hemoglobin, white blood cell count, platelet count, neutrophil count, and lymphocyte count)
2. Blood chemistry (including hepatic profile, renal profile, and metabolic profile)

Any unscheduled measurements were included in by-visit summaries and were used for the determination of worst grade during treatment.

For those parameters that were graded with 2-direction toxicities (hyper-, and hypo-), the toxicities were summarized separately. Low direction toxicity grades at baseline and postbaseline were set to 0 when the variables were derived for summarizing high direction toxicity, and vice versa.

Please refer to Section 8.1.1 for additional details on the procedures and schedule for safety assessments.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

8.2.4. Safety Results

Deaths

The Applicant's Position:

In the overall population, 165 participants died while on study; 65 participants (27.0%) in the dostarlimab plus carboplatin-paclitaxel arm, and 100 participants (40.7%) in the placebo plus carboplatin-paclitaxel arm. The primary cause of death, independent of the study period, was disease progression which was lower in the dostarlimab plus carboplatin-paclitaxel arm compared with the the placebo plus carboplatin-paclitaxel arm (23.7% versus 35.4%).

A total of 5 participants in the overall population, including 2 participants in the dMMR/MSI-H safety population, had TEAEs leading to death; all were in the dostarlimab plus carboplatin-paclitaxel arm (Applicant - Table 13). Of these, 2 deaths were treatment-related: myelosuppression was considered related to dostarlimab, carboplatin and paclitaxel, and hypovolemic shock was considered related to dostarlimab. Both participants were in the dMMR/MSI-H safety population.

Applicant - Table 13: Summary of treatment-emergent serious adverse events leading to death by system organ class and preferred term (Overall population, Safety analysis set)

System organ class, n (%) Preferred term, n (%)	Dostar + carbo/pac (N=241)	Placebo + carbo/pac (N=246)	Total (N=487)
Any TEAE leading to death	5 (2.1%)	0	5 (1.0%)
Blood and lymphatic system disorders	1 (0.4%)	0	1 (0.2%)
Myelosuppression	1 (0.4%)	0	1 (0.2%)
General disorders and administration site conditions	1 (0.4%)	0	1 (0.2%)
General physical health deterioration	1 (0.4%)	0	1 (0.2%)
Infections and infestations	1 (0.4%)	0	1 (0.2%)
COVID-19	1 (0.4%)	0	1 (0.2%)
Injury, poisoning and procedural complications	1 (0.4%)	0	1 (0.2%)
Overdose[a]	1 (0.4%)	0	1 (0.2%)
Vascular disorders	1 (0.4%)	0	1 (0.2%)
Hypovolaemic shock	1 (0.4%)	0	1 (0.2%)

carbo=carboplatin; Dostar=dostarlimab; pac=paclitaxel; TEAE=treatment-emergent adverse event.
Note: AEs are coded using MedDRA version 25.0.
[a] Overdose due to opiates
Source: Table 14.3.1.26

The FDA's Assessment:

FDA agrees with the Applicant's determination that the primary cause of death in RUBY Part 1 was disease progression in patients with advanced or metastatic EC. FDA agrees with the Applicant's position on the 5 patients that experienced TEAEs leading to death in the dostarlimab plus carboplatin-paclitaxel arm. However, FDA assessed that the death from hypovolemic shock was more appropriately characterized as distributive shock due to sepsis, (b) (4) The FDA conducted an independent analysis of deaths in cer in RUBY based on the death narratives provided by the Applicant. FDA disagrees with the Applicant's assessment that there were 2 cases of TEAEs leading to death in the dMMR/MSI-H population and found that 6% (3/52) of patients in the dMMR population died from TEAEs including: septic shock 3.8%, and myelosuppresion 1.9%.

Additional Death Narrative

Patient ID: (b) (6)
The patient was a (b) (6) with dMMR, stage IV endometrial cancer. (b) (6) received (b) (6) first and only dose of dostarlimab with carboplatin and paclitaxel on day 1. On day -25 the patient had hematoma evacuation of the infra-umbilical portion of a mid-line wound and a wound vaccum-assisted closure was placed. On day 1 the patient experienced a grade 2 infusion reaction to paclitaxel. Addtionally, (b) (6) had grade 3 increased bilirubin and increased lipase. The patient was hospitalized on day 3 for a grade 3 wound infection related to the vaccum-assisted closure. Wound culture showed *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. A CT of the abdomen demonstrated masses in the liver and increased bulky mesenteric and retroperitoneal lymphadenopathy. The patient died on day 28. The cause of death was assessed as progressive disease. It is unknown whether an autopsy was

performed. FDA disagrees with the Applicant's assessment that death was from progressive disease given the timing of the death in relation to treatment and ongoing wound infection and cannot exclude contribution of study treatment to death. The Applicant agreed to include this case in Section 6 of the label.

Serious Adverse Events

The Applicant's Position:

In the overall population, the incidence of SAEs was approximately 10% higher in the dostarlimab plus carboplatin-paclitaxel arm compared with placebo plus carboplatin-paclitaxel (37.8% versus 27.6%); however, individual SAE frequencies by preferred term were similar (<3% difference) between treatment arms. The most frequently reported SAEs in the dostarlimab plus carboplatin-paclitaxel arm were sepsis, pulmonary embolism, and pyrexia, while those in the placebo plus carboplatin-paclitaxel arm were anemia and asthenia.

Treatment-related SAEs were experienced by 15.2% of the participants in the overall population. The frequency of treatment-related SAEs was approximately 6% higher in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm. The most frequently reported treatment-related SAEs (>1%) in the dostarlimab plus carboplatin-paclitaxel arm were febrile neutropenia (1.7%), and pyrexia, sepsis, and muscular weakness (1.2% each), and in the placebo plus carboplatin-paclitaxel arm were anemia (2.0%), febrile neutropenia (1.6%), asthenia (1.6%), and diarrhea (1.2%). In the dostarlimab plus carboplatin-paclitaxel arm, treatment-related SAEs of febrile neutropenia and muscular weakness were generally related to carboplatin or paclitaxel, pyrexia was generally related to all 3 study drugs, and sepsis was generally not related to any study treatments.

SAEs considered not related to carboplatin/paclitaxel but related to dostarlimab/placebo only were comparable between arms (5.0% in the dostarlimab plus carboplatin-paclitaxel and 3.3% in the placebo plus carboplatin-paclitaxel arms). All SAEs related to dostarlimab/placebo occurred in 1 participant each. SAEs considered related to carboplatin/paclitaxel only were comparable between arms (7.1% in the dostarlimab plus carboplatin-paclitaxel and 6.1% in the placebo plus carboplatin-paclitaxel arms). SAEs related to carboplatin/paclitaxel only in both treatment arms occurred in ≤2 participants each with the exception of febrile neutropenia (1.2% in dostarlimab plus carboplatin-paclitaxel arm and 1.6% in placebo plus carboplatin-paclitaxel arm) and anemia (0% in dostarlimab plus carboplatin-paclitaxel arm and 1.6% in placebo plus carboplatin-paclitaxel arm.

In the dMMR/MSI-H safety population, the overall incidence of SAEs was comparable between the dostarlimab plus carboplatin-paclitaxel arm and the placebo plus carboplatin-paclitaxel arm (26.9% and 30.8%). The most frequently reported SAE (≥2% of participants) which was higher in participants in the dostarlimab plus carboplatin-paclitaxel arm versus the placebo plus carboplatin-paclitaxel arm was sepsis (3.8% versus 0%). The most frequently reported SAEs (≥2% of participants) which were higher in participants in the placebo plus carboplatin-paclitaxel arm versus the dostarlimab plus carboplatin-paclitaxel arm were urinary tract

infection (0% versus 6.2%), anemia (0% versus 4.6%), asthenia (0% versus 4.6%) and pulmonary embolism (0% versus 3.1%).

Treatment-related SAEs were experienced by 15.4% of the participants in the dMMR/MSI-H safety population. The frequency of treatment-related SAEs was approximately 4% higher in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm. None of the treatment-related SAEs was experienced by >1 participant in either treatment arm with the exception of anemia, experienced by 2 participants in the placebo plus carboplatin-paclitaxel arm. SAEs considered not related to carboplatin or paclitaxel and related to dostarlimab or placebo only were comparable in participants between arms (5.8% in the dostarlimab plus carboplatin-paclitaxel arm and 3.1% in the placebo plus carboplatin-paclitaxel arm); each SAE occurred in a single participant. SAEs considered related to carboplatin or paclitaxel only were comparable between arms (5.8% in the dostarlimab plus carboplatin-paclitaxel arm and 7.7% in the placebo plus carboplatin-paclitaxel arm).

The FDA's Assessment:
FDA agrees with the Applicant's assessment of serious adverse events in the overall and dMMR/MSI-H population. Sepsis was the only SAE to occur at ≥5% more in the dMMR/MSI-H population treated with dostarlimab with carboplatin and paclitaxel. FDA did not perform an analysis of treatment-related SAEs in any population as the assessment should be without regard to investigator attribution.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

In the overall population, TEAEs leading to discontinuation of any study treatment were experienced by 23.7% of participants in the dostarlimab plus carboplatin-paclitaxel arm compared with 16.7% in the placebo plus carboplatin-paclitaxel arm. The incidence in individual system organ class and TEAEs by preferred term were similar (<3% difference) between treatment arms. The most frequently reported TEAEs leading to discontinuation (≥2.0% of participants in either arm) were peripheral sensory neuropathy (2.9% dostarlimab versus 0.4% placebo), infusion-related reaction (2.1% versus 3.3%), neuropathy peripheral (1.2% versus 2.4%), and thrombocytopenia (0.4% versus 2.0%). TEAEs leading to discontinuation of dostarlimab or placebo were higher in participants in the dostarlimab plus carboplatin-paclitaxel arm (17.4%) compared with the placebo plus carboplatin-paclitaxel arm (9.3%). Individual system organ classes and TEAE by preferred term incidences were comparable (<3% difference) in participants between treatment arms. TEAEs leading to discontinuation of dostarlimab or placebo in both treatment arms occurred in ≤2 participants each with the exception of rash maculo-papular (1.2% in dostarlimab plus carboplatin-paclitaxel arm, 0% in placebo plus carboplatin-paclitaxel arm), infusion-related reaction (1.2% versus 0.4%), and thrombocytopenia (0.4% versus 1.2%).

In the dMMR/MSI-H safety population, TEAEs leading to discontinuation of any study treatment were comparable in the dostarlimab plus carboplatin-paclitaxel arm (17.3%) and the placebo

plus carboplatin-paclitaxel arm (16.9%). The most frequently reported TEAEs leading to discontinuation (≥2%) were neuropathy peripheral (6.2%) and thrombocytopenia (3.1%) in the placebo plus carboplatin-paclitaxel arm; all TEAEs leading to discontinuation in the dostarlimab plus carboplatin-paclitaxel arm occurred in 1 participant each. TEAEs leading to discontinuation of dostarlimab or placebo were higher in the dostarlimab plus carboplatin-paclitaxel arm (15.4%) compared with the placebo plus carboplatin-paclitaxel arm (10.8%). The only TEAE leading to discontinuation of dostarlimab or placebo in ≥2% was thrombocytopenia in the placebo plus carboplatin-paclitaxel arm; all TEAEs leading to discontinuation in the dostarlimab plus carboplatin-paclitaxel arm occurred in 1 participant each. TEAEs leading to discontinuation of carboplatin were comparable in participants between the dostarlimab plus carboplatin-paclitaxel arm and the placebo plus carboplatin-paclitaxel arm (<2% difference). All TEAEs leading to discontinuation of carboplatin in both treatment arms occurred in 1 participant each. TEAEs leading to discontinuation of paclitaxel were higher in the placebo plus carboplatin-paclitaxel arm (12.3%) compared with the dostarlimab plus carboplatin-paclitaxel arm (3.8%). The only TEAE leading to discontinuation of paclitaxel in ≥2% of participants was neuropathy peripheral in the placebo plus carboplatin-paclitaxel arm; all TEAEs leading to discontinuation in the dostarlimab plus carboplatin-paclitaxel arm occurred in 1 participant each.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the rates of discontinuation in the overall and dMMR/MSI-H populations. Additionally, FDA agrees that 15% (8/52) patients discontinued dostarlimab in the dMMR/MSI-H population. Treatement-emergent adverse events resulting in discontinuation occurred in 1.9% of patients each (1/52) including: rash maculo-papular, fatigue, general health deterioration, acute kidney injury, infustion related reaction, keratitis, muscular weakness, and myelosuppression. The Applicant agreed and these were added in the label.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

TEAEs Leading to Interruption of Infusion

In the overall population, incidences of TEAEs leading to infusion interruption of any drug component of study treatment were comparable between the dostarlimab plus carboplatin-paclitaxel arm (20.3%) and the placebo plus carboplatin-paclitaxel arm (19.9%) and were mostly due to infusion interruptions of carboplatin and/or paclitaxel. The most frequent TEAE leading to interruption of study treatment infusion was infusion-related reaction in both treatment arms (10.8% dostarlimab, 11.8% placebo). The incidence of TEAEs leading to infusion interruption of dostarlimab/placebo was 1.2% total. The incidence of TEAEs leading to infusion interruption of carboplatin was comparable between the dostarlimab plus carboplatin-paclitaxel arm and the placebo plus carboplatin-paclitaxel arm (<2% difference). In addition, the incidence of TEAEs leading to infusion interruption of paclitaxel was comparable in the dostarlimab plus carboplatin-paclitaxel arm and the placebo plus carboplatin-paclitaxel arm (<3% difference).

In the dMMR/MSI-H safety population, total TEAEs leading to infusion interruption of any drug component of study treatment were 30.8% in the dostarlimab plus carboplatin-paclitaxel arm compared with 21.5% in the placebo plus carboplatin-paclitaxel arm. The most frequently reported TEAE in participants in both treatment arms was infusion-related reaction; 13.5% in dostarlimab plus carboplatin-paclitaxel arm and 12.3% in the placebo plus carboplatin-paclitaxel arm. All other TEAEs occurred in ≤2 participants each, with the exception of drug hypersensitivity, reported in 3 participants (4.6%) in the placebo plus carboplatin-paclitaxel arm. Two participants, both in the dostarlimab plus carboplatin-paclitaxel arm (3.8%; abdominal pain upper, lipase increased) experienced TEAEs leading to infusion interruption of dostarlimab. The incidence of TEAEs leading to infusion interruption of carboplatin was increased in participants in the dostarlimab plus carboplatin-paclitaxel arm (9.6%) compared with the placebo plus carboplatin-paclitaxel arm (1.5%). However, aside from infusion-related reaction reported in 3 participants (5.8%) in the dostarlimab plus carboplatin-paclitaxel arm, all other TEAEs occurred in 1 participant each.

The incidence of TEAEs leading to infusion interruption of paclitaxel was comparable in participants in the dostarlimab plus carboplatin-paclitaxel arm (19.2%) and the placebo plus carboplatin-paclitaxel arm (20.0%). The most frequently reported TEAE in both treatment arms was infusion-related reaction; 7.7.% in the dostarlimab plus carboplatin-paclitaxel arm and 12.3% in the placebo plus carboplatin-paclitaxel arm. All other TEAEs occurred in 1 participant each with the exception of drug hypersensitivity (3 participants, 4.6%) and flushing (2 participants, 3.1%) in the placebo plus carboplatin-paclitaxel arm.

TEAEs Leading to Delays of Infusion

In the overall population, the incidence of TEAEs leading to delays of infusion of any drug component of study treatment was 45.2% in the dostarlimab plus carboplatin-paclitaxel arm compared with 39.4% in the placebo plus carboplatin-paclitaxel arm. The most frequently reported TEAEs (>5%) leading to delays of infusion were thrombocytopenia (7.5% dostarlimab versus 5.7% placebo), neuropathy peripheral (5.8% versus 2.0%) and anemia (5.4% versus 6.1%) in the dostarlimab plus carboplatin-paclitaxel arm, and platelet count decreased (5.0% versus 7.3%), neutrophil count decreased (1.2% versus 6.5%), anemia, thrombocytopenia and neutropenia (3.3% versus 5.3%) in the placebo plus carboplatin-paclitaxel arm.

The incidence of TEAEs leading to delays of dostarlimab/placebo infusion was 42.7% in participants in the dostarlimab plus carboplatin-paclitaxel arm compared with 37.0% in participants in the placebo plus carboplatin-paclitaxel arm. However, no notable differences were observed in system organ classes or preferred terms between treatment arms. The most frequently reported TEAEs (>5%) leading to delays of dostarlimab/placebo infusion in the dostarlimab plus carboplatin-paclitaxel arm were thrombocytopenia (7.1% versus 5.3%) and anemia (5.4% versus 6.1%), and in the placebo plus carboplatin-paclitaxel arm were platelet count decreased (4.1% versus 7.3%), neutrophil count decreased (1.2% versus 6.1%), anemia, thrombocytopenia and neutropenia (3.3% versus 5.3%).

The incidence of TEAEs leading to delays of carboplatin infusion in the overall population was

28.6% in the dostarlimab plus carboplatin-paclitaxel arm and 30.1% in the placebo plus carboplatin-paclitaxel arm. The most frequently reported TEAEs (>4%) leading to delays of carboplatin infusion in the dostarlimab plus carboplatin-paclitaxel arm were thrombocytopenia (4.6% versus 4.5%) and neuropathy peripheral (4.6% versus 1.6%), and platelet count decreased (3.7% versus 5.7%), neutrophil count decreased (1.2% versus 5.3%), anemia (3.7% versus 4.9%), thrombocytopenia and neutropenia (2.9% versus 4.5%) in the placebo plus carboplatin-paclitaxel arm. The incidence of TEAEs leading to delays of paclitaxel infusion was 27.4% in the dostarlimab plus carboplatin-paclitaxel arm and 27.2% in the placebo plus carboplatin-paclitaxel arm. The most frequently reported TEAEs (>4%) leading to delays of paclitaxel infusion in the dostarlimab plus carboplatin-paclitaxel arm were thrombocytopenia (4.6% versus 4.9%) and platelet count decreased (4.1% versus 6.5%), and thrombocytopenia, platelet count decreased, neutrophil count decreased (1.2% versus 4.5%) and anemia (3.3% versus 4.5%) in the placebo plus carboplatin-paclitaxel arm.

In the dMMR/MSI-H safety population, the incidence of TEAEs leading to delays of any drug component of any study treatment was comparable between the dostarlimab plus carboplatin-paclitaxel arm (46.2%) and the placebo plus carboplatin-paclitaxel arm (43.1%). The most frequently reported TEAEs (>5%) leading to delays of infusion were (dostarlimab plus carboplatin-paclitaxel, placebo plus carboplatin-paclitaxel) anemia (7.7%, 9.2%), thrombocytopenia (7.7%, 9.2%), platelet count decreased (7.7% each), neuropathy peripheral (5.8%, 4.6%), and neutropenia (1.9%, 6.2%).

The incidence of TEAEs leading to delays of dostarlimab or placebo infusion was 44.2% in the dostarlimab plus carboplatin-paclitaxel arm and 41.5% in the placebo plus carboplatin-paclitaxel arm. With the exception of neuropathy peripheral, the most frequently reported TEAEs (>5%) leading to delays of dostarlimab or placebo infusion were the same as those observed for the delay of any study treatment described above.

The incidence of TEAEs leading to delays of carboplatin infusion was lower in the dostarlimab plus carboplatin-paclitaxel arm (30.8%) compared with the placebo plus carboplatin-paclitaxel arm (41.5%). With the exception of neuropathy peripheral, the most frequently reported TEAEs (>5%) leading to delays of carboplatin infusion were the same as those observed for the delay of any study treatment described above.

The incidence of TEAEs leading to delays of paclitaxel infusion was lower in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm (25.0%, 35.4%). The most frequently reported TEAEs (>4%) leading to delays of paclitaxel infusion were (dostarlimab plus carboplatin-paclitaxel arm, placebo plus carboplatin-paclitaxel) thrombocytopenia (5.8%, 9.2%), platelet count decreased (5.8%, 7.7%), neutropenia (1.9%, 4.6%), anemia (5.8%, 4.6%), and neuropathy peripheral (0%, 4.6%).

The FDA's Assessment:

FDA agrees with the Applicant's assessment of TEAEs leading to interuption and delays of infusion of any drug component in the overall and dMMR/MSI-H population.

Significant Adverse Events

The Applicant's Position:
Significant adverse events included immune-related AEs (irAEs), which are described below in Section 8.2.5.1.

The FDA's Assessment:
Refer to FDA's assessment of irAE's in Section 8.2.5.1.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

In the overall population, all participants in both treatment arms experienced at least 1 TEAE (100%). The majority of TEAEs were not serious and did not require treatment interruption, treatment discontinuation or chemotherapy dose reduction.

Incidences of participants experiencing Grade ≥3 TEAEs and SAEs were higher in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm (Grade ≥3 TEAEs: 70.5% versus 59.8%, respectively and SAEs: 37.8% versus 27.6%, respectively). TEAEs leading to death were reported in 5 participants in total, all in the dostarlimab plus carboplatin-paclitaxel arm. Two (0.8%) of these TEAEs were assessed by the investigator as related to study treatment.

Consistent with the mechanism of action, dostarlimab/placebo-related immune-related TEAEs were higher (≥20%) in participants in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm. The incidences of participants experiencing TEAEs leading to treatment discontinuation, infusion delay or interruption, dose reduction, and infusion-related reactions were comparable with ≤10% differences between the treatment arms, although all but infusion-related reactions were numerically higher in the dostarlimab plus carboplatin-paclitaxel arm.

In the dMMR/ MSI-H safety population, all participants in both arms experienced at least 1 TEAE (Applicant - Table 14). All parameters were comparable between arms (≤10% differences) with the exception of participants experiencing immune-related TEAEs and treatment-related immune-related TEAEs, although generally numerically higher in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm. The incidence of participants experiencing immune-related TEAEs and treatment-related immune-related TEAEs were notably higher (>30%) in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm. TEAEs leading to death were reported in 2 participants, both in the dostarlimab plus carboplatin-paclitaxel arm and assessed by the Investigator as related to study treatment (Applicant - Table 14).

