Final Decision on the Proposal to Withdraw Approval of Pepaxto (melphalan flufenamide) for Injection
Docket No. FDA-2023-N-3167
February 23, 2024

This document is the final decision of the Food and Drug Administration (FDA or the agency), pursuant to section 506(c)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 356(c)(3), as amended most recently by the Food and Drug Omnibus Reform Act of 2022 as part of the Consolidated Appropriations Act, 2023 (Pub. L. 117–328), on the Center for Drug Evaluation and Research's (CDER's) proposal to withdraw approval of Pepaxto (melphalan flufenamide) for injection, approved under new drug application (NDA) 214383, held by Oncopeptides AB (Oncopeptides). As described below, after reviewing the record and considering the arguments on appeal, I have determined that the grounds for withdrawing approval have been met because: (1) the confirmatory study conducted as a condition of accelerated approval did not confirm Pepaxto's clinical benefit and (2) the available evidence demonstrates that Pepaxto is not shown to be safe or effective under its conditions of use.

Multiple myeloma is a serious disease that remains a notable cause of cancer morbidity and mortality in the United States, with an estimated 35,730 cases and 12,590 deaths in 2023.[1] Available treatments include chemotherapy agents, cellular immunotherapies, and autologous hematopoietic stem cell transplant (HSCT). Candidates for autologous HSCT tend to be younger and have fewer comorbidities than those deemed ineligible. Since none of these therapies are curative, individuals tend to experience disease relapse and require additional therapy. Therefore, FDA recognizes that there remains a need for additional safe and effective treatments.

On February 26, 2021, Pepaxto, or melphalan flufenamide, received accelerated approval for the treatment of patients with multiple myeloma who had received 4 or more prior lines of therapy and were refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed antibody (i.e., triple class refractory patients). This approval was based on a single-arm phase 2 study. Subsequently, a randomized, controlled phase 3 trial was conducted comparing melphalan flufenamide and dexamethasone to pomalidomide and dexamethasone and did not achieve its pre-specified primary endpoint of improvement in progression free survival (PFS), showing instead a detrimental effect on overall survival (OS). Contrary to the agreed-upon, pre-specified statistical analysis plan, the sponsor subsequently performed a reanalysis of the data reassessing 29 patients from the control arm who had unconfirmed disease progression and concluded that the primary endpoint was achieved with a 1.9-month median improvement in PFS, despite a notable detrimental effect on OS that remained after their reanalysis.

Because clinical benefit in PFS was not confirmed by the phase 3 trial, and because a safety concern of decreased OS was observed, on July 7, 2023, CDER initiated the process to withdraw Pepaxto from the market following a process that included discussion of the issue at an

[1] NIH. Cancer Stat Facts: Myeloma. https://seer.cancer.gov/statfacts/html/mulmy.html.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Oncology Drugs Advisory Committee (ODAC) meeting on September 22, 2022,[2] at which a 14-2 majority of the Committee voted that that the benefit-risk profile of Pepaxto was not favorable for the indicated patient population. Ultimately, the sponsor appealed the withdrawal of Pepaxto, and the Commissioner assigned me as his designee in this matter.

Both the sponsor and CDER had the opportunity to discuss their positions in writing and during a virtual meeting. The sponsor offered several arguments why Pepaxto should remain on the market. These arguments included their reanalysis of the phase 3 trial noting a benefit in PFS despite a detrimental effect on OS as well as an assertion that the apparent detrimental effect of Pepaxto on OS is due to a dissociation of PFS and OS with the pomalidomide-containing regimen that was used for comparison. Alternatively, the sponsor argued that Pepaxto should remain on the market for a subset of the currently indicated population based on the evidence that it provided in post-hoc analyses submitted to FDA. CDER did not agree with the sponsor's proposals and arguments and provided detailed comments explaining their thinking. In particular, among other issues, CDER: (1) did not agree with the sponsor's post-hoc reanalysis of the PFS data, (2) reiterated their safety concerns based on the detrimental effect on OS observed in a randomized, controlled trial, (3) disagreed with the concept that immune modulatory drugs such as pomalidomide are associated with a dissociation between PFS and OS, and (4) disagreed that a population existed for which substantial evidence of effectiveness of Pepaxto is demonstrated.