Applicant - Table 14: Overall summary of treatment-emergent adverse events (dMMR/MSI-H population, Safety analysis set)

	dMMR/MSI-H Population		Overall Population	
Adverse event category, n (%)	**Dostar + carbo/pac (N=52)**	**Placebo + carbo/pac (N=65)**	**Dostar + carbo/pac (N=241)**	**Placebo + carbo/pac (N=246)**
Any TEAEs	52 (100%)	65 (100%)	241 (100%)	246 (100%)
Any treatment-related TEAEs	52 (100%)	65 (100%)	236 (97.9%)	243 (98.8%)
Any Grade ≥3 TEAEs	37 (71.2%)	42 (64.6%)	170 (70.5%)	147 (59.8%)
Any Grade ≥3 treatment-related TEAEs	30 (57.7%)	32 (49.2%)	122 (50.6%)	114 (46.3%)
Any serious TEAEs	14 (26.9%)	20 (30.8%)	91 (37.8%)	68 (27.6%)
Any treatment-related serious TEAEs	9 (17.3%)	9 (13.8%)	44 (18.3%)	30 (12.2%)
Any TEAE leading to infusion interruption	16 (30.8%)	14 (21.5%)	49 (20.3%)	49 (19.9%)
Any TEAE leading to infusion delay	24 (46.2%)	28 (43.1%)	109 (45.2%)	97 (39.4%)
Any TEAE leading to dose reduction	11 (21.2%)	18 (27.7%)	68 (28.2%)	68 (27.6%)
Any TEAE leading to treatment discontinuation	9 (17.3%)	11 (16.9%)	57 (23.7%)	41 (16.7%)
Any TEAE with the outcome of death	2 (3.8%)	0	5 (2.1%)	0
Any treatment-related TEAE leading to death	2 (3.8%)	0	2 (0.8%)	0
Any immune-related TEAE	38 (73.1%)	24 (36.9%)	137 (56.8%)	88 (35.8%)
Any dostarlimab/placebo-related immune-related TEAE	25 (48.1%)	8 (12.3%)	92 (38.2%)	38 (15.4%)
Any infusion-related reactions	12 (23.1%)	13 (20.0%)	44 (18.3%)	49 (19.9%)

carbo=carboplatin; Dostar=dostarlimab; pac=paclitaxel; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
Source: Table 14.3.1.1

Adverse Drug Reactions

Adverse drug reactions (ADRs) occurring in ≥10% of participants with dMMR/MSI-H EC are provided in Applicant - Table 15. Clinically relevant ADRs occurring in < 10% of participants with dMMR/MSI-H EC identified from this data cut were all irAEs and included immune-mediated hypothyroidism, hyperthyroidism, thyroiditis, colitis, pancreatitis, aspartate aminotransferase increased and type 1 diabetes mellitus; all occurred in 1 participant (1.9%) each with the exception of aspartate aminotransferase increased (5 participants, 9.6%) and hyperthyroidism (3 participants, 5.8%).

Applicant - Table 15. Adverse Reactions (>10%) in Patients with Primary Advanced or Recurrent dMMR/MSI-H EC Who Received JEMPERLI with Chemotherapy in RUBY

Adverse Reaction	Dostar + carbo/pac N = 52		Placebo + carbo/pac N = 65	
	All Grades %	Grade 3 or 4 %	All Grades %	Grade 3 or 4 %
Skin and subcutaneous tissue				
Rash[a]	40	7.7	16	0
Dry skin	11.5	0	6.3	0
General and administration site				
Pyrexia	13.5	0	1.6	0
Endocrine Disorders				
Hypothyroidism[b]	23	0	4.8	0
Investigations				
Alanine aminotransferase increased	11.5	0	4.8	0

dMMR = Mismatch Repair Deficient, MSI-H = Microsatellite Instability-High.
a Includes rash, rash maculo-papular
b Includes hypothyroidism and immune-mediated hypothyroidism
Graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

The majority of the ADRs for dostarlimab plus carboplatin-paclitaxel were previously identified as ADRs for dostarlimab monotherapy in 2L+ treated participants with advanced or recurrent solid tumors (provided in the GARNET IA3, module 2.7.4, Sequence 0134). New terms included as ADRs for dostarlimab plus carboplatin-paclitaxel based on data from RUBY Part 1 are immune-related hypothyroidism and dry skin.

Additional supporting data for the US Prescribing Information is provided for dostarlimab adverse reactions, identified as TEAEs considered related to dostarlimab by Investigators with frequencies based on all causality incidence (e.g. based on related plus not related incidence) for the dostarlimab-related preferred terms in the dMMR/MSI-H safety population. Similar data for dostarlimab adverse reactions identified as TEAEs considered related to dostarlimab by Investigators with frequencies based on all causality incidence is provided for Grade 3 and 4 TEAEs, SAEs, and for TEAEs leading to treatment interruption or discontinuation.

The FDA's Assessment:

FDA agrees with the Applicant that irAEs for dostarlimab in combination with carboplatin and paclitaxel are similar to those observed in the GARNET study. However, the rates of certain irAEs are higher in the overall population of the RUBY study when combining dostarlimab with carboplatin and paclitaxel including: hypothyroidism 12% (28/241), hyperthyroidism 3.3% (8/241), and type 1 diabetes mellitus 0.4% (1/241). These were updated in Section 5.1 of the label. The irAEs of infusion related reaction, keratitis, and rash each lead to discontinuation of dostarlimab in 1 patient. FDA disagrees with the Applicant's assessment of adverse rections ≥10% and finds that diarrhea and hypertension are increased in patients treated with dostarlimab in combination with carboplatin and paclitaxel versus placebo in combination with carboplatin and paclitaxel, (b) (4) and 21% versus 11%, respectively. These were updated in Section 6.1, Table 3 of the label.

Laboratory Findings
The Applicant's Position:

Clinical Chemistry

In the overall population, baseline chemistry results were generally Grade 0 (>80% of participants) in either treatment arm. For hyperglycemia, the Grade 0 incidence was 50.2% in the dostarlimab plus carboplatin-paclitaxel arm and 47.6% in the placebo plus carboplatin-paclitaxel arm.

Shifts to Grade 3 or 4 chemistry parameters of >2 grades from Baseline to maximum postbaseline value in the overall population were most frequently (>3%) reported in participants in the dostarlimab plus carboplatin-paclitaxel arm for hyponatremia (4.1%), hyperglycemia (3.3%) and serum amylase increased (3.3%). No shifts to Grade 3 or 4 chemistry parameters of >2 grades from Baseline to maximum postbaseline value were reported in the placebo plus carboplatin-paclitaxel arm.

In the dMMR/MSI-H safety population, baseline chemistry results were generally Grade 0 (>80% of participants) in either treatment arm, with the exception of hyperglycemia where the Grade 0 incidence was similar in both arms (hyperglycemia: dostarlimab plus carboplatin-paclitaxel arm 51.9%, placebo plus carboplatin-paclitaxel arm 46.2%).

Shifts to Grade 3 or 4 chemistry parameters of >2 grades from Baseline to maximum postbaseline value in the dMMR/MSI-H safety population were most frequently (>3%) reported in participants in the dostarlimab plus carboplatin-paclitaxel arm for hyponatremia (7.7%) and hypokalemia (3.8%), and in the placebo plus carboplatin-paclitaxel arm for hypokalemia (6.2%) and hypophosphatemia (4.6%).

Hematology

In the overall population, baseline hematology results were generally Grade 0 (≥95% of participants) in both arms, with the exception of hemoglobin decreased (Grade 0: 56.4% in the dostarlimab plus carboplatin-paclitaxel arm, 63.4% in the placebo plus carboplatin-paclitaxel arm) and lymphocyte count decreased (Grade 0: 71.8% in the dostarlimab plus carboplatin-paclitaxel arm, 71.1% in the placebo plus carboplatin-paclitaxel arm).

Shifts to Grade 3 or 4 hematology parameters of >2 grades from Baseline to maximum postbaseline value in the overall population were most frequently (>10%) reported in participants in the dostarlimab plus carboplatin-paclitaxel arm for neutrophil count decreased (13.7%) and white blood cell count decreased (10.7%), and in the placebo plus carboplatin-paclitaxel arm for neutrophil count decreased (17.9%).

In the dMMR/MSI-H safety population, baseline hematology results were generally Grade 0 (>94% of participants) in both arms, with the exception of hemoglobin decreased (Grade 0: 48.1% in the dostarlimab plus carboplatin-paclitaxel arm, 56.9% in the placebo plus carboplatin-paclitaxel arm) and lymphocyte count decreased (Grade 0: 75.0% in the

dostarlimab plus carboplatin-paclitaxel arm, 72.3% in the placebo plus carboplatin-paclitaxel arm).

Shifts to Grade 3 or 4 hematology parameters of >2 grades from Baseline to maximum postbaseline value in the dMMR/MSI-H safety population were most frequently (>10%) reported in participants in the dostarlimab plus carboplatin-paclitaxel arm for neutrophil count decreased (15.4%), and in the placebo plus carboplatin-paclitaxel arm for neutrophil count decreased (23.1%), white blood cell count decreased (12.4%), platelet count decreased (12.3%) and lymphocyte count decreased (10.8%).

Clinical Coagulation and Urinalysis

In the overall population, baseline coagulation results were generally Grade 0 (>89% of participants) in any arm. No baseline Grade 3 or Grade 4 coagulation results or shift to Grade 3 or Grade 4 were reported. Results for shifts from baseline coagulation were generally similar in the dMMR/MSI-H safety population.

Fluctuations in urinalysis parameters were observed during the study, but no concerning trend was identified for any of the parameters.

Liver Assessments

In the overall population, the incidence of potential liver toxicity events was generally higher in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm, however, the difference between arms arms for each parameter was <5%. ALT ≥20×ULN and AST ≥20×ULN were reported by 1 participant, in the placebo plus carboplatin-paclitaxel arm. The toxicity criterion with the highest overall frequency (6.6%) and greatest difference in frequency between treatment arms was (ALT or AST) ≥3×ULN; 10.4% and 2.8% in the dostarlimab plus carboplatin-paclitaxel arm and the placebo plus carboplatin-paclitaxel arm, respectively. No potential Hy's law cases were reported.

In the dMMR/MSI-H safety population, ALT or AST ≥3×ULN was higher in the dostarlimab plus carboplatin-paclitaxel arm (19.2%) as compared with the placebo plus carboplatin-paclitaxel arm (1.5%). No incidences of ≥10×ULN or ≥20×ULN ALT or AST were reported in either treatment arm.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment. However, three possible Hy's Law cases were assessed to not be Hy's Law cases after FDA review as follows:

- (b) (6) The patient had a peak alkaline phosphatase of 3.55x ULN consistent with cholestatic liver injury.
- (b) (6) The patient had a peak alkaline phosphatase of 4.39x ULN consistent with cholestatic liver injury.
- (b) (6) The patient narrative is consistent with immune-related hepatitis and therefore not a Hy's Law case.

Vital Signs

The Applicant's Position:

In general, findings for vital signs were consistent with the patient population and disease state under study.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Electrocardiograms (ECGs)

The Applicant's Position:

In general, findings for ECG were consistent with the patient population and disease state under study.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

QTcF generally similar between arms

The Applicant's Position:

No dedicated QT studies were conducted for dostarlimab.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Immunogenicity

The Applicant's Position:

Immunogenicity was assessed using a risk-based bioanalytical strategy to determine if ADA responses against dostarlimab affect safety, efficacy or PK. Based on the low immunogenicity risk for dostarlimab, a validated, multi-tiered approach to evaluating anti-dostarlimab antibodies, consisting of screening, confirmation, titration, and neutralizing assays was implemented.

There were 241 participants enrolled in the dostarlimab plus carboplatin-paclitaxel arm and treated with dostarlimab. Of these, 239 participants had at least one immunogenicity sample result and were included in the ADA Analysis Set, and 225 participants were included in the ADA Population.

Overall, in this study, none of the 225 participants had treatment-induced ADA or treatment-boosted ADA for an overall incidence of treatment-emergent ADA of 0.0%. There were 34 participants (15.1%) with treatment-unaffected ADA (preexisting ADA at baseline with no meaningful increase in titer postdose). One hundred eighty-five (185) participants (82%) were classified as negative, and 6 participants (3%) were classified as inconclusive with respect to treatment-emergent ADA (Applicant - Table 16).

There were 17 participants who were categorized as having treatment-unaffected ADA (preexisting ADA with no meaningful increase in titer), who were positive for NAb at baseline and also at Cycle 2 for one of the subjects. None of the subjects who were classified as inconclusive had positive NAb results during the study (Applicant - Table 17). Immunogenicity results were similar in the dMMR/MSI-H safety population.

Pre-dose dostarlimab serum concentrations were similar in participants with treatment-unaffected ADA and participants who tested negative at all time points. Therefore, preexisting ADA did not seem to affect dostarlimab PK.

The efficacy and safety results were similar between participants with treatment-unaffected ADA and participants who tested negative at all time points. Furthermore, at this point in time, there is no evidence of a clinically meaningful impact of preexisting ADA or NAb on any safety or efficacy measures.

In summary, there were no treatment-emergent ADAs and no observed impact of dostarlimab immunogenicity on safety, efficacy and PK. This is consistent with the low immunogenicity risk of dostarlimab and other anti-PD 1 antibodies [Keytruda USPI; Opdivo USPI].

Applicant - Table 16: Incidence of Participants with and without Treatment-Emergent Anti-Dostarlimab Antibodies Postbaseline, Overall and by MMR Status (ADA Population)

		Treatment-Emergent ADA [a]		Treatment-Unaffected ADA [b]		Negative for ADA [b]		Inconclusive ADA Status [b]	
Population	**N**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Overall Population	225	0	0.0	34	15.1	185	82.2	6	2.7
dMMR/MSI-H	50	0	0.0	8	16.0	41	82.0	1	2.0
MMRp/MSS	175	0	0.0	26	14.9	144	82.3	5	2.9

ADA=antidrug antibody.
[a] Treatment-induced or -boosted
[b] Using drug tolerance limit of 250 µg/mL

Applicant - Table 17: Subjects with Positive Neutralizing Antibodies Results by ADA Response (ADA Population)

	Treatment-Emergent ADA [a] (N=0)		Treatment-Unaffected ADA [b] (N= 34)		Inconclusive ADA Status [b] (N=6) [c]	
	n	**%**	**n**	**%**	**n**	**%**
Positive for NAb	0	0.0	17	50.0	-	-
Negative for NAb	0	0.0	17	50.0	1	16.7

ADA=antidrug antibody; NAb=neutralizing antibody.
[a] Treatment-induced and treatment-boosted;
[b] Using drug tolerance limit of 250 µg/mL;

[c] Subjects with inconclusive ADA status may not have had any positive ADA results and, therefore, may not have been tested for Nab.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment of immunogenicity. See also FDA's clinical pharmacology assessment in Section 6.3.1.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Immune-Related Adverse Events (irAEs)

The Applicant's Position:

In the overall and dMMR/MSI-H safety populations, the incidences of irAEs were generally higher in the dostarlimab plus carboplatin-paclitaxel arm and consistent with the dostarlimab mechanism of action (Applicant - Table 18).

In the overall population, 38.2% of participants in the dostarlimab plus carboplatin-paclitaxel arm and 15.4% in the placebo plus carboplatin-paclitaxel arm had dostarlimab or placebo-related irAEs. The most frequently reported (≥5%) dostarlimab or placebo-related irAEs were hypothyroidism, rash, arthralgia and alanine aminotransferase increased; all but arthralgia were higher in incidence in the dostarlimab plus carboplatin-paclitaxel arm. In the dostarlimab plus carboplatin-paclitaxel arm potential irAEs which were Grade ≥3, SAEs or leading to discontinuation were reported in 1 or 2 participants each with the exception of potential irAEs Grade ≥3 of rash (4.1%) and rash maculo-papular, alanine aminotransferase increased and aspartate aminotransferase increased (2.1% each), and potential irAEs leading to discontinuation of rash and infusion-related reactions (1.2% each). There were no reported potential irAEs leading to death.

For the dMMR/MSI-H safety population, 48.1% of participants in the dostarlimab plus carboplatin-paclitaxel arm, and 12.3% of participants in the placebo plus carboplatin-paclitaxel arm, had irAEs assessed by the investigator as related to dostarlimab or placebo. The most frequently reported dostarlimab or placebo-related irAE was hypothyroidism (15.4%) in the dostarlimab plus carboplatin-paclitaxel arm, and hypothyroidism and arthralgia (4.6% each) in the placebo plus carboplatin-paclitaxel arm. Dostarlimab/placebo-related Grade ≥3 irAEs were observed in 17.3% of participants in the dostarlimab plus carboplatin-paclitaxel arm. The most frequently observed dostarlimab-related Grade ≥3 irAE was rash (5.8% dostarlimab versus 0% placebo), all other dostarlimab-related Grade ≥3 irAEs occurred in 1 participant each. Serious irAEs were observed in 2 participants (3.8%; type 1 diabetes mellitus, pancreatitis) in the dostarlimab plus carboplatin-paclitaxel arm, and in 1 participant (1.5%, colitis) in the placebo plus carboplatin-paclitaxel arm.

Applicant - Table 18. Summary of treatment-emergent immune-related adverse events by immune-related adverse event category and preferred term (Overall population, Safety analysis set)

Category, n (%) Preferred term, n (%)	Dostar + carbo/pac (N=241)		Placebo + carbo/pac (N=246)	
	All events	Dostarlimab-related	All events	Placebo-related
Any immune-related AE	**137 (56.8%)**	**92 (38.2%)**	**88 (35.8%)**	**38 (15.4%)**
Arthralgia	32 (13.3%)	14 (5.8%)	31 (12.6%)	16 (6.5%)
Infusion-related reaction	31 (12.9%)	4 (1.7%)	30 (12.2%)	0
Hypothyroidism	27 (11.2%)	27 (11.2%)	8 (3.3%)	7 (2.8%)
Hypersensitivity/ Drug hypersensitivity	6 (2.5%)/ 7 (2.9%)	0/ 0	4 (1.6%)/ 11 (4.5%)	1 (0.4%)/ 1 (0.4%)
Rash	21 (8.7%)	16 (6.6%)	6 (2.4%)	5 (2.0%)
Rash maculo-papular	16 (6.6%)	11 (4.6%)	0	0
Pruritus	15 (6.2%)	8 (3.3%)	4 (1.6%)	3 (1.2%)
ALT increased	15 (6.2%)	14 (5.8%)	2 (0.8%	2 (0.8%)
AST increased	12 (5.0%)	10 (4.1%)	1 (0.4%)	1 (0.4%)
Hyperthyroidism	8 (3.3%)	8 (3.3%)	1 (0.4%)	1 (0.4%)

Abbreviations: AE=adverse event; carbo=carboplatin; Dostar=dostarlimab; pac=paclitaxel.
Immune-related AEs are identified as any ≥Grade 2 AEs based on a prespecified preferred terms list.
Source: Table 14.3.1.41

The FDA's Assessment:
FDA agrees with the Applicant's assessment of all treatment-emergent immune-related adverse events (irAEs). No analysis was performed by the FDA of investigator assessed dostarlimab-related or placebo-related events as the assessment should be regardless of attribution. Section 5 of the label was updated with the incidence of irAEs for the overall population that occurred regardless of investigator attribution.

The rates of certain irAEs are higher in the overall population of the RUBY study when combining dostarlimab with carboplatin and paclitaxel including: hypothyroidism 12% (28/241), hyperthyroidism 3.3% (8/241), and type 1 diabetes mellitus 0.4% (1/241). The irAEs of infusion related reaction, keratitis, and rash each lead to discontinuation of dostarlimab in 1 patient.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Participants treated with dostarlimab plus carboplatin-paclitaxel had clinically similar QoL outcomes in all populations compared with those who received placebo plus carboplatin-paclitaxel demonstrating that significant improvements in PFS due to the addition of dostarlimab to standard of care chemotherapy were not accompanied by any substantial deterioration in QoL.

The FDA's Assessment:
The COA and QoL analysis was not alpha allocated in the statistical assessment plan (SAP) and is

therefore considered exploratory by the FDA. Therefore, there is uncertainty in interpretation of these results.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Subgroup analyses of TEAEs in the dMMR/MSI-H safety population are limited in interpretation by the small sample size of participants with specific TEAEs. Overall, no notable differences were identified in the safety profiles of dostarlimab in combination with carboplatin-paclitaxel for intrinsic and extrinsic factors. No dose adjustment is expected to be required and therefore is not recommended in the labelling.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
Not applicable

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

No human carcinogenicity studies were conducted.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Human Reproduction and Pregnancy

The Applicant's Position:

Dostarlimab has not been studied in pregnant or lactating women.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

A study of dostarlimab, in combination with niraparib, in pedatric participants is on going. A waiver for the PREA requirement for pediatric evaluation was requested for the proposed

indication in EC based on pediatric studies being "impossible or highly impractical" given the extreme rarity of the condition in the pediatric population.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

No cases of overdose, drug abuse, withdrawal and rebound with dostarlimab have been reported. No known abuse potential exists because dostarlimab is administered in a hospital setting.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
The Applicant's Position:

The dostarlimab periodic safety update report (PBRER Dostarlimab 21Apr2022-20Oct2022) can be found at m5.3.6. No new safety signals have been identified in the post-marketing population.

The FDA's Assessment:
FDA agrees with the Applicant's assesment. FDA will continue to monitor any new safety signals in the postmarketing setting.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Potential safety risks are described in the proposed labeling with associated management recommendations. While additional adverse drug reactions are anticipated to be identified in subsequent data cuts, and with the potential for pooled safety analyses, significant potential safety risks are well-described in the proposed labeling. Routine pharmacovigilance will be conducted to monitor for unexpected adverse events.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

The Applicant provided some additional information in the sBLA submission for updated safety events across the dostarlimab development program in the Periodic Benefit Risk Evaluation Report. FDA noted an irAR of fatal encephalitis in a patient treated with niraparib and dostarlimab for relapsed neuroblastoma. The patient was placed on palliative management after developing severe, progressive encephalitis and intractable seizures. One other death was

attributed to cardiac decompensation and renal failure in the setting of pneumonitis and assessed as inconsistent with fatal immune-mediated pneumonitis. New adverse reactions to dostarlimab were encephalitis, gastritis, esophagitis, immune-mediated lung disease, immune-mediated enterocolitis, and immune-mediated myositis.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

- The overall safety profile for dostarlimab plus carboplatin-paclitaxel combination treatment was generally consistent with the known safety profiles of the individual agents. The proposed regimen in the indicated population was tolerable and the toxicities were generally manageable. The nature and types of immune-related events in the safety profile are consistent with the mechanism of action of dostarlimab and are similar to those reported for other PD-1 inhibitors.
- In the overall population, severe and serious TEAEs were approximately 10% higher in the dostarlimab plus carboplatin-paclitaxel arm compared with the placebo plus carboplatin-paclitaxel arm with generally similar incidence of individual TEAEs between treatment arms. The most frequently reported treatment-related severe (anemia, neutropenia and neutrophil count decreased) and serious (febrile neutropenia, pyrexia, sepsis, muscular weakness) TEAEs were generally not related to dostarlimab only treatment.
- Most common potential overlapping toxicities (anemia, nausea, vomiting, diarrhea, myalgia) in the overall population were not increased in incidence or severity in either treatment arm as compared with the safety profiles of the individual agent with the highest incidence/severity. No clinically significant differences were observed for carboplatin-paclitaxel-related AEs between the treatment arms.
- Cases of rash and rash maculo-papular were increased in the dostarlimab plus carboplatin-paclitaxel arm as compared with placebo plus carboplatin-paclitaxel but were generally not severe, serious, or leading to treatment discontinuation.
- Two participants in the dostarlimab plus carboplatin-paclitaxel arm had treatment-related deaths (myelosuppression related to all treatments; hypovolemic shock related to dostarlimab); both were in the dMMR/MSI-H safety population.
- Adverse drug reactions from dostarlimab in combination with carboplatin-paclitaxel are generally immune-related with most labeled for dostarlimab monotherapy.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that an increased rate of adverse events occurred in the dostarlimab in combination with carboplatin and paclitaxel arm. Additionally, hypothyroidism occurred more often in the combination than for dostarlimab alone. Adverse events in patients receiving dostarlimab with carboplatin and paclitaxel were generally consistent with the respective USPIs and no new safety signals were noted.

The most common adverse reactions, including laboratory abnormalities (≥20%), were decreased hemoglobin, decreased white blood cell count, decreased lymphocytes, increased glucose, decreased neutrophils, rash, diarrhea, increased aspartate aminotransferase, increased alanine aminotransferase, decreased sodium, hypothyroidism, and hypertension.

Serious adverse reactions occurred in 13% of patients receiving dostarlimab in combination with carboplatin and paclitaxel; the most common serious adverse reaction was sepsis, including urosepsis (6%).

Discontinuations of dostarlimab in combination with carboplatin and paclitaxel occurred in 15% of patients for adverse events including: rash maculo-papular, fatigue, general physical health deterioration, acute kidney injury, infusion related reaction, keratitis, muscular weakness, and myelosuppression. Three patients also died from causes where a contribution from dostarlimab cannot be excluded. These included 2 cases of septic shock and 1 case of myelosuppression. These were updated in section 6 of the label.

Overall, an acceptable safety profile was demonstrated for the intended population with a serious and life threatening condition.

APPEARS THIS WAY ON ORIGINAL

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

FDA efficacy evaluation was based on data from Part 1 of Ruby trial. RUBY Part 1 demonstrated a statistically significant improvement in investigator-assessed PFS in the dMMR/MSI-H subpopulation and all-comers population. However, improvement in PFS in the all-comer population was primarily attributed to results from patients in the dMMR/MSI-H subgroup. Results for BICR-assessed PFS are generally consistent with the primary findings of investigator-assessed PFS in the dMMR/MSI-H subpopulation. OS in the all-comers population, while not statistically significant, did not show a trend towards OS detriment. OS in the dMMR/MSI-H subpopulation was not formally tested. Although OS data in the dMMR/MSI-H subpopulation are not mature, it shows a positive trend in favor of dostarlimab plus carboplatin and paclitaxel arm.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Based upon a favorable benefit-risk profile dMMR/MSI-H population, as stated in the FDA assessments above, the clinical and statistical FDA reviewers recommend regular approval of dostarlimab, in combination with carboplatin and paclitaxel, for the following indication:

JEMPERLI, in combination with carboplatin and paclitaxel, followed by JEMPERLI as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient (dMMR), as determined by an FDA-approved test, or microsatellite instability-high (MSI-H).

X X

Hui Zhang, PhD
Primary Statistical Reviewer

Shenghui Tang, PhD
Statistical Team Leader

X X

Sakar Wahby, PharmD (Efficacy)

Joshua Donaldson, MD (Safety)	Preeti Narayan, MD
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
No advisory committee discussion or consultations external to the FDA were deemed necessary for this supplemental BLA application.

APPEARS THIS WAY ON ORIGINAL

10 Pediatrics

The Applicant's Position:

Dostarlimab was not studied in pediatric patients. GSK submitted a Pediatric Study Plan waiver for endometrial cancer under PREA.

The FDA's Assessment:

FDA is waiving the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable because dMMR/MSI-H EC is rare in the pediatric population.

11 Labeling Recommendations

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Highlights of Prescribing Information	Added indication, dosing and adverse reactions for JEMPERLI (b) (4) (b) (4) (b) (4) as seen in the RUBY clinical trial.	FDA agrees with corresponding revisions annotated for Section 1 and Section 6.1 (common adverse reactions and laboratory abnormalities) below. FDA also removed (b) (4) (b) (4) to use bulleted format and reduce redundancy.
Indications and Usage (1.1)	Added JEMPERLI combination therapy indication (b) (4) (b) (4)	FDA agrees with the addition of the indication with revision of (b) (4) (b) (4) to "with carboplatin and paclitaxel, followed by JEMPERLI as a single agent". This text was also revised in all applicable labeling sections that follow.
Patient selection (2.1)	Provided selection criteria for biomarker testing for dMMR/MSI-H patients.	FDA agrees.
Recommended Dosage (2.2)	Included dosing information for JEMPERLI (b) (4) (b) (4)	FDA agrees with addition of this recommended dosage with an edit to identify these dosages are for "adults".
Warnings and Precautions, Severe and Fatal Immune-Mediated Adverse Reactions (5.1)	Based on FDA IR request received May 8, 2023, Hypophysitis, Hypothyroidism, Hyperthyroidism and T1 Diabetes Mellitus events were added for JEMPERLI (b) (4) (b) (4) submitted May 22, 2023)	FDA agrees with the IR response with a revision of the T1 diabetes case outcome based on FDA safety review [i.e., revised (b) (4) to "did not resolve"].
Adverse Reactions, Clinical Trials Experience (6.1)	Included information from RUBY clinical trial for the dMMR/MSI-H subpopulation.	FDA agreed to addition of the RUBY trial to 6.1 with the following revisions: • Revision of the safety population used for Warnings and Precautions • Increased serious adverse reactions from 13% (b) (4) (b) (4) identified during FDA safety review • Increased fatal adverse reactions from (b) (4) to 6%; revised (b) (4) (b) (4) to "septic shock" • Increased permanent discontinuation of Jemperli from (b) (4) to 15% by (b) (4) (b) (4) in accordance with FDA labeling guidance • Added "peripheral neuropathy" and "rash" as most common reasons for dosage interruption • Revised the most common adverse reactions table to remove (b) (4) (b) (4) more accurately captured in the laboratory abnormalities table (Table 3).

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		• Added "diarrhea" and "hypertension" to the common adverse reactions in Table 3 based on FDA safety review • Added "keratitis" and "encephalopathy" to clinically relevant adverse reactions that occurred at <10%. • Added liver function tests (AST. ALT) to laboratory abnormalities table (Table 4)
Use in Specific Populations, Geriatric Use (8.5)	Included information from RUBY clinical trial.	FDA agrees with minor revisions.
Clinical Pharmacology, Pharmacokinetics (12.3)	Modified language to incorporate outcomes from RUBY clinical trial.	• FDA agrees with minor revisions. • FDA disagreed with (b) (4) (b) (4) (b) (4) and removed this information.
Immunogenicity (12.6)	Modified language to incorporate outcomes from RUBY clinical trial. Revised to conform with FDA guidance.	FDA agrees with the addition with revision to add exposure intervals for the anti-drug antibody analyses performed.
Clinical Studies, Endometrial Cancer (14.1)	Included information from RUBY clinical trial for the dMMR/MSI-H subpopulation.	FDA agrees with the addition of this information. FDA made several minor revisions, reordered information, and added a description of how patients were assessed for dMMR/MSI-H tumors in the trial.
Clinical Studies, Endometrial Cancer (14.1)	Based on FDA IR request received May 16, 2023, RUBY study demography and Table 9 and Figure 1 updated to reflect patient population with MMR/MSI status used for randomization. Table 9 updated to reflect results based on confirmed ORR in patients with measureable disease at baseline (submitted May 22, 2023)	• FDA agrees with revisions to study demographics. FDA requested addition of ethnicity for Hispanic or Latino patients, but there were no patients with this ethnicity enrolled in this trial (no labeling revisions were made). • FDA agreed with results for PFS and ORR • FDA revised DoR to remove (b) (4) (b) (4) results (not required); and revised the proposed median (b) (4) or DoR to "(range)". • FDA removed (b) (4) (b) (4) (not required or informative); and clarified the 1-sided p-value for the stratified log-rank test was statistically significant (PFS) • FDA removed (b) (4) (b) (4) and clarified that "Overall survival data in this subpopulation were immature with 27% deaths." • FDA revised the y-axis in Figure 1 from (b) (4) to "progression-free survival probability" (Kaplan-Meier Curve for PFS)

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Medication Guide	Modified language to incorporate outcomes from the RUBY clinical trial for the dMMR/MSI-H subpopulation.	FDA agrees with addition of this information with revisions based on changes to made to the USPI in Section 6.1 above. See the OPDP/DMPP review of Patient Labeling for full information.

The FDA's Assessment:
The table above summarizes significant changes to the proposed prescribing information made by the FDA.

APPEARS THIS WAY ON ORIGINAL

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
No REMS is recommended for dostarlimab.

APPEARS THIS WAY ON ORIGINAL

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The following Postmarketing Commitments (PMCs) were agreed upon by FDA and the Applicant under Supplemental BLA 006.

PMC 4481-1:

Complete the ongoing clinical trial, RUBY Part 1, titled "A Phase 3, Randomized, Double-blind, Multicenter Study of Dostarlimab (TSR-042) plus Carboplatin-paclitaxel versus Placebo plus Carboplatin-paclitaxel in Patients with Recurrent or Primary Advanced Endometrial Cancer (RUBY)", to provide the pre-specified interim and final overall survival (OS) analyses.

Interim Report Submission: *12/2024*
Trial Completion: *12/2028*
Final Report Submission: *06/2029*

Submit the datasets with the interim and final report.

PMC 4481-2:

Commitment to establish and support the availability of a nucleic acid based in vitro diagnostic device that is essential to support the safe and effective use of Jemperli, in combination with carboplatin and paclitaxel, for patients with endometrial cancer (EC) that are microsatellite instability high (MSI-H) through an appropriate analytical and clinical validation study using clinical trial data.

Study Completion: *03/2027*
Final Report Submission: *09/2027*

Submit a summary of study results in the final report submission.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed? No
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	_X_ Yes __ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes _X_ No

□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes _X_ No

APPEARS THIS WAY ON ORIGINAL

14 Division Director (DHOT) (NME ONLY)

X

APPEARS THIS WAY ON ORIGINAL

15 Division Director (OCP)

X

APPEARS THIS WAY ON ORIGINAL

16 Division Director (OB)

X

Shenghui Tang, PhD

APPEARS THIS WAY ON ORIGINAL

17 Division Director (Clinical)

X

Laleh Amiri-Kordestani, MD

APPEARS THIS WAY ON ORIGINAL

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Laleh Amiri-Kordestani, MD

APPEARS THIS WAY ON ORIGINAL

19 Appendices

19.1. References

The Applicant's References:

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The FDA's References:

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19.2. Financial Disclosure

The Applicant's Position:

All Investigators on RUBY (Study 213361) were assessed for significant equity or payments, proprietary interest, and other compensation. Of the 819 total Clinical Investigators, certification of due diligence was provided for 8 (approximately 0.98%) Investigators. Ten clinical Investigators (approximately 1.2%) had financial information to disclose.

Covered Clinical Study (Name and/or Number):* RUBY (213361)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 819		

Number of investigators who are Sponsor employees (including both full-time and part-time employees): No		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 10		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: No Significant payments of other sorts: Yes Proprietary interest in the product tested held by investigator: No Significant equity interest held by investigator in study: No Sponsor of covered study: No		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 8 (List B)		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

There are no nonclinical pharmacology/toxicology appendices.

The FDA's Assessment:
FDA agrees.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:
The PPK model generally adequately characterizes dostarlimab PK, and the model-predicted exposure metrics of Cycle 1 C_{min}, C_{max}, and AUC are adequate for use in E-R analysis.

Population PK analysis suggested a similar exposure of dostarlimab after the combination therapy and monotherapy at the same dose level. The recommended dosage for combination therapy is supported by the population PK analysis results as well as other analyses results (ie., clinical efficacy, safety, and ER analyses).

19.4.1.2. PPK Assessment Summary

The Applicant's Position:

General Information		
Objectives of PPK Analysis		• *Characterize dostralimab's PK profile* • *To do an external validation of current structural PopPK model and refine if necessary.* • *Identify the covariates of clinical interest;Predict individual exposure for E-R assessment*
Study Included		GARNET, RUBY
Dose(s) Included		Applicant - Table 19, Applicant - Table 20
Population Included		Applicant - Table 21, Applicant - Table 22
Population Characteristics (Table 2)	General	Applicant - Table 21, Applicant - Table 22
	Organ Impairment	Applicant - Table 21, Applicant - Table 22
	Pediatrics (if any)	*None*
No. of Patients, PK Samples, and BLQ		*Post-dose BLQ 0.1%*
Sampling Schedule	Rich Sampling	*Garnet (Part 1 and Part 2A)*
	In ITT Population	*Sparse (Garnet Part 2B and RUBY)*

Covariates Evaluated	Static	*age, body weight (WT), sex (male/female), geographical location (Eastern Europe, Western Europe, North America), dostarlimab monotherapy, Eastern Cooperative Oncology Group Performance Status (ECOG; 0 or fully active vs. 1 or ambulatory), disease state, creatinine clearance (CLcr), alanine aminotransferase (ALT), albumin (ALB), bilirubin (BILI), renal impairment (mild, moderate, normal), liver impairment (mild, normal), tumor diagnosis (MMR/MSS status), use of corticosteroids, objective response rate (ORR), disease state (primary stage III, primary stage IV, recurrent) and presence of anti-drug antibody (ADA) (yes/no).*
	Time-varying	*(ADA) (yes/no), ALB, CLcr, ALT, BILI, lymphocyte count (LYM), renal impairment, and liver impairment categories*

Final Model	***Summary***	**Acceptability [FDA's comments]**
Software and Version	*NONMEM 7.4*	Acceptable
Model Structure	*2-compartment model* with a time-dependent linear elimination.	Acceptable
Model Parameter Estimates	Applicant - Table 23	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	*none*	Acceptable
BLQ for Parameter Accuracy	*Not applicable (0.1% post dose BQL)*	Acceptable
GOF, VPC	*External validation with GARNET data:* Applicant - Figure 9 *to* Applicant - Figure 12*;* *GOF:* Applicant - Figure 13 *to* Applicant - Figure 15*;* *Covariate plots:*Applicant - Figure 16 *to* Applicant - Figure 20	Acceptable. No apparent bias was observed in the overall model fit. VPC stratified by study and treatment showed a general agreement between model predicted and observed values for 5th, 50th, and 95th percentiles.
Significant Covariates and Clinical Relevance	Applicant - Figure 21	None were likely to have clinically

		meaningful impact on exposure.
Analysis Based on Simulation (optional)	*none*	N/A
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	The exposure of dostarlimab-gxly administered in combination with platinum-containing chemotherapy and as a single agent were (b) (4) No clinically significant differences in the pharmacokinetics of dostarlimab-gxly were observed based on age (24 to 86 years), sex, race/ethnicity (75% White, 2% Asian, and 5% African American), tumor type, and renal impairment based on the estimated creatinine clearance and mild [total bilirubin (TB) > ULN to 1.5 times ULN or aspartate aminotransferase (AST) > ULN] to moderate (TB > 1.5 to 3 times ULN and any AST) hepatic impairment.	Yes. The proposed labeling is acceptable upon the Applicant and FDA reaching agreements to the FDA-recommended revisions to the labeling.

Applicant - Table 19. Overview of Study Data Included in the Analyses, 4010-01-001

Study Part	Dose Level	N Patients Available (November 01 2021 Data Cut)
Part 1	1 mg/kg, 3 mg/kg and 10 mg/kg	N=21
Part 2A	500 mg Q3W or 1000 mg Q6W	N=13
Part 2B	500 mg Q3W 4 cycles followed by 1000 mg Q6W	N=602

Q3W: Once every third week; Q6W: Once every sixth week

Applicant - Table 20. Overview of Study Data Included in the Analyses, 4010-03-001

Arm	Dostarlimab Dose Level	N Subjects available in this data cut
dostarlimab + carboplatin-paclitaxel	500 mg Q3W 6 cycles followed by 1000 mg Q6W	N≈235
placebo + carboplatin-paclitaxel	placebo	N≈235

Q3W: Once every third week; Q6W: Once every sixth week

Applicant - Table 21. Summary of Demographics by Study

Treatment	4010-01-001	4010-03-001	All
	(N = 636)	(N = 233)	(N = 869)
Age (yr)			
Mean (SD)	62.3 (11)	63.8 (9.2)	62.7 (11)
Median (range)	64.0 (24.0 - 86.0)	64.0 (41.0 - 81.0)	64.0 (24.0 - 86.0)
Elderly patients			
75 years and older	74 (11.6%)	25 (10.7%)	99 (11.4%)
Younger than 75 years	562 (88.4%)	208 (89.3%)	770 (88.6%)
Sex			
Female	480 (75.5%)	233 (100.0%)	713 (82.0%)
Male	156 (24.5%)		156 (18.0%)
Race			
American Indian or Alaska native	4 (0.6%)	1 (0.4%)	5 (0.6%)
Asian	13 (2.0%)	7 (3.0%)	20 (2.3%)
Black or African American	21 (3.3%)	26 (11.2%)	47 (5.4%)
Native Hawaiian or other Pacific Islander		1 (0.4%)	1 (0.1%)
Not reported	121 (19.0%)	5 (2.1%)	126 (14.5%)
Other	6 (0.9%)		6 (0.7%)
Unknown	4 (0.6%)	12 (5.2%)	16 (1.8%)
White	467 (73.4%)	181 (77.7%)	648 (74.6%)
Ethnicity			
Hispanic or Latino	23 (3.6%)	7 (3.0%)	30 (3.5%)
Non-Hispanic or Latino	479 (75.3%)	213 (91.4%)	692 (79.6%)
Not reported	126 (19.8%)	5 (2.1%)	131 (15.1%)
Unknown	8 (1.3%)	8 (3.4%)	16 (1.8%)
Geographic Location			
Europe	388 (61.0%)	68 (29.2%)	456 (52.5%)
North America	248 (39.0%)	165 (70.8%)	413 (47.5%)
Weight (kg)			
Mean (SD)	73.7 (20)	84.1 (23)	76.5 (21)
Median (range)	71.0 (34.0 - 182)	80.9 (42.8 - 181)	73.0 (34.0 - 182)
Hepatic Impairment			
Mild	74 (11.6%)	18 (7.7%)	92 (10.6%)
Moderate	5 (0.8%)		5 (0.6%)
Normal	557 (87.6%)	215 (92.3%)	772 (88.8%)
Renal Impairment			
Mild	270 (42.5%)	127 (54.5%)	397 (45.7%)
Moderate	114 (17.9%)	50 (21.5%)	164 (18.9%)
Normal	250 (39.3%)	55 (23.6%)	305 (35.1%)
Severe	2 (0.3%)	1 (0.4%)	3 (0.3%)

n=1 patients with missing WT were imputed to sex median.

Applicant - Table 22. Summary of Demographics by Study

Treatment	4010-01-001	4010-03-001	All
	(N = 636)	(N = 233)	(N = 869)
Immuno Modulators			
No	634 (99.7%)	231 (99.1%)	865 (99.5%)
Yes	2 (0.3%)	2 (0.9%)	4 (0.5%)
Immuno Stimulants			
No	631 (99.2%)	198 (85.0%)	829 (95.4%)
Yes	5 (0.8%)	35 (15.0%)	40 (4.6%)
Corticosteroids			
No	379 (59.6%)	214 (91.8%)	593 (68.2%)
Yes	257 (40.4%)	19 (8.2%)	276 (31.8%)
ADAs if ever positive			
ADA ever positive	101 (15.9%)		101 (11.6%)
ADA never positive	445 (70.0%)	230 (98.7%)	675 (77.7%)
Missing	90 (14.2%)	3 (1.3%)	93 (10.7%)
ECOG			
Ambulatory	373 (58.6%)	90 (38.6%)	463 (53.3%)
Fully active	262 (41.2%)	143 (61.4%)	405 (46.6%)
Missing	1 (0.2%)		1 (0.1%)
Diagnosis			
EC MSI-H/dMMR	153 (24.1%)	50 (21.5%)	203 (23.4%)
EC MSS/MMRp	160 (25.2%)	183 (78.5%)	343 (39.5%)
Missing	47 (7.4%)		47 (5.4%)
Non-EC MSI-H and POLE-mutated	209 (32.9%)		209 (24.1%)
NSCLC	67 (10.5%)		67 (7.7%)
Disease Status			
Primary Stage III		45 (19.3%)	45 (5.2%)
Primary Stage IV		72 (30.9%)	72 (8.3%)
Recurrent	636 (100.0%)	116 (49.8%)	752 (86.5%)

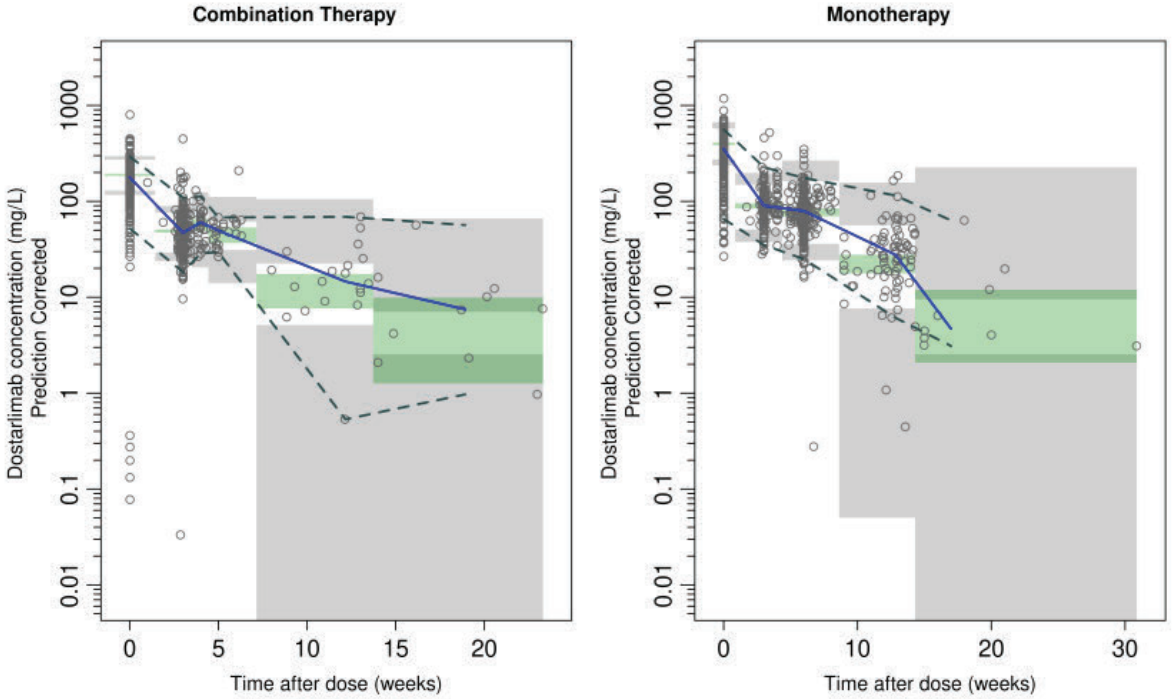
Patients had Eastern Cooperative Oncology Group Performance Status (ECOG) grade 0 or 1; these grades will be referred to as "fully active" and "ambulatory" in this report. See note about ADA definition in 3.8. **ADA:** anti-drug antibody; **ECOG:** Eastern cooperative oncology group performance status; **EC:** endometrial cancer; **dMMR:** deficient mismatch repair; **MSI-H:** microsatellite instability high; **MSS:** microsatellite stable; **MMRp:** mismatch repair proficient; **NSCLC:** non-small cell lung cancer.