After reviewing the record and considering the arguments on appeal, I have determined that the grounds for withdrawing approval have been met because: (1) the confirmatory study conducted as a condition of accelerated approval did not confirm Pepaxto's clinical benefit and (2) the available evidence demonstrates that Pepaxto is not shown to be safe or effective under its conditions of use. While withdrawal is not contingent on meeting both grounds, both statutory grounds for withdrawal are satisfied in this matter. Additionally, I have considered Oncopeptides' policy arguments and find that FDA should not allow Pepaxto to remain on the market while an additional study is conducted to assess the safety and efficacy of the drug, whether for a narrower patient population or otherwise. I recognize that the decision to withdraw Pepaxto might be upsetting for patients who have exhausted all their options among drugs approved for their condition, and for their loved ones and providers. However, I believe that patients deserve FDA-approved treatments that are safe and effective.

1. Legal Background

a. Summary of the Accelerated Approval Process

Section 506 of the FD&C Act provides that a drug sponsor may request to expedite the review and approval of a drug intended to treat an unmet need related to a serious or life-threatening disease or condition. Under this accelerated approval pathway, FDA may approve a drug based on the drug's effect on a surrogate or intermediate clinical endpoint. FDA's regulations, at 21 CFR 314.510, require that accelerated approval be subject to a sponsor's engaging in further

[2] September 22-23, 2022: Meeting of the Oncologic Drugs Advisory Committee Announcement, FDA, available at https://www.fda.gov/advisory-committees/advisory-committee-calendar/september-22-23-2022-meeting-oncologic-drugs-advisory-committee-announcement-09222022.

study "to verify and describe [the drug's] clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome."

b. Summary of the Withdrawal Process

Under section 506(c)(3) of the FD&C Act, FDA may withdraw approval of a drug approved under the accelerated approval pathway using expedited procedures if, among other reasons, "a study required to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit of the product fails to verify and describe such effect or benefit," or "other evidence demonstrates that the product is not shown to be safe or effective under the conditions of use."

Pursuant to section 506(c), FDA begins the withdrawal process by providing a sponsor with due notice of the proposed withdrawal, an explanation for the proposed withdrawal, an opportunity for a meeting with the Commissioner or the Commissioner's designee, and an opportunity for written appeal to the Commissioner or the Commissioner's designee.[3] If an applicant submits an appeal, the Commissioner may decide to either review the matter or identify an appropriate designee. The Commissioner's designee must be an individual who has not participated in the proposed withdrawal of approval and is not the subordinate of an individual who participated in the proposed withdrawal.[4] For the purposes of this matter, the Commissioner of Food and Drugs designated me to decide the appeal and to meet with the sponsor in response to its request for a meeting.[5]

If the Center has not already held an advisory committee to address the issues contained in the proposed withdrawal, and if requested by the sponsor, FDA will convene an advisory committee to consider these issues.[6] Lastly, FDA will provide an opportunity for the public to comment on the proposed withdrawal and will publish on the agency's website a summary of the comments received and the agency's response to such comments.[7]

2. Factual and Procedural Background

Below is a summary of the factual and procedural background of this proceeding. More detailed information, particularly on the post-approval confirmatory study and the September 2022 Oncologic Drugs Advisory Committee (ODAC) meeting, can be found on websites such as FDA's advisory committee website and clinicaltrials.gov. Additional relevant documents and information are posted to the docket.[8]

[3] *See* section 506(c)(3)(B)(i) of the FD&C Act.
[4] *See* section 506(c)(3)(B)(i)(IV) of the FD&C Act.
[5] *See* Pepaxto Designation and Delegation Memo Aug 2023, available in docket FDA-2023-N-3167.
[6] *See* section 506(c)(3)(B)(iv) of the FD&C Act.
[7] *See* section 506(c)(3)(B)(iii) of the FD&C Act.
[8] FDA-2023-N-3167, https://www.regulations.gov/docket/FDA-2023-N-3167/.

a. Basis for Accelerated Approval of Pepaxto

As described in CDER's notice of proposed withdrawal of approval, FDA approved the NDA for Pepaxto on February 26, 2021, under the accelerated approval pathway, "for use in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma [RRMM] who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory drug, and one CD38-directed monoclonal antibody (triple class refractory)."[9]

As CDER explained in the notice proposing withdrawal:

> [Approval of Pepaxto] relied on evidence from Trial OP-106, also known as HORIZON, . . . which was a single-arm, open-label, phase 2 multicenter clinical trial that enrolled patients with [RRMM] and who received at least two lines of prior therapy including an immunomodulatory drug and a proteasome inhibitor. In the HORIZON trial, the primary endpoint was overall response rate (ORR), . . . as assessed by the investigator, which CDER considered as an intermediate endpoint. The accelerated approval indication was granted based on efficacy evaluated in 97 patients who had received 4 or more prior lines of therapy and were refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed antibody (i.e., triple class refractory). These patients had limited treatment options and the benefit-risk assessment in this context supported accelerated approval for this population based on an intermediate endpoint of ORR supported by duration of response (DOR).[10]

b. Required Post Approval Confirmatory Study

As described in CDER's notice of proposed withdrawal, the approval letter for Pepaxto directed Oncopeptides to submit the final study report and datasets from a randomized phase 3 clinical trial that verifies and describes the clinical benefit of Pepaxto in patients with RRMM, referred to as Trial OP-103, also known as OCEAN.[11]