Applicant - Table 23. Parameter Estimates of the Final PopPK Model

Parameter	Alias	Estimate	Relative SE (%)	95% CI
θ_1	Clearance (CL ($L \cdot h^{-1}$))	0.00732	2.03	(0.00704 - 0.00761)
θ_2	Central volume of distribution (Vc (L))	3.09	0.754	(3.04 - 3.13)
θ_3	Proportional Error, GARNET	0.16	3.09	(0.151 - 0.170)
θ_4	Additive Error (mg/L)	4.22	19.7	(2.60 - 5.85)
θ_5	Intercompartmental clearance (Q ($L \cdot h^{-1}$))	0.0191	12.0	(0.0153 - 0.0239)
θ_6	Peripheral volume of distribution (Vp (L))	2.48	5.18	(2.25 - 2.74)
θ_7	Imax	-0.113	19.4	(-0.157 - -0.0704)
θ_8	T50 (days)	145	12.9	(109 - 182)
θ_9	Hill	7.05	29.1	(3.03 - 11.1)
θ_{10}	Effect of WT on CL	0.523	7.78	(0.443 - 0.602)
θ_{11}	Effect of WT on Vc and Vp	0.48	4.75	(0.435 - 0.525)
θ_{12}	Proportional Error, RUBY	0.246	3.79	(0.228 - 0.264)
θ_{13}	Effect of age on CL	-0.238	26.2	(-0.360 - -0.116)
θ_{14}	Effect of ALB on CL	-0.922	7.93	(-1.06 - -0.778)
θ_{15}	Effect of ALT on CL	-0.0623	26.5	(-0.0947 - -0.0300)
θ_{16}	Effect of Combination Therapy on CL	-0.0779	25.9	(-0.118 - -0.0384)
θ_{17}	Effect of male on CL	0.15	18.8	(0.0948 - 0.205)
θ_{18}	Effect of ALB on Vc	-0.132	35.0	(-0.222 - -0.0409)
θ_{19}	Effect of male on Vc	0.137	14.1	(0.0992 - 0.175)
$\omega_{1.1}$	ω^2_{CL}	0.0563 (23.7% CV)	6.97	(0.0486 - 0.0639)
$\omega_{2.1}$	$\text{Covariance}_{CL,Vc}$	0.0193	11.4	(0.0150 - 0.0236)
$\omega_{2.2}$	ω^2_{Vc}	0.0278 (16.7% CV)	8.30	(0.0232 - 0.0323)
$\omega_{5.5}$	ω^2_{Imax}	0.903 (95.0% CV)	27.5	(0.417 - 1.39)

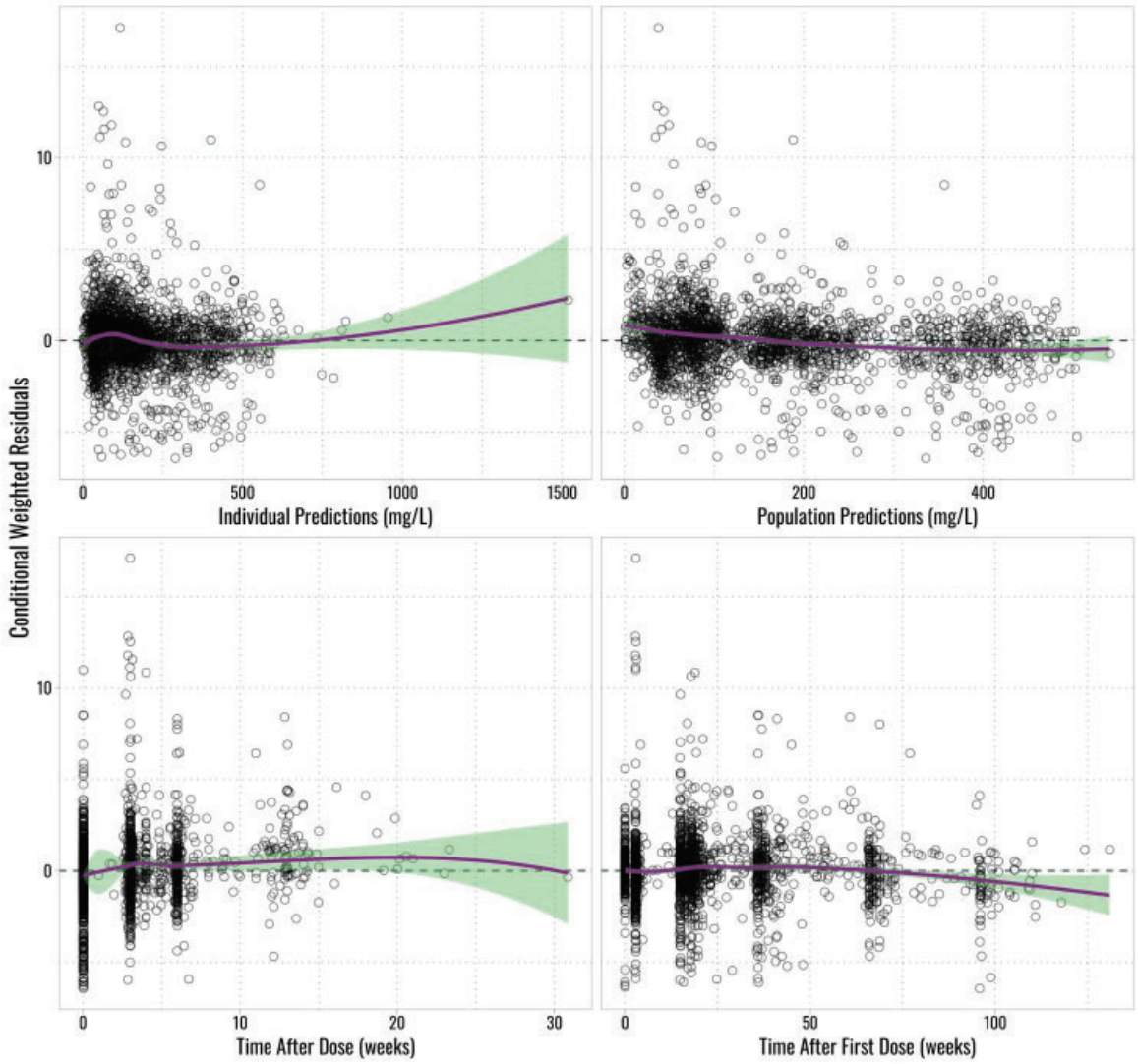
Parameter values for the final PopPK model. **CL:** systemic clearance; **Vc:** central volume of distribution; **Q:** intercompartment clearance; **Vp:** peripheral volume of distribution; **WT:** body weight; **ALB:** albumin; **ALT:** alanine aminotransferase; **Imax:** maximal decrease in clearance relative to baseline; **T50:** time at which 50% of Imax is reached; **Relative SE:** relative standard error; **CI:** confidence interval; ω^2_X: variance of the IIV of parameter X, IIV is derived from variance according to $\sqrt{\omega^2_X} \cdot 100$.

Applicant - Figure 10. Prediction Corrected Visual Predictive Check, 4010-03-001 External Validation.



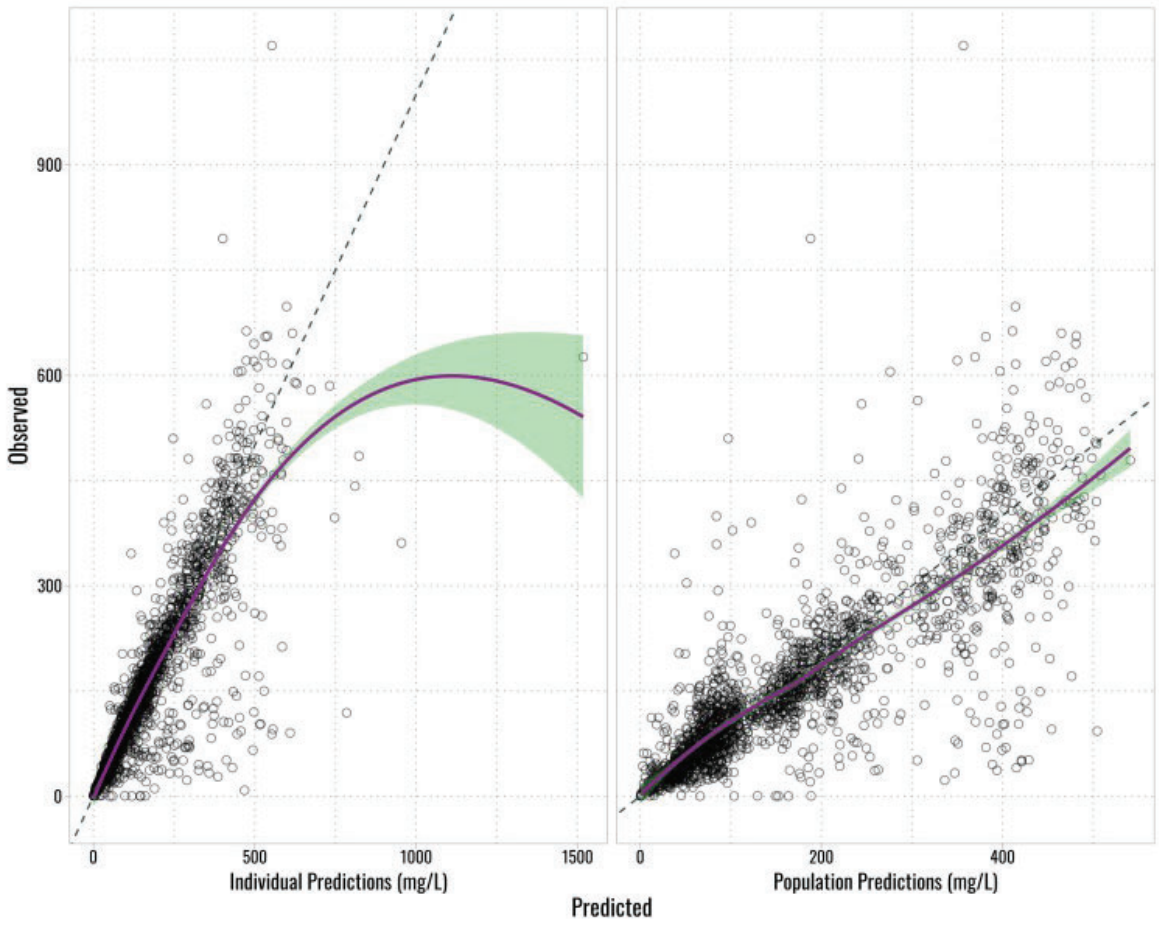
Solid Blue Line: Median of the observed dostarlimab concentrations; **Dashed Lines**: 2.5^{th} and 97.5^{th} percentiles of the observed dostarlimab concentrations; **Shaded Area**: The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5^{th} and 97.5^{th} percentiles of the simulated concentrations (grey areas); **Grey Circles:** Observations. All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. Bergstrand et al. (2011). 4010-03-001 (RUBY) data only.

Applicant - Figure 11. Conditional Weighted Residuals vs Predictions and Time, 4010-03-001 External Validation.



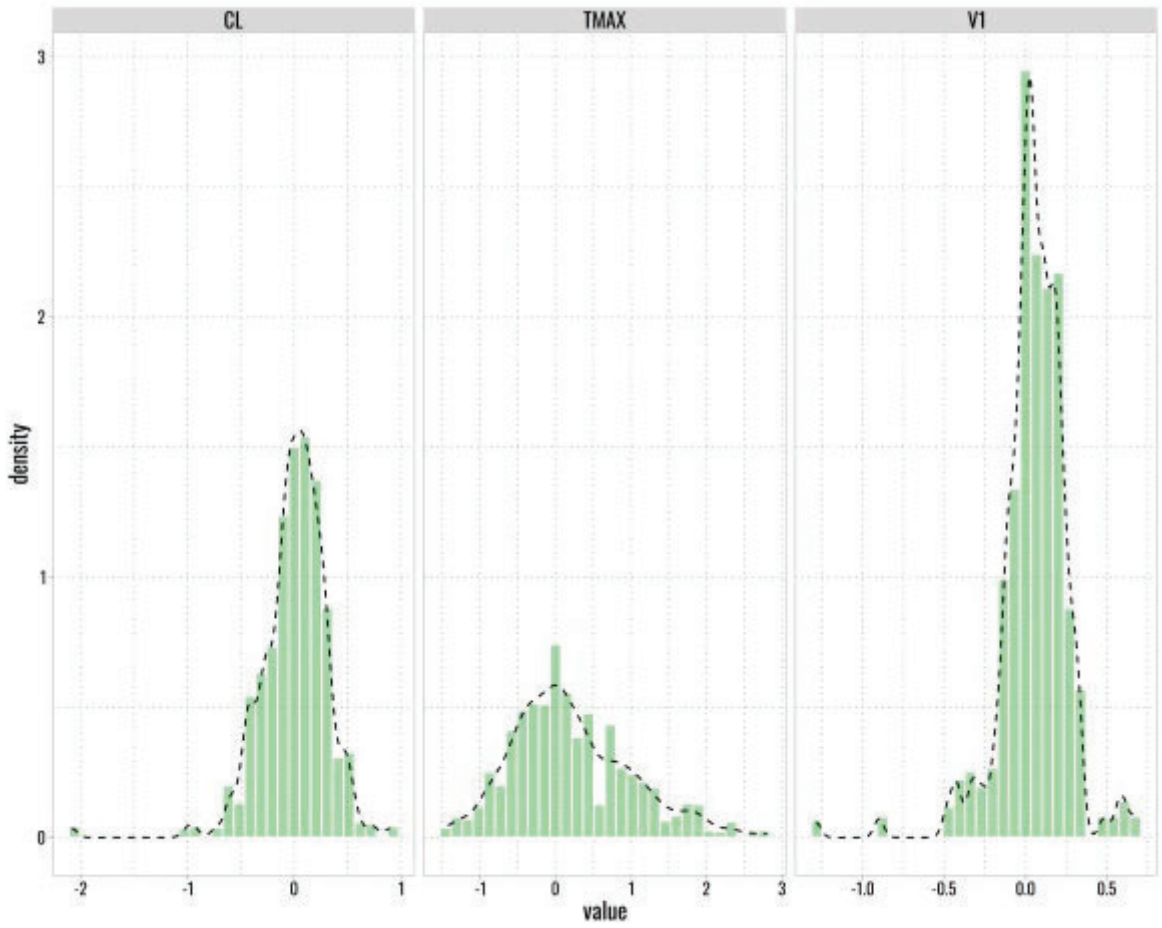
Purple line and green area: Loess smooth with 95% CI; **Circles:** Observed values. 4010-03-001 (RUBY) data only.

Applicant - Figure 12. Observations (DV) vs Population and Individual Predictions, 4010-03-001 External Validation



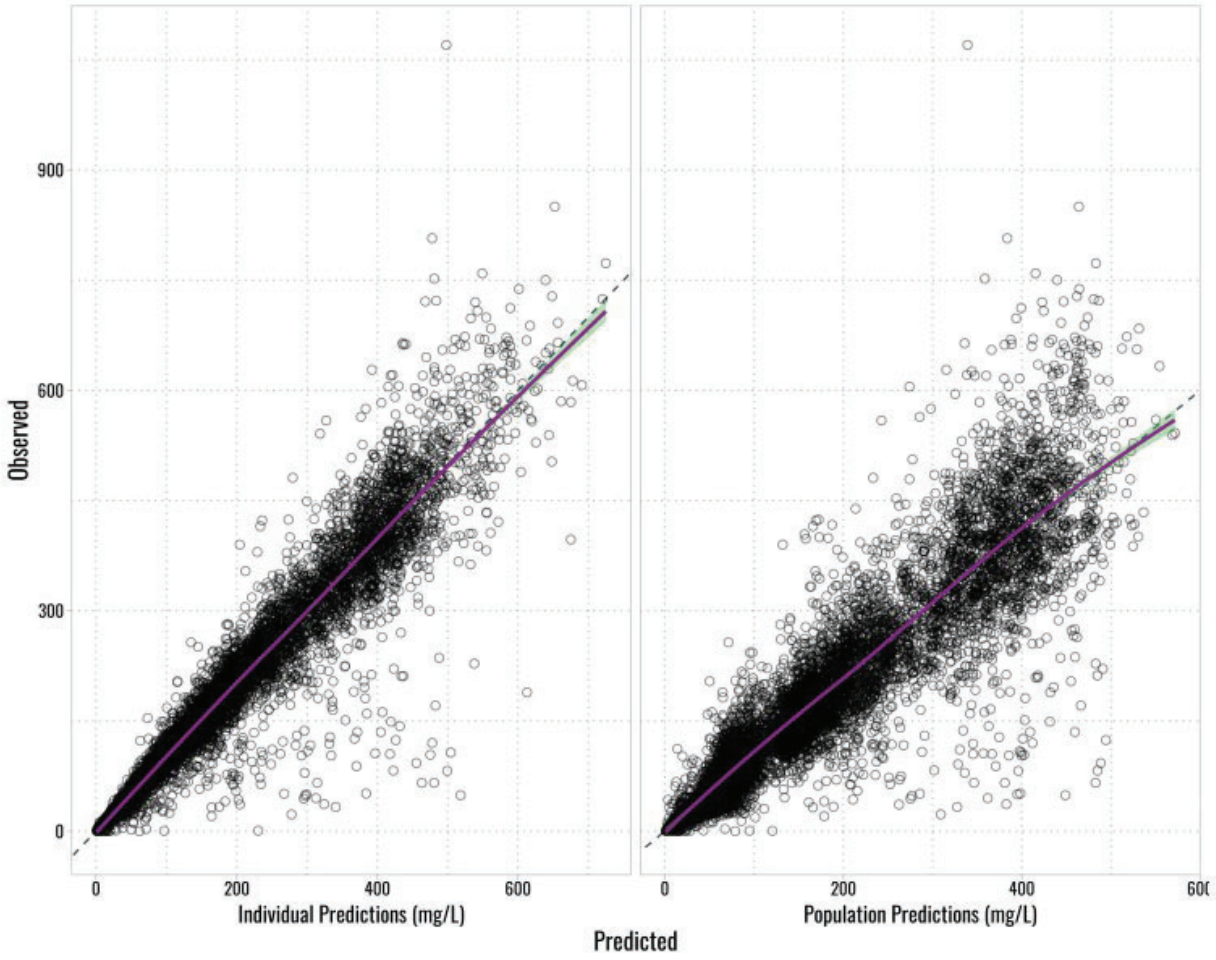
Purple line and green area: Loess smooth with 95% CI; **Black dashed line:** Line of identity; **Circles:** Observed values. 4010-03-001 (RUBY) data only.

Applicant - Figure 13. Eta Distribution, 4010-03-001 External Validation



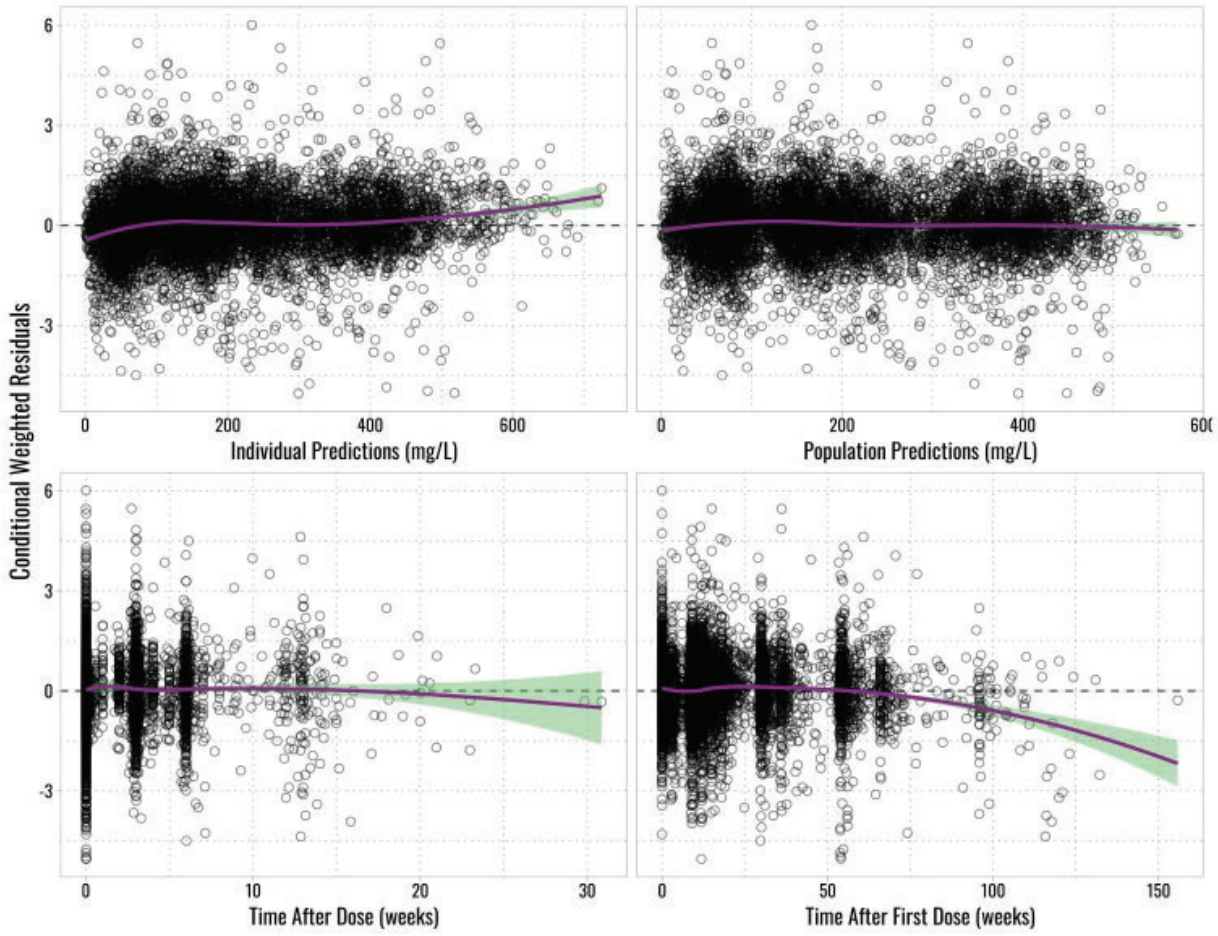
Black dashed line: Density (kernel) line. 4010-03-001 (RUBY) data only.

Applicant - Figure 14. Observations (DV) vs Population and Individual Predictions, Final Model



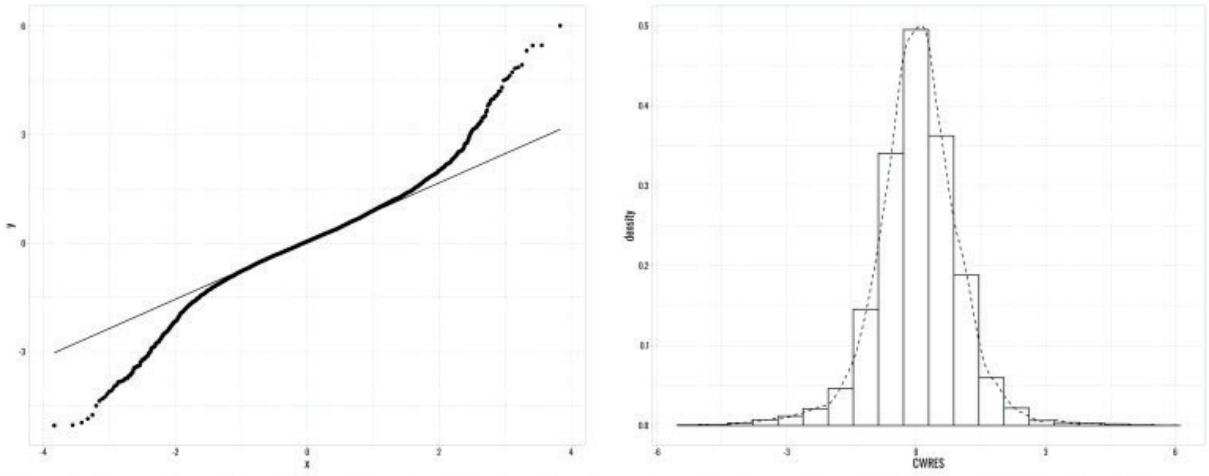
Purple line and green area: Loess smooth with 95% CI; **Black dashed line:** Line of identity; **Circles:** Observed values.

Applicant - Figure 15. Conditional Weighted Residuals vs Time and Predictions, Final Model



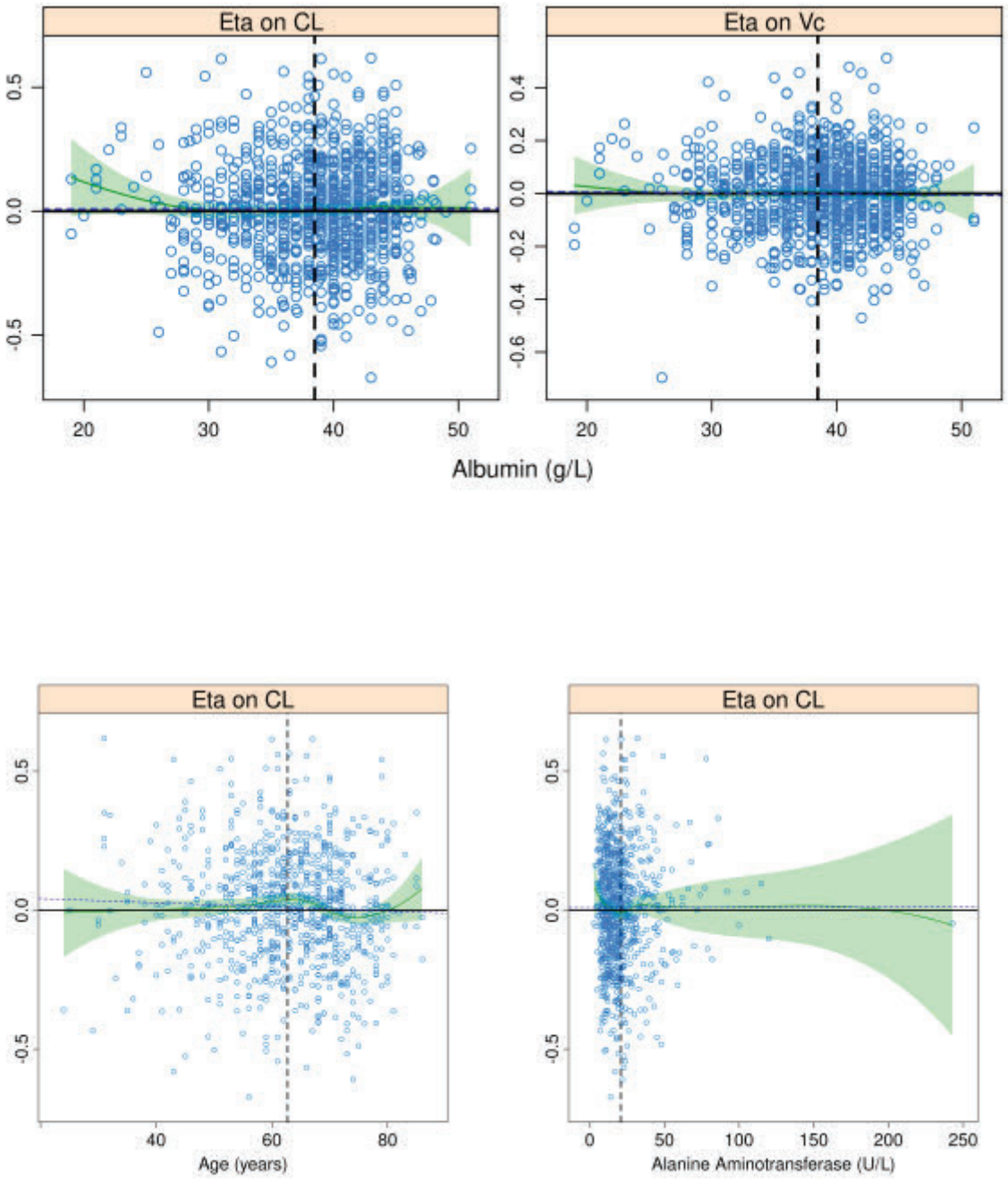
Purple line and green area: Loess smooth with 95% CI; **Circles:** Observed values.

Applicant - Figure 16. Distribution of Weighted Residuals, Final Model



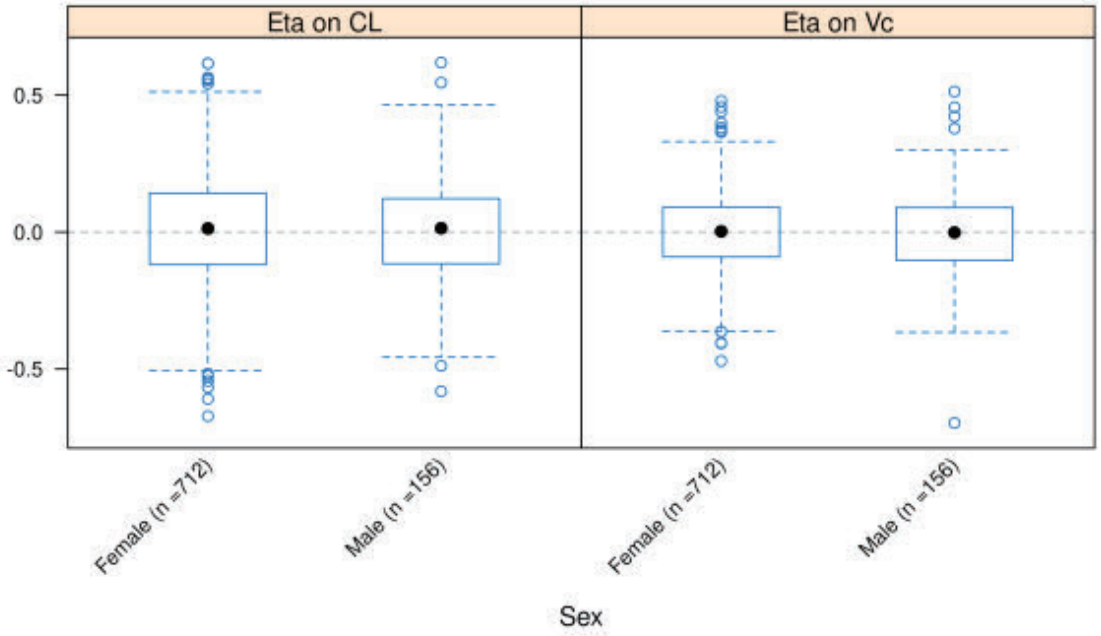
Left panel: Shows the estimated conditional weighted residuals vs. theoretical quantiles of the normal distribution. The solid line is a straight line through the 25^{th} and 75^{th} percentiles; **Right panel:** Shows the density of the conditional weighted residuals.

Applicant - Figure 17. Distribution of ETAs vs Continuous Covariates, Final Model



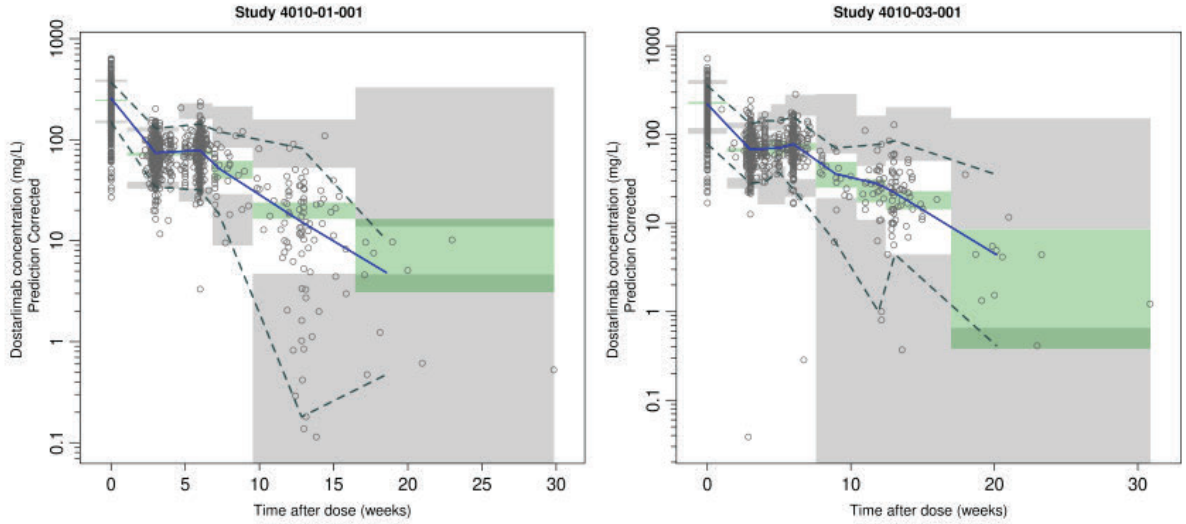
Circles: Observed values; **Solid Black Line:** IIV CL or Vc zero line; **Dashed Black Line:** Mean covariate value; **Dashed Blue Line:** Linear regression line; **Solid Green Line and Shaded Area:** Smoother with the 95% CI; **CL:** Clearance; **Vc:** Central volume of distribution.

Applicant - Figure 18. Distribution of ETAs vs Categorical Covariates, Final Model



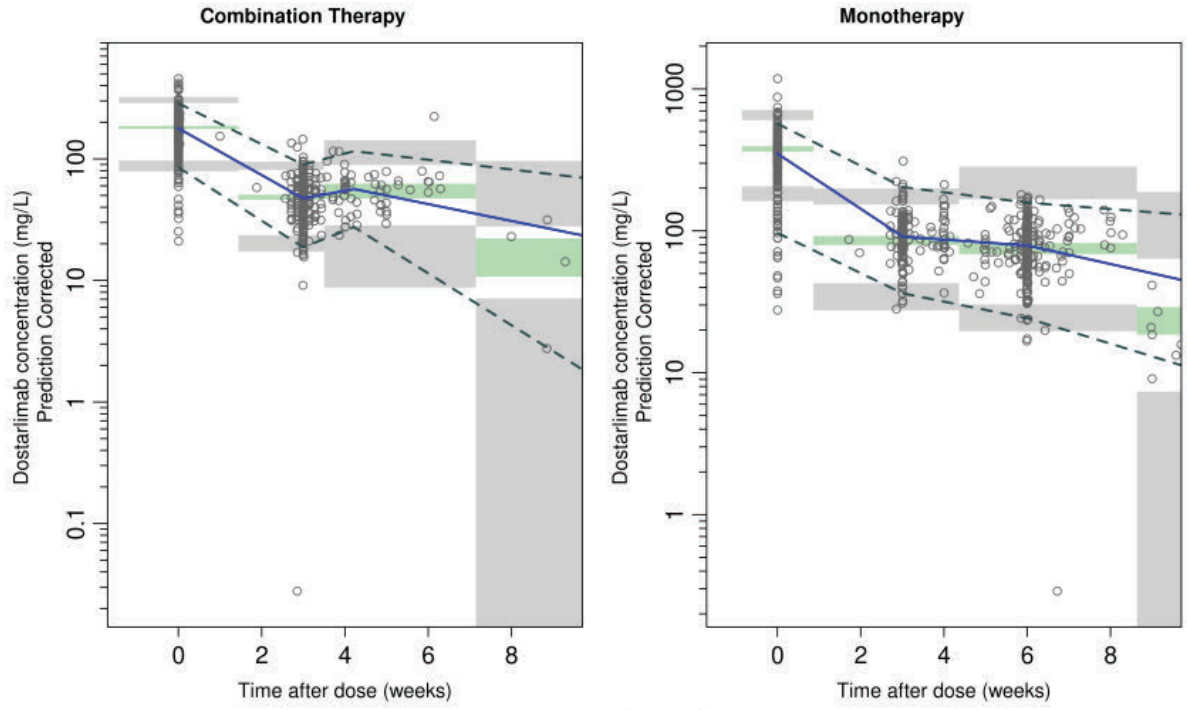
Box and whisker plot: The central circle is the sample median, the boxes denote the interquartile range, the whiskers extend to 1.5 times the interquartile range, and any blue circle represent data outside the whiskers. **Dashed line:** reference line of zero; **CL:** Clearance; **Vc:** Central volume of distribution.

Applicant - Figure 19. Prediction Corrected Visual Predictive Check by Study, Final Model



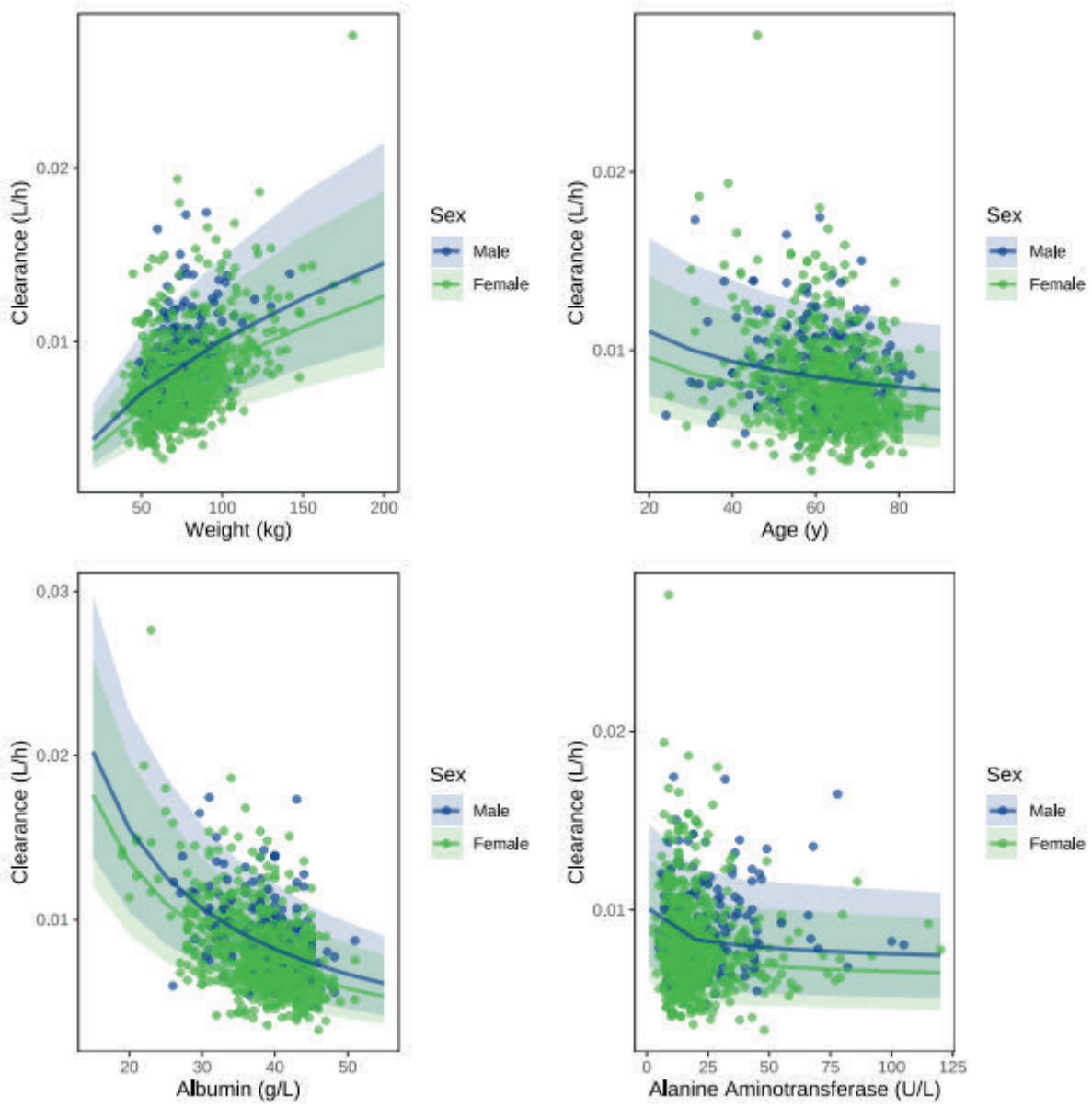
Solid Blue Line: Median of the observed dostarlimab concentrations; **Dashed Lines:** 2.5^{th} and 97.5^{th} percentiles of the observed dostarlimab concentrations; **Shaded Area:** The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5^{th} and 97.5^{th} percentiles of the simulated concentrations (grey areas). **Grey Circles:** Observations. All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. Bergstrand et al. (2011). VPC is based on data for the RTD (500 mg dostarlimab Q3W for the first 4 cycles followed by 1000 mg dostarlimab Q6W for 4010-01-001 and 500 mg dostarlimab Q3W for the first 6 cycles followed by 1000 mg dostarlimab Q6W for 4010-03-001).

Applicant - Figure 20. Prediction Corrected Visual Predictive Check by Monotherapy, Final Model

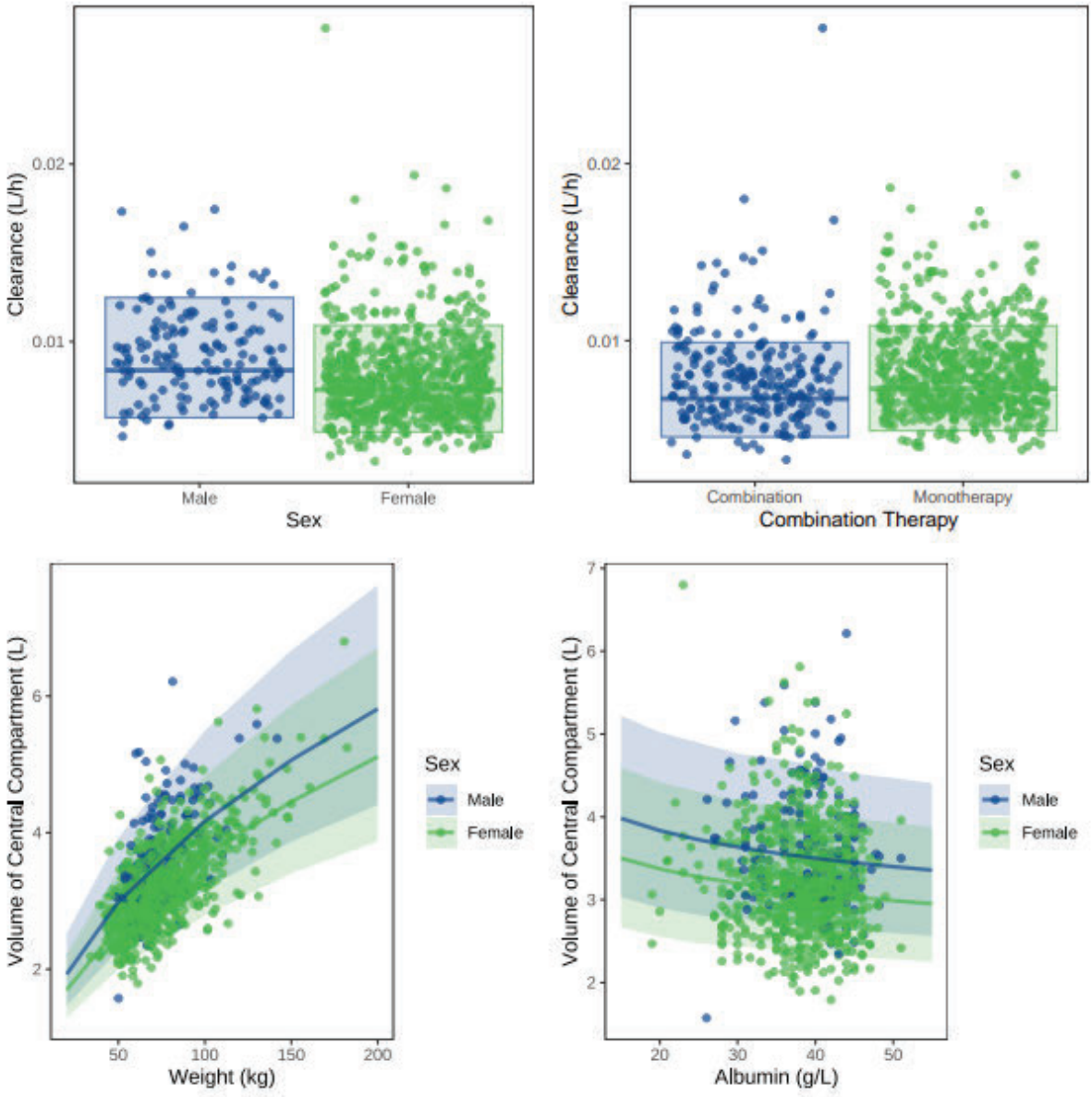


Solid Blue Line: Median of the observed dostarlimab concentrations; **Dashed Lines:** 2.5^{th} and 97.5^{th} percentiles of the observed dostarlimab concentrations; **Shaded Area:** The shaded areas indicate the 95% CI around the prediction-corrected median (green area), and 2.5^{th} and 97.5^{th} percentiles of the simulated concentrations (grey areas). **Grey Circles:** Observations.All observations and predictions are adjusted using prediction correction as described in Bergstrand et al. Bergstrand et al. (2011). VPC is based on data from study 4010-03-001. x-axis cut at 10 weeks to increase visibility.

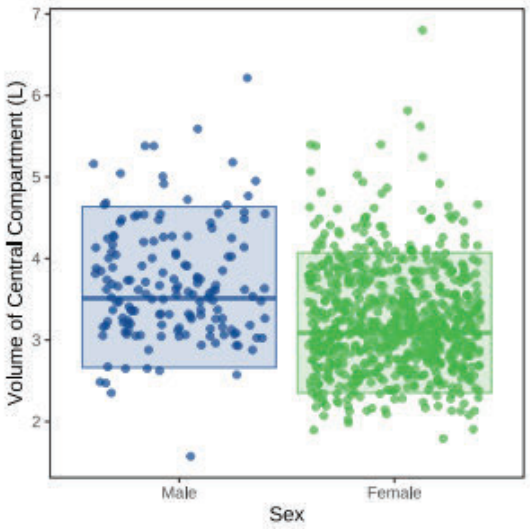
Applicant - Figure 21. Covariate Effects on Parameter Values, Final Model



Applicant - Figure 20. Covariate Effects on Parameter Values, Final Model

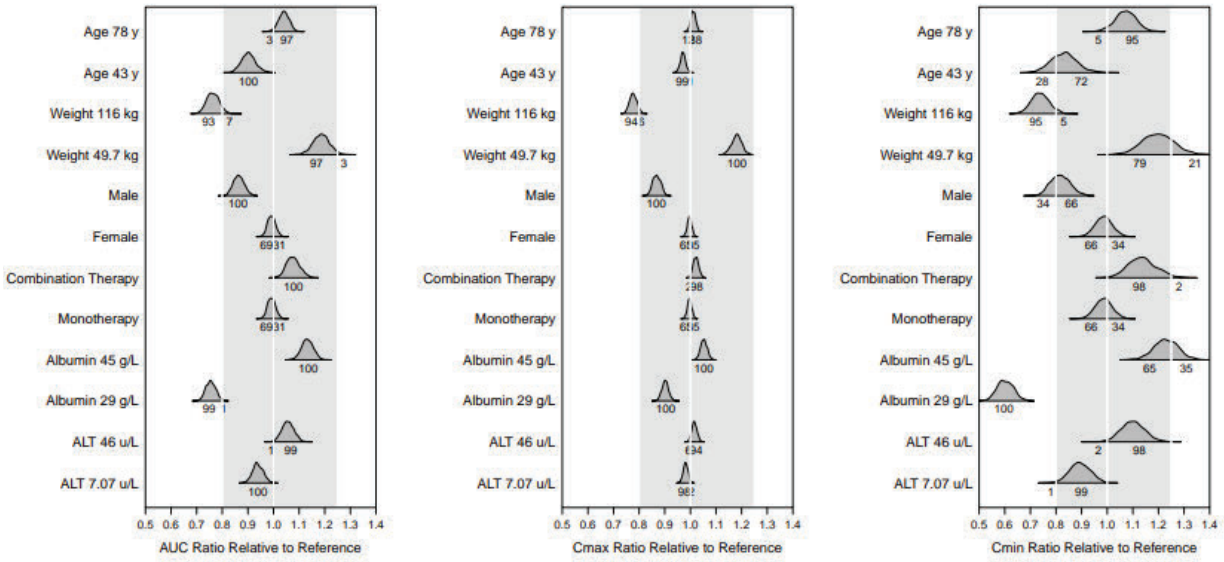


Applicant - Figure 20. Covariate Effects on Parameter Values, Final Model



Circles: Represent posthoc parameter estimates; **Shaded area**: confines 90% prediction interval of simulated data; **Solid line**: typical covariate effect relationship. One outlying ALT was removed from the figure.

Applicant - Figure 22. Forest Plots Illustrating the Covariate Effects on Exposure At Steady State



Forest plot of AUC_{ss} $C_{max,ss}$ and $C_{min,ss}$ ratios as compared to median reference patient (female, 70 kg, age 64 years, ALB 39 g/L and ALT 17 U/L). The distributions represent the ratios based on 1,000 set of parameter estimates re-sampled from the variance covariance matrix. Plotted numbers indicate actual percent of each distribution in a bounded region (here the central reference line). The grey area represent the 0.8 and 1.25 boundaries.

The FDA's Assessment:
The Applicant's population PK analysis is acceptable. Overall, the final population PK model is adequate to characterize the PK profile of dostarlimab as indicated in the Applicant's goodness-of-fit plots and VPC plots. The FDA reviewer was able to repeat and verify the Applicant's analysis with no significant discordance identified. The reviewer agrees with the Applicant's conclusion regarding the effect of covariates on dostarlimab exposure. There was no evident difference in dostarlimab PK parameters in patients with recurrent or primary advanced EC and receiving combination treatment with carboplatin and paclitaxel compared to patients with advanced solid tumors receiving dostarlimab monotherapy. There is no evidence of drug-drug interaction or altered PK of dostarlimab when administered in combination with carboplatin and paclitaxel in this population. FDA accepted the labeling language in 12.3 related to PK parameters and effect of covariates (age, sex, race, tumor type, renal impairment and hepatic impairment).

19.4.1.3. PPK Review Issues

No substantive issue.

19.4.1.4. Reviewer's Independent Analysis

Reviewer's independent analysis was not performed

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:
The E-R analysis for efficacy is considered exploratory due to immature data for efficacy endpoints including OS and DOR. There was no significant relationship between dostarlimab exposure and PFS. The ER relationship was not fully characterized due to the narrow range of exposure from one dose regimen in the pivotal study 4010-03-001. Dose modifications could also confound the results of these ER analyses.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position:

General Information

Goal of ER analysis		*Evaluate the exposure-response relationship between dostarlimab, PFS and DOR*
Study Included		*RUBY*
Endpoint		*Primary:PFS* *Secondary:DOR*
No. of Patients (total, and with individual PK)		*232 (PFS)* *147 (DOR)*
Population Characteristics (Table XX)	General	Applicant - Table 24
	Pediatrics (if any)	*none*
Dose(s) Included		*500 mg dostarlimab Q3W for the first 6 cycles followed by 1000 mg dostarlimab Q6W*
Exposure Metrics Explored (range)		Applicant - Table 25
Covariates Evaluated		*tumor diagnosis (MMR/MSI status in EC), disease state (primary stage III, primary stage IV, recurrent), prior external pelvic radiotherapy (yes, no), baseline ECOG (0 or fully active vs. 1 or ambulatory) performance, geographic location (Eastern Euorope, Western Euorope, North America), PD-L1 expression and histology (endometrioid carcinoma vs. other).*
Final Model Parameters	**Summary**	**Acceptability [FDA's comments]**
Model Structure	*Cox proportional hazard model*	Acceptable
Model Parameter Estimates	Applicant - Table 26 *to* Applicant - Table 31	Acceptable
Model Evaluation	*Not applicable*	N/A
Covariates and Clinical Relevance	*No exposure-response relationship for PFS or DOR*	Acceptable
Simulation for Specific Population	*Not applicable*	N/A
Visualization of E-R relationships	*Exploratory only*	Acceptable
Overall Clinical Relevance for ER	Flat exposure-response relationship (Applicant - Figure 22 to Applicant - Figure 26)	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	Dostarlimab-gxly provides sustained target engagement as measured by direct PD-1 binding and stimulation of IL-2 production	N/A.

	throughout the dosing interval at the recommended dose.	

Applicant - Table 24. Summary of Covariates for Dostarlimab Treated Patients

Covariate	Level	Count
ADBAS	Missing	3
	Negaitve	229
ANBAS	Missing	196
	Negative	18
	Positive	18
DIAG	dMMR/MSI-H	49
	MMRp/MSS	183
DISSTAT	Primary Stage III	45
	Primary Stage IV	72
	Recurrent	115
DMMR	No	183
	Yes	49
ECOG	Ambulatory	90
	Fully active	142
GL	Eastern Europe	13
	North America	164
	Western Europe	55
HISTOLOG	EC	109
	Other	123
PDL1CAT	Negative	37
	Positive	94
	Unknown	101
PELRAD	No	192
	Yes	40

ADBAS: Anti drug antibody status; **ANBAS:** Neutralizing antibody status; **DIAG:** Tumor Diagnosis; **DISSTAT:** Disease status in EC; **dMMR:** deficient mismatch repair; **MSI-H:** microsatellite instability high; **MSS:** microsatellite stable; **MMRp:** mismatch repair proficient; **ECOG:** Baseline ECOG performance; **GL:** Geographic location; **HISTOLOG:** Histology; **PDL1CAT:** Combined positive score category at baseline; **PELRAD:** Prior external pelvic radiotherapy. All dostarlimab treated patients in the tumor diagnosis category dMMR/MSI-H were dMMR.

Applicant - Table 25. Summary of Predicted Cycle 1 Cmin, Cmax, and AUC for Patients in the Analysis of Progression Free Survival

Metric	Minimum	Maximum	Mean	SD
C_{min} (mg/L)	10.10	67.60	39.70	9.94
C_{max} (mg/L)	73.40	246.00	147.00	26.40
AUC (mg*h/L)	13300.00	48800.00	32300.00	5850.00

SD: standard deviation. **AUC**: Area under the curve during the first 21 days; $\mathbf{C}_{max}$: Maximum concentration during the first 21 days; $\mathbf{C}_{min}$: Minimum concentration at Day 21.

Applicant - Table 26. Hazard Ratio Mutlivariate PFS Analysis, AUC

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	1.00	1-1	0.90
DISSTATPrimary Stage IV	1.26	0.7356-2.161	0.40
DISSTATRecurrent	1.59	0.9295-2.725	0.09
PELRADYes	0.85	0.5133-1.411	0.53
ECOGFully active	0.78	0.5348-1.135	0.19
GLEastern Europe	1.99	1.008-3.91	0.05
GLWestern Europe	1.44	0.9349-2.209	0.10
HISTOLOGOther	0.82	0.5503-1.234	0.35

PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference EC); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); AUC - Area under the concentration versus time curve during first 21 days.

Applicant - Table 27. Hazard Ratio Multivariate PFS Analysis, Cmax

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	1.00	0.9971-1.01	0.28
DISSTATPrimary Stage IV	1.30	0.7577-2.231	0.34
DISSTATRecurrent	1.60	0.9332-2.738	0.09
PELRADYes	0.84	0.5055-1.394	0.50
ECOGFully active	0.77	0.5273-1.115	0.16
GLEastern Europe	1.93	0.9846-3.784	0.06
GLWestern Europe	1.40	0.9126-2.136	0.12
HISTOLOGOther	0.87	0.5845-1.308	0.51

PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference EC); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); C_{max} - maximum concentration during first 21 days.

Applicant - Table 28. Hazard Ratio Multivariate PFS Analysis, Cmin

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	0.99	0.9745-1.01	0.40
DISSTATPrimary Stage IV	1.25	0.7279-2.138	0.42
DISSTATRecurrent	1.60	0.9331-2.733	0.09
PELRADYes	0.85	0.5107-1.402	0.52
ECOGFully active	0.79	0.5445-1.156	0.23
GLEastern Europe	2.08	1.052-4.105	0.04
GLWestern Europe	1.48	0.9615-2.278	0.07
HISTOLOGOther	0.79	0.5308-1.185	0.26

PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference EC); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); C_{min} - Minimum concentration after first dose, day 21.

Applicant - Table 29. Hazard Ratio Multivariate DOR Analysis, AUC

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	1.00	1-1	0.69
DIAGMMRp/MSS	2.56	1.375-4.784	0.00
DISSTATPrimary Stage IV	1.53	0.6866-3.432	0.30
DISSTATRecurrent	1.72	0.7813-3.775	0.18
PELRADYes	0.56	0.2894-1.066	0.08
ECOGFully active	0.75	0.46-1.229	0.26
GLEastern Europe	2.48	1.187-5.162	0.02
GLWestern Europe	0.90	0.5024-1.598	0.71
HISTOLOGOther	1.00	0.6071-1.635	0.99

PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference EC); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); AUC - Area under the concentration versus time curve during first 21 days.

Applicant - Table 30. Hazard Ratio Multivariate DOR Analysis, Cmax

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	1.00	0.9946-1.012	0.45
DIAGMMRp/MSS	2.59	1.383-4.844	0.00
DISSTATPrimary Stage IV	1.59	0.7057-3.566	0.26
DISSTATRecurrent	1.75	0.7926-3.864	0.17
PELRADYes	0.53	0.2762-1.027	0.06
ECOGFully active	0.72	0.4372-1.17	0.18
GLEastern Europe	2.33	1.125-4.822	0.02
GLWestern Europe	0.86	0.4856-1.533	0.61
HISTOLOGOther	1.03	0.6236-1.694	0.91

PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference EC); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); C_{max} - maximum concentration during first 21 days.

Applicant - Table 31. Hazard Ratio Multivariate DOR Analysis, Cmin

Covariate	Hazard Ratio	95% CI of Hazard Ratio	p-value
Exposure metric	0.99	0.965-1.012	0.32
DIAGMMRp/MSS	2.55	1.37-4.748	0.00
DISSTATPrimary Stage IV	1.55	0.6923-3.465	0.29
DISSTATRecurrent	1.73	0.788-3.801	0.17
PELRADYes	0.56	0.2909-1.068	0.08
ECOGFully active	0.77	0.4727-1.259	0.30
GLEastern Europe	2.62	1.251-5.466	0.01
GLWestern Europe	0.92	0.5147-1.64	0.77
HISTOLOGOther	0.98	0.6007-1.608	0.95

PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference EC); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); C_{min} - Minimum concentration after first dose, day 21.

Applicant - Table 32. Odds Ratio Multivariate Analysis, Arthralgia, Cycle 7 and Beyond, Dostarlimab Treated, AUC

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1	1-1	0.0243
DIAGMMRp/MSS	0.396	0.1432-1.156	0.0775
DISSTATPrimary Stage IV	1.06	0.2136-5.897	0.942
DISSTATRecurrent	2.19	0.5757-10.92	0.281
PELRADYes	0.555	0.1143-2.055	0.411
ECOGFully active	0.934	0.3374-2.748	0.898
GLEurope	0.97	0.314-2.714	0.955

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference Ambulatory); GL - Geographic location (reference North America); AUC - Area under the concentration versus time curve during first 21 days.

Applicant - Table 33. Odds Ratio Multivariate Analysis, Arthralgia, Cycle 7 and Beyond, Dostarlimab Treated, Cmin

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.06	1.01-1.116	0.0206
DIAGMMRp/MSS	0.406	0.1474-1.183	0.085
DISSTATPrimary Stage IV	1	0.2033-5.501	0.999
DISSTATRecurrent	2.09	0.5523-10.32	0.308
PELRADYes	0.583	0.1203-2.153	0.45
ECOGFully active	0.897	0.3204-2.657	0.839
GLEurope	0.963	0.3113-2.697	0.945

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference Ambulatory); GL - Geographic location (reference North America); C_{min} - Minimum concentration after first dose, day 21.

Applicant - Table 34. Odds Ratio Multivariate Analysis, Rash, cycle 1-6, All Patients, AUC

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1	1-1	0.0003
DIAGMMRp/MSS	0.801	0.433-1.54	0.492
DISSTATPrimary Stage IV	0.745	0.356-1.58	0.435
DISSTATRecurrent	0.635	0.304-1.34	0.228
PELRADYes	0.903	0.383-2	0.806
ECOGFully active	2.16	1.18-4.17	0.0158
GLEurope	0.647	0.321-1.22	0.199

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference Ambulatory); GL - Geographic location (reference North America); AUC - Area under the concentration versus time curve during first 21 days.

Applicant - Table 35. Odds Ratio Multivariate Analysis, Rash, cycle 1-6, All Patients, Cmax

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.01	1-1.01	0.0004
DIAGMMRp/MSS	0.794	0.429-1.53	0.475
DISSTATPrimary Stage IV	0.753	0.36-1.6	0.452
DISSTATRecurrent	0.643	0.308-1.36	0.241
PELRADYes	0.898	0.381-1.98	0.795
ECOGFully active	2.19	1.2-4.22	0.0143
GLEurope	0.657	0.326-1.24	0.214

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference Ambulatory); GL - Geographic location (reference North America); C_{max} - maximum concentration during first 21 days.

Applicant - Table 36. Odds Ratio Multivariate Analysis, Rash, cycle 1-6, All Patients, Cmin

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.02	1.01-1.04	0.0003
DIAGMMRp/MSS	0.807	0.436-1.55	0.507
DISSTATPrimary Stage IV	0.742	0.355-1.57	0.429
DISSTATRecurrent	0.631	0.302-1.34	0.223
PELRADYes	0.907	0.385-2.01	0.814
ECOGFully active	2.12	1.16-4.09	0.0183
GLEurope	0.64	0.318-1.21	0.189

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference Ambulatory); GL - Geographic location (reference North America); C_{min} - Minimum concentration after first dose, day 21.

Applicant - Table 37. Odds Ratio Multivariate Analysis, Rash, Cycle 7 and Beyond, All Patients, AUC

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1	1-1	0.0003
DIAGMMRp/MSS	0.801	0.433-1.54	0.492
DISSTATPrimary Stage IV	0.745	0.356-1.58	0.435
DISSTATRecurrent	0.635	0.304-1.34	0.228
PELRADYes	0.903	0.383-2	0.806
ECOGFully active	2.16	1.18-4.17	0.0158
GLEurope	0.647	0.321-1.22	0.199

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference Ambulatory); GL - Geographic location (reference North America); AUC - Area under the concentration versus time curve during first 21 days.

Applicant - Table 38. Odds Ratio Multivariate Analysis, Rash, Cycle 7 and Beyond, All Patients, Cmax

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.01	1-1.01	0.0004
DIAGMMRp/MSS	0.794	0.429-1.53	0.475
DISSTATPrimary Stage IV	0.753	0.36-1.6	0.452
DISSTATRecurrent	0.643	0.308-1.36	0.241
PELRADYes	0.898	0.381-1.98	0.795
ECOGFully active	2.19	1.2-4.22	0.0143
GLEurope	0.657	0.326-1.24	0.214

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference Ambulatory); GL - Geographic location (reference North America); C_{max} - maximum concentration during first 21 days.

Applicant - Table 39. Odds Ratio Multivariate Analysis, Rash, Cycle 7 and Beyond, All Patients, Cmin

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.02	1.01-1.04	0.0003
DIAGMMRp/MSS	0.807	0.436-1.55	0.507
DISSTATPrimary Stage IV	0.742	0.355-1.57	0.429
DISSTATRecurrent	0.631	0.302-1.34	0.223
PELRADYes	0.907	0.385-2.01	0.814
ECOGFully active	2.12	1.16-4.09	0.0183
GLEurope	0.64	0.318-1.21	0.189

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference Ambulatory); GL - Geographic location (reference North America); C_{min} - Minimum concentration after first dose, day 21.

Applicant - Table 40. Odds Ratio Multivariate Analysis, Rash, all cycles, All Patients, AUC

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1	1-1	0.0003
DIAGMMRp/MSS	0.801	0.433-1.54	0.492
DISSTATPrimary Stage IV	0.745	0.356-1.58	0.435
DISSTATRecurrent	0.635	0.304-1.34	0.228
PELRADYes	0.903	0.383-2	0.806
ECOGFully active	2.16	1.18-4.17	0.0158
GLEurope	0.647	0.321-1.22	0.199

DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference Ambulatory); GL - Geographic location (reference North America); AUC - Area under the concentration versus time curve during first 21 days.

Applicant - Table 41. Odds Ratio Multivariate Analysis, Rash, all cycles, All Patients, Cmax

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.01	1-1.01	0.0004
DIAGMMRp/MSS	0.794	0.429-1.53	0.475
DISSTATPrimary Stage IV	0.753	0.36-1.6	0.452
DISSTATRecurrent	0.643	0.308-1.36	0.241
PELRADYes	0.898	0.381-1.98	0.795
ECOGFully active	2.19	1.2-4.22	0.0143
GLEurope	0.657	0.326-1.24	0.214

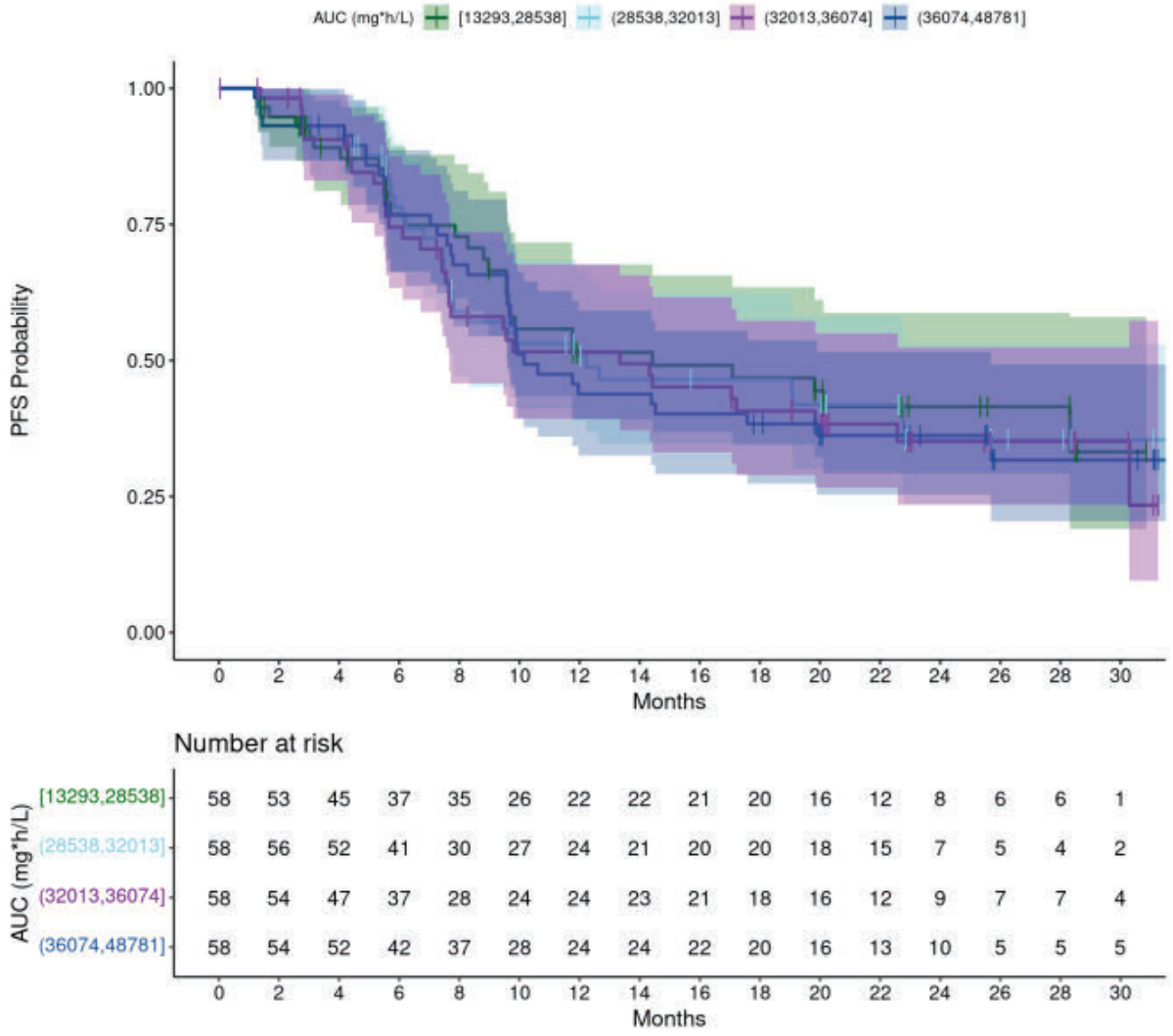
DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference Ambulatory); GL - Geographic location (reference North America); C_{max} - maximum concentration during first 21 days.

Applicant - Table 42. Odds Ratio Multivariate Analysis, Rash, all cycles, All Patients, Cmin

Covariate	Odds Ratio	95% CI of Odds Ratio	p-value
Exposure metric	1.02	1.01-1.04	0.0003
DIAGMMRp/MSS	0.807	0.436-1.55	0.507
DISSTATPrimary Stage IV	0.742	0.355-1.57	0.429
DISSTATRecurrent	0.631	0.302-1.34	0.223
PELRADYes	0.907	0.385-2.01	0.814
ECOGFully active	2.12	1.16-4.09	0.0183
GLEurope	0.64	0.318-1.21	0.189

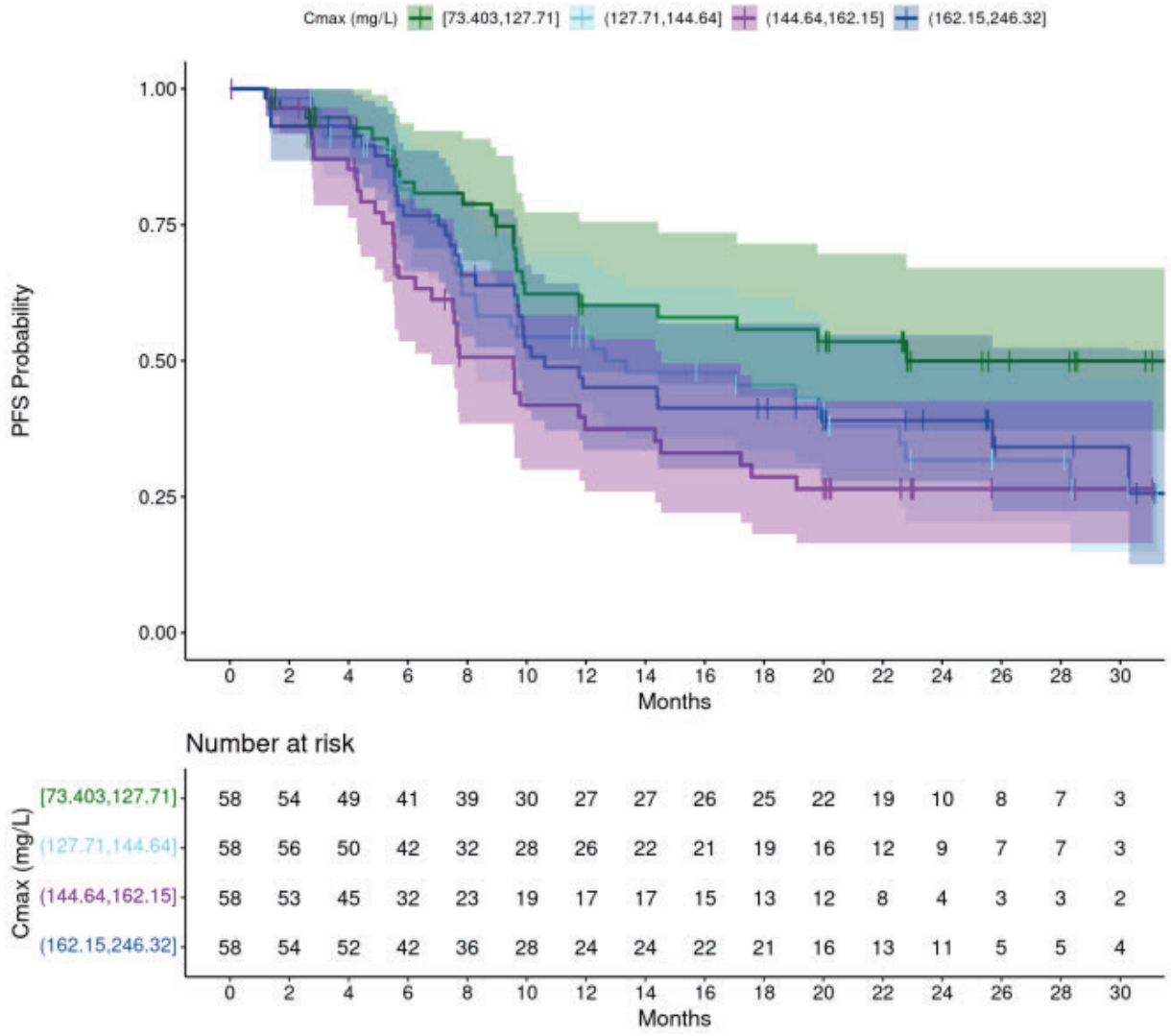
DIAG - Tumor diagnosis (reference dMMR/MSI-H); DISSTAT - Disease status in EC (reference Primary Stage III); PELRAD - Prior external pelvic radiotherapy (reference No); ECOG - Baseline ECOG performance (reference Ambulatory); GL - Geographic location (reference North America); C_{min} - Minimum concentration after first dose, day 21.

Applicant - Figure 23. PFS vs. Time Stratified by AUC Exposure Quartiles



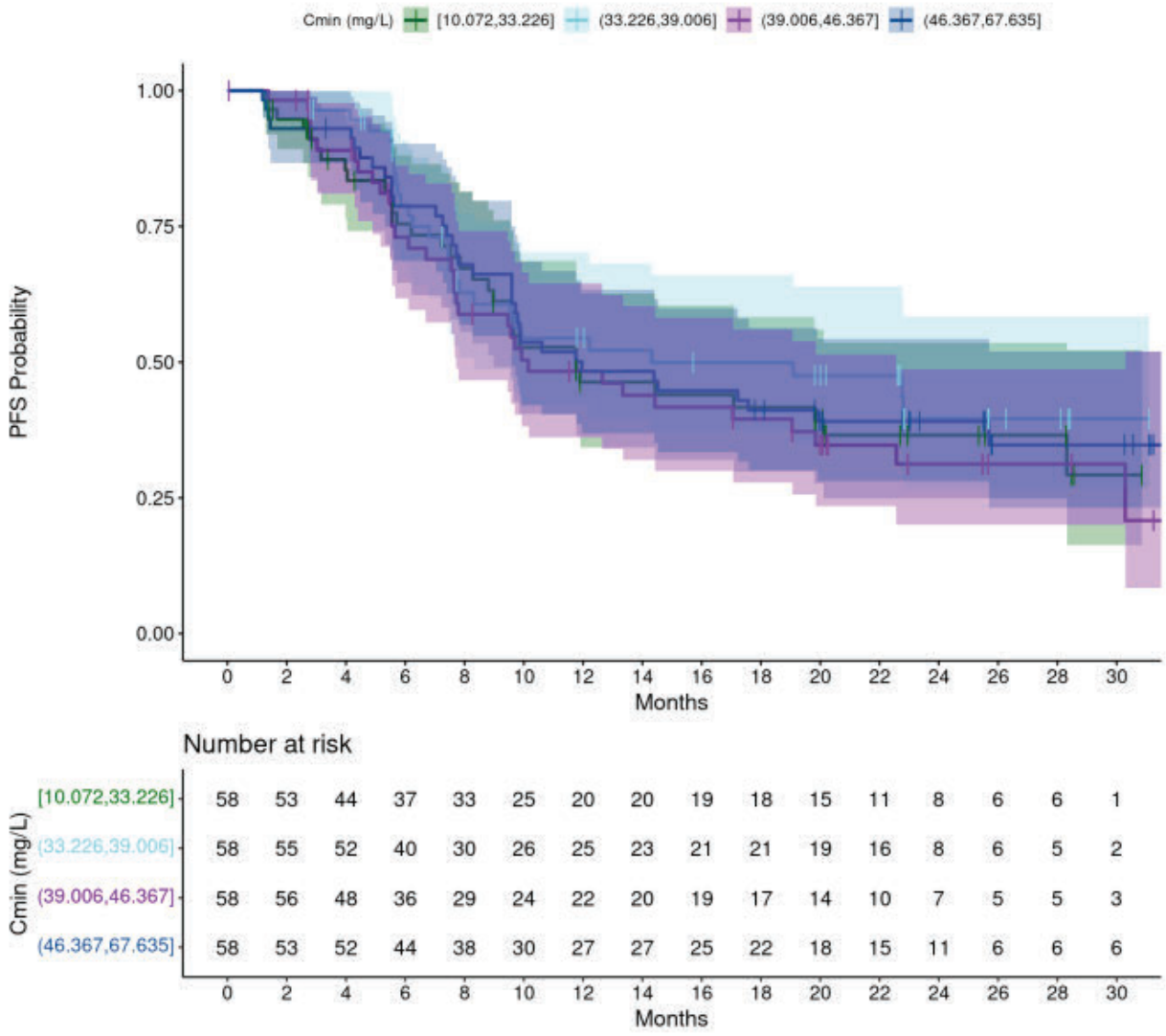
Lines: progression-free survival probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval; **AUC**: area under the curve during the first 21 days.

Applicant - Figure 24. PFS vs. time Stratified by Cmax Exposure Quartiles



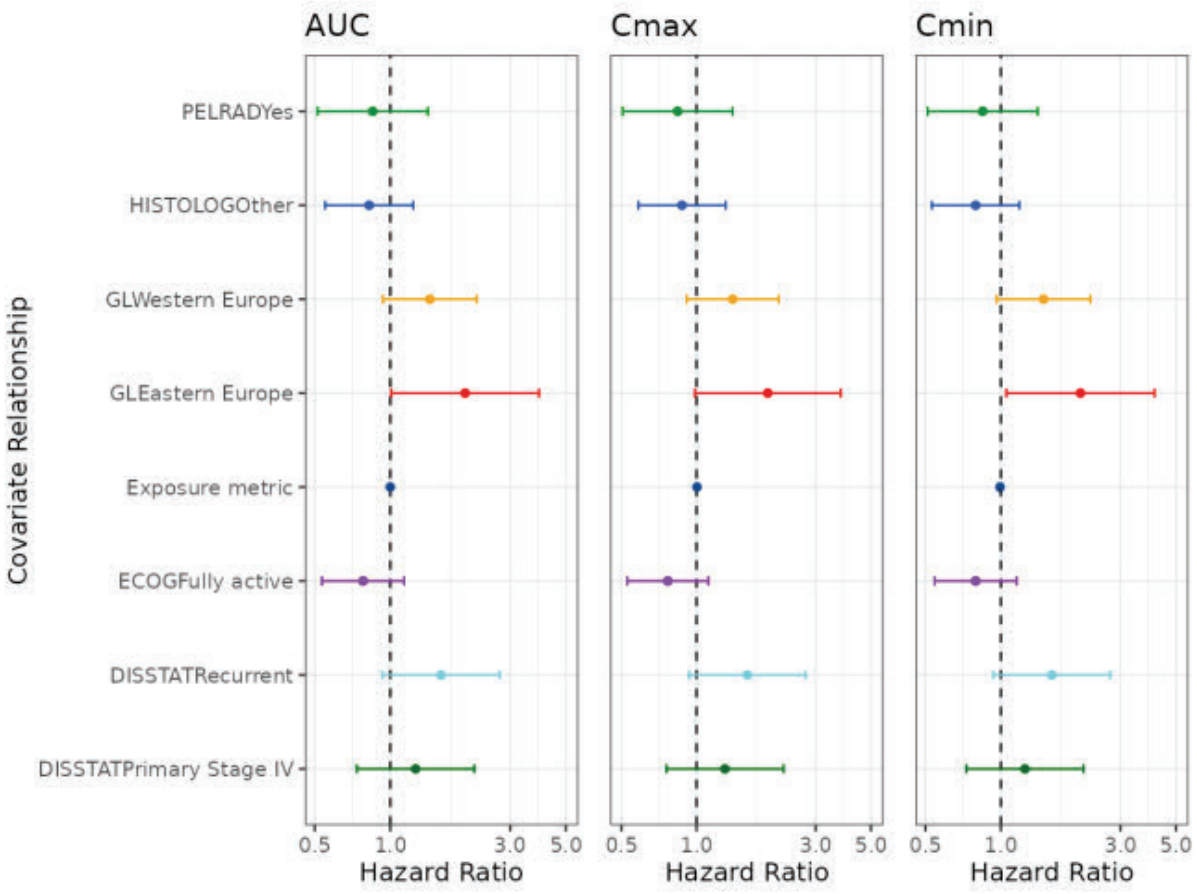
Lines: progression-free survival probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval; C_{max}: Maximum concentration during the first 21 days.

Applicant - Figure 25. PFS vs Time Stratified by Cmin Exposure Quartiles



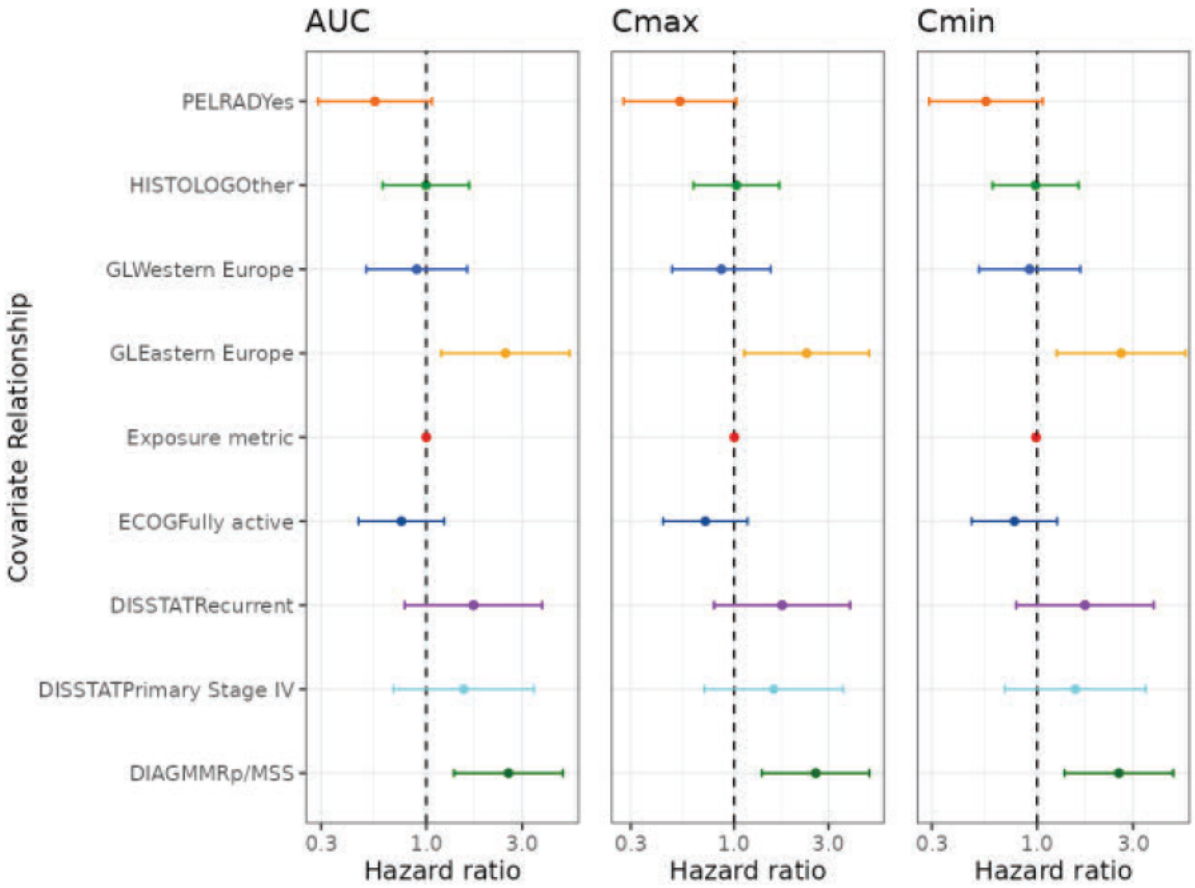
Lines: progression-free survival probability; **Vertical lines:** censoring; **Shaded area:** 95% confidence interval; C_{min}: Minimum concentration at Day 21.

Applicant - Figure 26. Hazard Ratio Multivariate Analysis, PFS



Circle: Hazard ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference EC); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); **AUC**: Area under the curve during the first 21 days; $\mathbf{C}_{max}$: Maximum concentration during the first 21 days; $\mathbf{C}_{min}$: Minimum concentration at Day 21.

Applicant - Figure 27. Hazard Ratio Multivariate Analysis, DOR



Circle: Hazard ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); HISTOLOG - Histology (reference EC); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); DIAG - Tumor diagnosis (reference dMMR/MSI-H); **AUC**: Area under the curve during the first 21 days; $\mathbf{C}_{max}$: Maximum concentration during the first 21 days; $\mathbf{C}_{min}$: Minimum concentration at Day 21.

19.4.2.3. ER (safety) Executive Summary

The FDA's Assessment:

The Applicant explored the relationship between dostarlimab and AE of interest (diarrhea, fatigue, nausea, arthralgia, and rash) using data from pivotal study 4010-03-001. The univariate logistic regression suggested a lack of statistically significant exposure-response relationship for diarrhea, fatigue, and nausea. Exposure-response relationships for arthralgia in patients on Dostarlimab in Cycle 7 and beyond as well as rash in all patients and all cycles were statistically significant but not clinically relevant. While the analysis is reasonable, the conclusion should be explained with caution, as the data only included one study and one dose regimen. To reach a more reliable conclusion, full analyses should be conducted with multiple

studies and multiple dose levels.

19.4.2.4. ER (safety) Assessment Summary

The Applicant's Position:

General Information			
Goal of ER analysis		Evaluate the exposure-response relationship between dostarlimab and occurrence of relevant AEs	
Study Included		*RUBY*	
Population Included		*Endometrial cancer*	
Endpoint		arthralgia, diarrhoea, fatigue, nausea and rash	
No. of Patients (total, and with individual PK)		478 patients (232 in the dostarlimab arm with PK, 246 in the placebo arm)	
Population Characteristics (Table XX)	General	Applicant - Table 24 *for dostarlimab treated subjects and* Applicant - Table 43 *for placebo subjects*	
	Pediatrics (if any)	*None*	
Dose(s) Included		*(500 mg Q3Wfor 6 cycles followed by 1000 mg Q6W thereafter)*	
Exposure Metrics Explored (range)		*Cycle 1 exposure Cmin, Cmax, and AUC* (Applicant - Table 45	
Covariates Evaluated		*tumor diagnosis (MMR/MSI status in EC), disease state (primary stage III, primary stage IV, recurrent), prior external pelvic radiotherapy (yes, no), baseline ECOG (0 or fully active vs. 1 or ambulatory) performance, geographic location (Eastern Euorope, Western Euorope, North America)*	
Final Model Parameters		**Summary**	**Acceptability [FDA's comments]**
Model Structure		*Logistic regression*	Acceptable
Model Parameter Estimates		Applicant - Table 32 to Applicant - Table 42	Acceptable
Model Evaluation		*Not applicable*	N/A
Covariates and Clinical Relevance		*Some signals for arthralgia and rash, however not clinically relevant*	Acceptable
Simulation for Specific Population		Not applicable	N/A

Visualization of E-R relationships	Applicant - Figure 27 *to* Applicant - Figure 30	Acceptable
Overall Clinical Relevance for ER	none	Acceptable
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	Not applicable	N/A

Applicant - Table 43. Summary of Covariates for Placebo Patients

Covariate	Level	Count
ADBAS	Missing	246
ANBAS	Missing	246
DIAG	dMMR/MSI-H	65
	MMRp/MSS	181
DISSTAT	Primary Stage III	44
	Primary Stage IV	83
	Recurrent	119
DMMR	No	183
	Yes	63
ECOG	Ambulatory	86
	Fully active	160
GL	Eastern Europe	14
	North America	186
	Western Europe	46
HISTOLOG	EC	111
	Other	135
PDL1CAT	Negative	36
	Positive	91
	Unknown	119
PELRAD	No	201
	Yes	45

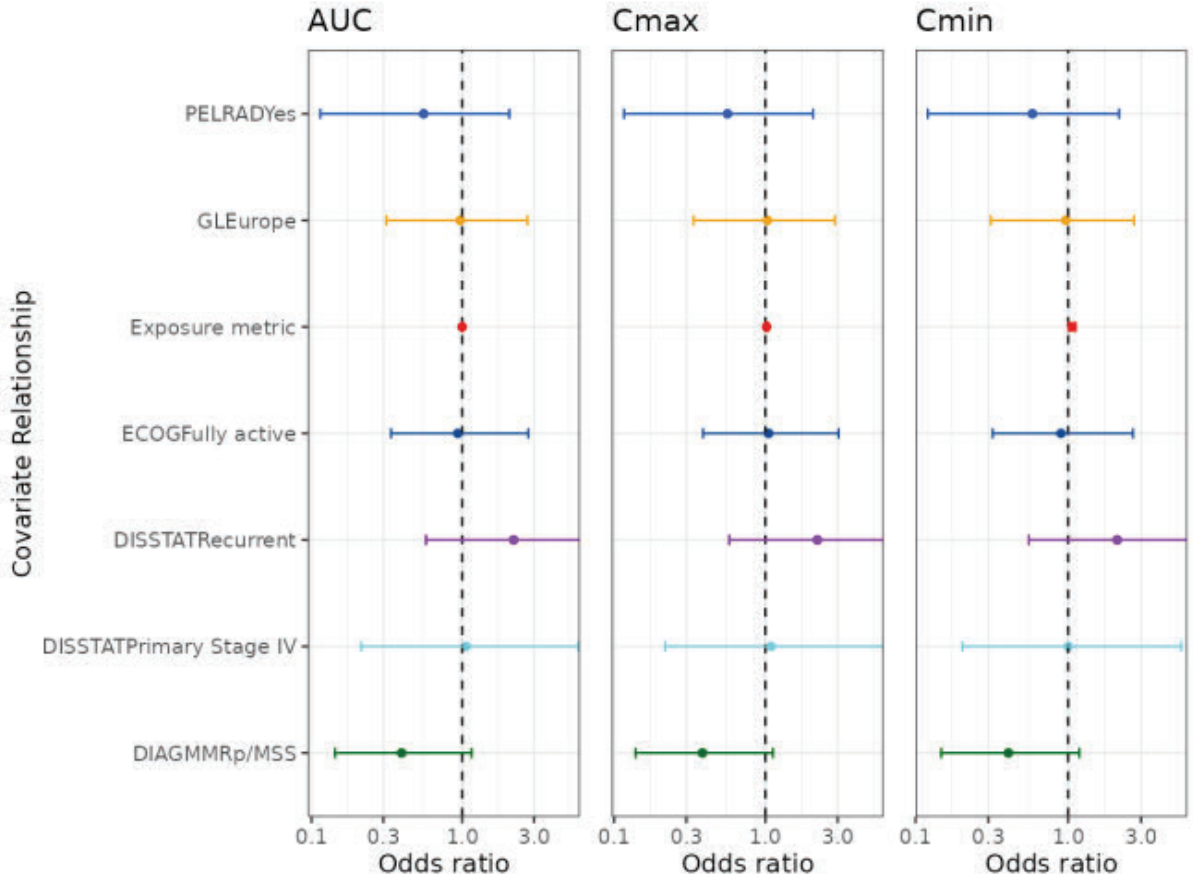
ADBAS: Anti drug antibody status; **ANBAS:** Neutralizing antibody status; **DIAG:** Tumor Diagnosis; **DISSTAT:** Disease status in EC; **dMMR:** deficient mismatch repair; **MSI-H:** microsatellite instability high; **MSS:** microsatellite stable; **MMRp:** mismatch repair proficient; **ECOG:** Baseline ECOG performance; **GL:** Geographic location; **HISTOLOG:** Histology; **PDL1CAT:** Combined positive score category at baseline; **PELRAD:** Prior external pelvic radiotherapy. Only two of the placebo patients in the tumor diagnosis category dMMR/MSI-H were not dMMR.

Applicant - Table 44. Summary of Predicted Cycle 1 Cmin, Cmax, and AUC for Dostarlimab Treated Patients in the Safety Analysis

Metric	Minimum	p10	p90	Maximum	Mean	SD
C_{min} (mg/L)	10.10	27.80	53.70	67.60	39.70	9.94
C_{max} (mg/L)	73.40	116.00	183.00	246.00	147.00	26.40
AUC (mg*h/L)	13300.00	25200.00	40100.00	48800.00	32300.00	5850.00

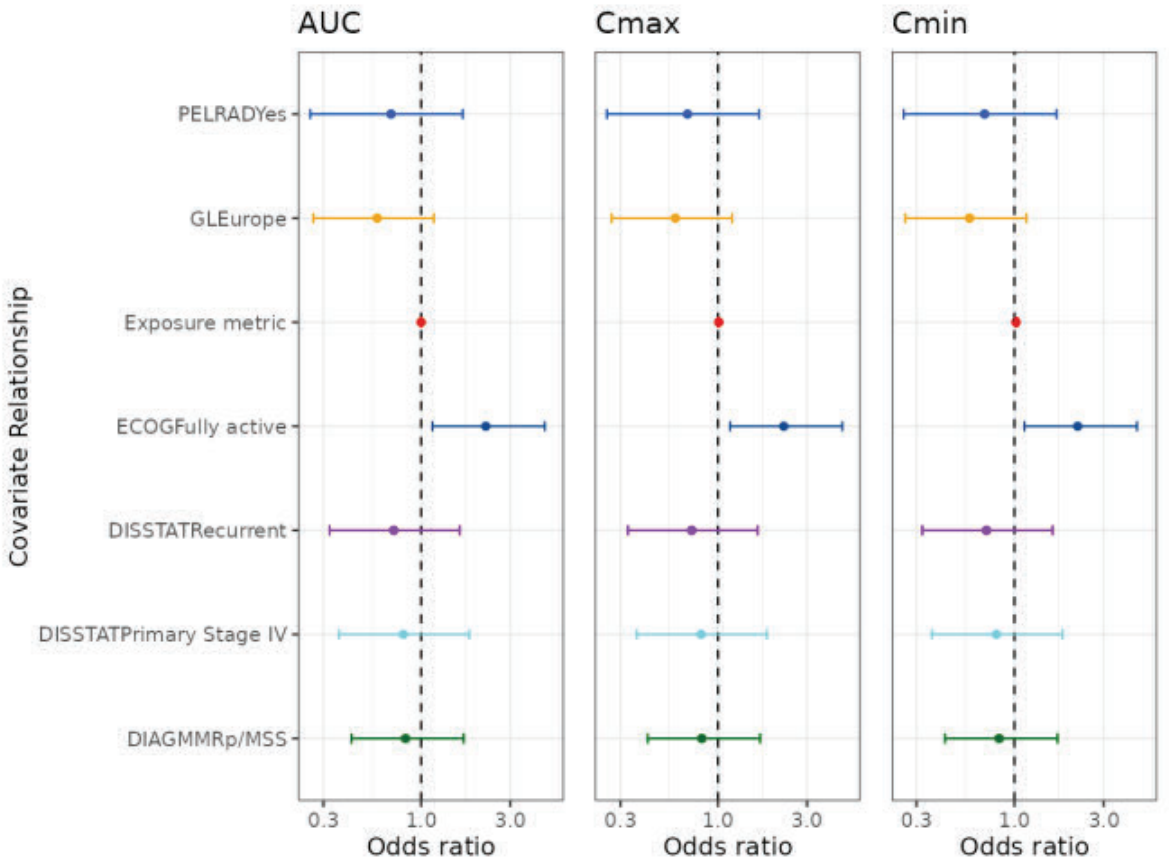
AUC: Area under the curve during the first 21 days; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21; **P10**: 10^{th} percentile; **P90**: 90^{th} percentile.

Applicant - Figure 28. Odds Ratio Multivariate Analysis, Arthralgia, Cycle 7 and Beyond, Dostarlimab treated



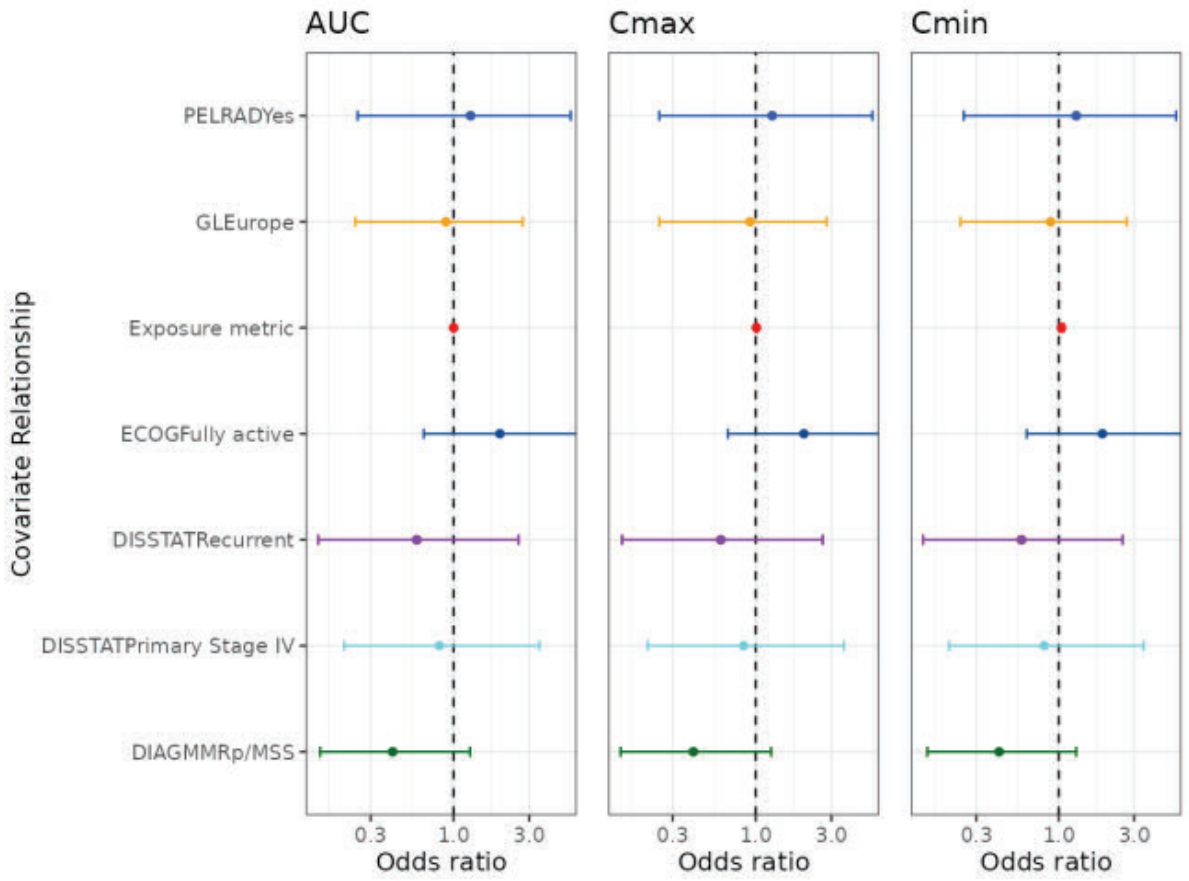
Circles: Odds ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); DIAG - Tumor diagnosis (reference dMMR/MSI-H); **AUC**: Area under the curve during the first 21 days; C_{max}: Maximum concentration during the first 21 days; C_{min}: Minimum concentration at Day 21.

Applicant - Figure 29. Odds Ratio Multivariate Analysis, Rash, Cycle 1-6, All Patients



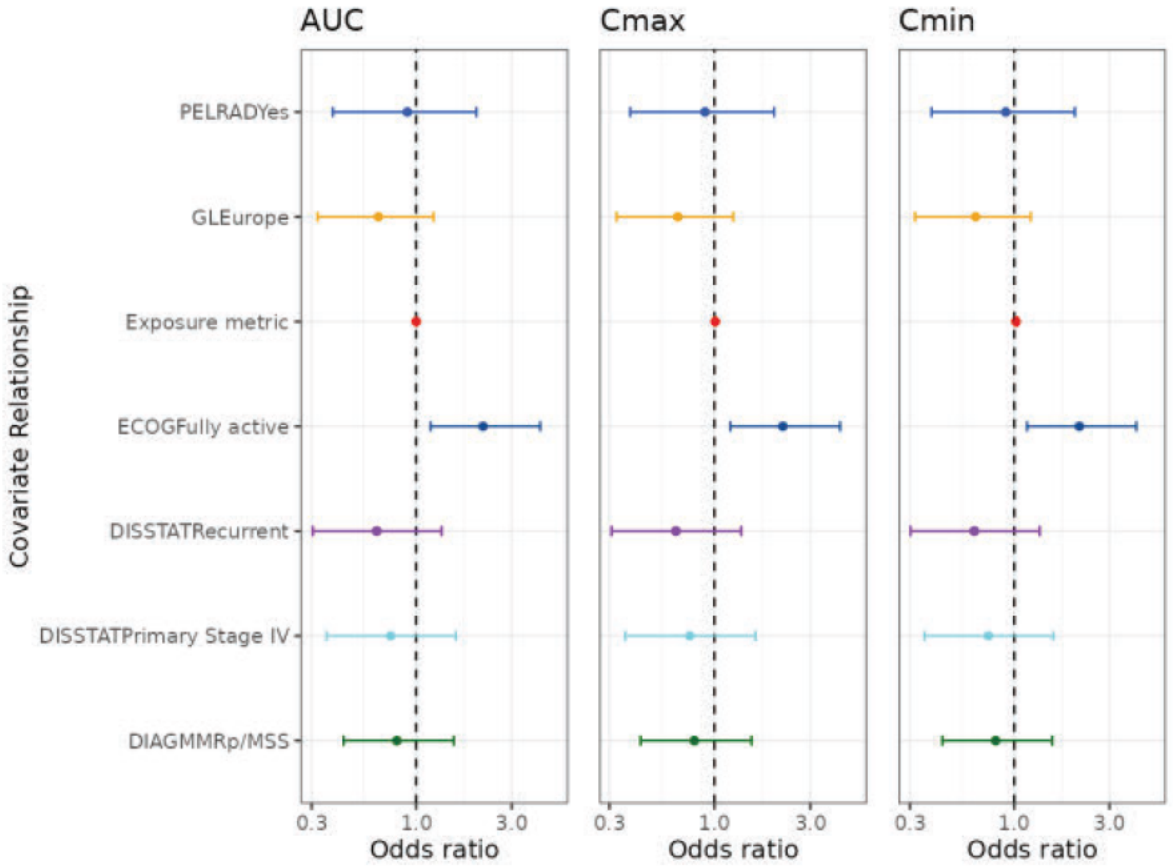
Circles: Odds ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); DIAG - Tumor diagnosis (reference dMMR/MSI-H); **AUC**: Area under the curve during the first 21 days; $\mathbf{C}_{max}$: Maximum concentration during the first 21 days; $\mathbf{C}_{min}$: Minimum concentration at Day 21.

Applicant - Figure 30. Odds Ratio Multivariate Analysis, Rash, Cycle 7 and Beyond, All Patients



Circles: Odds ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); DIAG - Tumor diagnosis (reference dMMR/MSI-H); **AUC**: Area under the curve during the first 21 days; $\mathbf{C}_{max}$: Maximum concentration during the first 21 days; $\mathbf{C}_{min}$: Minimum concentration at Day 21.

Applicant - Figure 31. Odds Ratio Multivariate Analysis, Rash, All Cycles, All Patients



Circles: Odds ratio; **Lines:** 95% confidence interval; PELRAD - Prior external pelvic radiotherapy (reference No); GL - Geographic location (reference North America); ECOG - Baseline ECOG performance (reference Ambulatory); DISSTAT - Disease status in EC (reference Primary Stage III); DIAG - Tumor diagnosis (reference dMMR/MSI-H); **AUC**: Area under the curve during the first 21 days; $\mathbf{C}_{max}$: Maximum concentration during the first 21 days; $\mathbf{C}_{min}$: Minimum concentration at Day 21.

The FDA's Assessment:

In general, the Applicant's E-R analyses for dostarlimab are considered acceptable for the purpose of supporting analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

19.4.2.5. ER Review Issues

No substantive issues.

19.4.2.6. Reviewer's Independent Analysis

Reviewer's independent analysis was not performed

19.4.2.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

The FDA's Assessment:
Not Applicable. Refer to other clinical pharmacology sections of the Assessment Aid for the FDA review.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
Refer to Section 8 of this Assessment Aid for the FDA safety review.

APPEARS THIS WAY ON ORIGINAL

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology	Vicky Hsu, PhD	OCP/DCPI	Sections: 6	**Select one:** X Authored ___ Approved
	Signature: Wenchi Hsu -S Digitally signed by Wenchi Hsu -S Date: 2023.07.27 13:06:49 -04'00'			
Clinical Pharmacology (TL)	Salaheldin Hamed, PhD	OCP/DCPII	Sections: 6	**Select one:** x Authored x Approved
	Signature: Salaheldin S. Hamed -S Digitally signed by Salaheldin S. Hamed -S Date: 2023.07.27 13:43:46 -04'00'			
Pharmacometrics	Huali Wu, PhD	OCP/DPM	Sections:6, 19.4	**Select one:** X Authored ___ Approved
	Signature: Huali Wu -S Digitally signed by Huali Wu -S Date: 2023.07.27 14:23:33 -04'00'			
Pharmacometrics (TL)	Jingyu Yu, PhD	OCP/DPM	Sections: 6, 19.4	**Select one:** X Authored X Approved
	Signature: Jingyu Yu -S Digitally signed by Jingyu Yu -S Date: 2023.07.27 14:55:32 -04'00'			
Biometrics Reviewer	Hui Zhang, PhD	OB/DBV	Sections: 8.1, 8.3	**Select one:** X Authored ___ Approved
	Signature: Hui Zhang -S Digitally signed by Hui Zhang -S Date: 2023.07.27 16:16:57 -04'00'			
Biometrics (TL)	Shenghui Tang, PhD	OB/DBV	Sections: All	**Select one:** ___ Authored X Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2023.07.27 16:59:43 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Efficacy	Sakar Wahby, PharmD	DO1	Sections: 2, 3, 4, 7, 8.1, 8.4, 10, 13, 19.2	**Select one:** X Authored ___ Approved
	Signature: Sakar M. Wahby -S Digitally signed by Sakar M. Wahby -S Date: 2023.07.28 11:45:38 -04'00'			
Clinical Safety	Joshua Donaldson, MD, PhD	DO1	Sections: Section 8.2	**Select one:** X Authored ___ Approved
	Signature: Joshua M. Donaldson -S Digitally signed by Joshua M. Donaldson -S Date: 2023.07.28 10:49:40 -04'00'			
Clinical Team Leader	Preeti Narayan, MD	OOD/DO1	Sections: All	**Select one:** X Authored ___ Approved
	Signature: Preeti Narayan -S Digitally signed by Preeti Narayan -S Date: 2023.07.28 12:15:09 -04'00'			
Associate Director for Labeling	William Pierce, Pharm D, MPH	OOD	Sections: 11, Prescribing Information, Patient Information	**Select one:** X Authored X Approved
	Signature: Doris Auth -S Digitally signed by Doris Auth -S Date: 2023.07.28 13:09:28 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Preeti Narayan, MD	OOD/DO1	Sections: All	**Select one:** X Authored X Approved
	Signature: Preeti Narayan -S Digitally signed by Preeti Narayan -S Date: 2023.07.28 12:14:38 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Director DCPII/OCP	Nam Atiqur Rahman, PhD	OCP	Sections: 6, 19.4	**Select one:** ___ Authored _X_ Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2023.07.28 15:52:25 -04'00'			
Director OB	Shenghui Tang, PhD	OB/DBV	Sections: All	**Select one:** ___ Authored _X_ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2023.07.27 17:00:23 -04'00'			
Director	Laleh Amiri-Kordestani, MD	DO1	Sections: All	**Select one:** ___ Authored _X_ Approved
	Signature: Laleh Amiri Kordestani -S Digitally signed by Laleh Amiri Kordestani -S Date: 2023.07.28 17:03:06 -04'00'			

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LALEH AMIRI KORDESTANI
07/31/2023 10:54:15 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761174Orig1s006

OTHER REVIEW(S)

LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	July 25, 2023
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	BLA 761174/S-006
Product Name, Dosage Form, and Strength:	Jemperli (dostarlimab-gxly) Injection, 500 mg/10 mL (50 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	GlaxoSmithKine LLC
FDA Received Date:	March 23, 2023 and July 6, 2023
TTT ID #:	2023-4338
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 REASON FOR REVIEW

GlaxoSmithKine LLC submitted an Efficacy Supplement for Jemperli (dostarlimab-gxly) Injection to propose an additional indication:

(b) (4)

Subsequently, the Division of Oncology 1 (DO1) requested that we review the proposed Jemperli prescribing information (PI) for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

GlaxoSmithKine submitted the proposed Jemperli PI[a] received on March 23, 2023 and proposed changes to Section 2.4 Preparation and Administration (b) (4) (b) (4) (b) (4) However, both proposed changes were rejected by reviewers from Office of Pharmaceutical Quality (OPQ). (b) (4) (b) (4) (b) (4) After this was communicated to GlaxoSmithKline, a revised Jemperli PI was submitted on July 6, 2023, which DMEPA reviewed from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A

[a] Available from \\CDSESUB1\EVSPROD\bla761174\0221\m1\us\114-labeling\1141-draft\draft-proposed.docx

[b] Available from \\CDSESUB1\EVSPROD\bla761174\0287\m1\us\114-labeling\1141-draft\draft-annotated.docx

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the July 6, 2023 Jemperli PI and noted that GlaxoSmithKine accepted OPQ's edits to Section 2.4 Preparation and Administration and we have no medication error concerns with the proposed information in Section 2.4 Preparation and Administration. We note that there are no changes to Section 3 Dosage Forms and Strengths, Section 16 How Supplied/Storage and Handling, and Section 17 Patient Counseling Information.

Additionally, our routine postmarket safety surveillance did not identify any medication errors related to label and labeling that is relevant for this review. Therefore, we have no recommendations for the proposed Jemperli PI from a medication error perspective.

4 CONCLUSION & RECOMMENDATIONS

The July 6, 2023 Jemperli PI is acceptable from a medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Jemperli received on March 23, 2023 from GlaxoSmithKine LLC.

Table 2. Relevant Product Information for Jemperli	
Initial Approval Date	4/22/2021
Proper Name	dostarlimab-gxly
Indication	Endometrial Cancer (b) (4) • as a single agent for the treatment of adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen in any setting and are not candidates for curative surgery or radiation. Mismatch Repair Deficient Recurrent or Advanced Solid Tumors • as a single agent for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.
Route of Administration	Intravenous
Dosage Form	Injection
Strength	500 mg/10 mL (50 mg/mL)
Dose and Frequency	500 mg every 3 weeks for 6 doses followed by 1,000 mg monotherapy every 6 weeks
How Supplied	Carton of one single-dose vial
Storage	Store vial refrigerated at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze or shake.
Container Closure	10 mL (b) (4) clear glass vial with a (b) (4) (b) (4) stopper laminated with (b) (4) and a 20 mm aluminum overseal with a white matte flip-off top.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On May 4, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, Jemperli. Our search identified 4 previous reviews[c,d,e,f], and we considered our previous recommendations to see if they are applicable for this current review.

[c] Gao, T. Label and Labeling Review for Jemperli (BLA 761223). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Mar 2. OSE RCM No.: 2020-2696.

[d] Gao, T. Memorandum Review of Revised Label and Labeling. Jemperli (BLA 761174). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Aug 27. OSE RCM No.: 2019-2380-2.

[e] Gao, T. Memorandum Review of Revised Label and Labeling. Jemperli (BLA 761174). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Mar 9. OSE RCM No.: 2019-2380-1.

[f] Gao, T. Label and Labeling Review for Jemperli (BLA 761174). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Feb 19. OSE RCM No.: 2019-2380.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Jemperli labels and labeling submitted by GlaxoSmithKine LLC.

- Prescribing Information and Medication Guide (Image not shown) received on March 23, 2023, available from \\CDSESUB1\EVSPROD\bla761174\0221\m1\us\114-labeling\1141-draft\draft-proposed.docx
- Prescribing Information and Medication Guide (Image not shown) received on July 6, 2023, available from \\CDSESUB1\EVSPROD\bla761174\0287\m1\us\114-labeling\1141-draft\draft-annotated.docx

F.2 Label and Labeling Images

N/A

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: July 10, 2023

To: Amy Tilley, Regulatory Project Manager,
Division of Oncology 1 (DO1)

From: Adesola Adejuwon, PharmD, MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, MS, RN, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for JEMPERLI (dostarlimab-gxly) injection, for intravenous use

BLA: 761174, S-006

In response to DO1's consult request dated April 4, 2023, OPDP has reviewed the proposed Prescribing Information (PI) and Medication Guide for supplement 006 for JEMPERLI (dostarlimab-gxly) injection, for intravenous use (Jemperli). This supplement proposes to provide the results from Part 1 of the RUBY Study and is seeking the following proposed indication:

(b) (4)

PI/Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on June 29, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on July 5, 2023.

Thank you for your consult. If you have any questions, please contact Adesola Adejuwon at 240 402 5773 or Adesola.Adejuwon@fda.hhs.gov.

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/s/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 5, 2023
To:	Amy Tilley Regulatory Project Manager **Division of Oncology I (DO1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adesola Adejuwon, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	JEMPERLI (dostarlimab-gxly)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761174
Supplement Number:	S-006
Applicant:	GlaxoSmithKline LLC

1 INTRODUCTION

On March 23, 2023, GlaxoSmithKline LLC submitted for the Agency's review a Prior Approval Supplement (PAS)- Efficacy to their approved Biologics Review Application (BLA) 761174/S-006 for JEMPERLI (dostarlimab-gxly) injection. The basis for this sBLA is the results from Part 1 of the RUBY Study. With this supplement, the Applicant is seeking the following proposed indication:

(b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology I (DO1) on April 4, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for JEMPERLI (dostarlimab-gxly) injection.

2 MATERIAL REVIEWED

- Draft JEMPERLI (dostarlimab-gxly) injection MG and received from DO1 by DMPP and OPDP on June 29, 2023.
- Draft JEMPERLI (dostarlimab-gxly) injection Prescribing Information (PI) received on March 23, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 29, 2023.
- Approved JEMPERLI (dostarlimab-gxly) injection labeling dated February 9, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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