CDER described OCEAN as follows:

> OCEAN was a randomized, controlled, open-label, confirmatory study of melphalan flufenamide/dexamethasone (MelDex) compared to pomalidomide/dexamethasone (PomDex) in patients with [RRMM] who were refractory to lenalidomide. The primary efficacy endpoint was progression free survival (PFS). The secondary endpoints included, overall survival (OS), defined as time from date of randomization to death due to any cause.[12]

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[9] CDER Notice of Proposed Withdrawal of Approval (CDER Proposed Withdrawal), dated July 7, 2023. This document is posted to the docket at https://www.regulations.gov/document/FDA-2023-N-3167-0002.
[10] *Id.* at 2.
[11] *See id.*
[12] *Id.* at 2-3.

OCEAN randomized a total of 495 individuals who were relapsed or refractory to between two and four prior regimens to either MelDex, i.e., the Pepaxto-containing regimen, or PomDex. The topline OCEAN results were submitted to FDA on May 7, 2021, and they indicated that the primary endpoint of improved PFS was not met and that a detrimental effect on OS was observed on the MelDex arm compared to the PomDex arm.[13] As described in CDER's proposal to withdraw, there was a lower median OS in the MelDex arm compared to the PomDex arm with a HR of 1.104 (95% CI 0.846, 1.441) indicating an increased risk of death in the MelDex arm compared to the PomDex arm.[14]

After reviewing the topline OCEAN results, Oncopeptides conducted several post-hoc exploratory analyses in its efforts to argue that the primary endpoint of PFS was met, and to explain the detrimental effect on OS.[15] These post-hoc analyses included conducting a revised efficacy analysis that included 29 individuals who had unconfirmed progression in the PomDex arm.[16] The inclusion of individuals with unconfirmed progression was outside of the prespecified statistical analysis plan agreed upon with CDER.[17] Oncopeptides' inclusion of these 29 individuals resulted in the paradoxical finding of an improved PFS but inferior OS in the OCEAN outcome.

On July 7, 2021, FDA placed all Pepaxto clinical trials on partial clinical hold and then issued a safety alert on July 28, 2021.[18] In the safety alert, FDA alerted patients and healthcare providers that the OCEAN trial results showed an increased risk of death with Pepaxto. FDA noted that it would continue to evaluate the OCEAN results as well as potentially hold a "public meeting to discuss these safety findings and explore the continued marketing of Pepaxto."[19]

c. Summary of the September 2022 ODAC Meeting and Related Events

As described in CDER's proposal to withdraw, CDER originally scheduled an ODAC meeting for October 28, 2021, to discuss the OCEAN trial results.[20] However, on October 22, 2021, Oncopeptides requested voluntary withdrawal of approval of Pepaxto pursuant to 21 CFR 314.150(d).[21] After receiving Oncopeptides' request, CDER cancelled the scheduled ODAC

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[13] On appeal, Oncopeptides states that certain CDER staff listed as authors in Merino M, Kasamon Y, et al. Irreconcilable Differences: The Divorce Between Response Rates, Progression Free Survival, and Overall Survival. J Clin Oncol. 2023 May 20;41 (15):2706-2712 concluded that OCEAN met its primary endpoint of superior PFS and published this (*see* Oncopeptides Written Appeal at 5-6). However, Oncopeptides mischaracterizes the inclusion of OCEAN in this article. In the Merino article, OCEAN is referenced as an example of where there is a disconnect between PFS and OS, specifically as an example of a trial where there was a potential detriment in OS. Nowhere in this article do the authors state that the OCEAN trial met its primary endpoint of PFS or that the PFS results showed the statistical superiority of MelDex to PomDex.

[14] *See* CDER Proposed Withdrawal at 3.

[15] *See generally* CDER Decisional Memorandum at 3, 12, and 14.

[16] *See* CDER Decisional Memorandum at 3; CDER September 8, 2023, Response to Oncopeptides Written Appeal (CDER September Response) at 4.

[17] *See* CDER Decisional Memorandum at 3; CDER September Response at 4.

[18] *See* https://www.fda.gov/drugs/drug-safety-and-availability/fda-alerts-patients-and-health-care-professionals-about-clinical-trial-results-showing-increased.

[19] *Id.*

[20] *See* CDER Proposed Withdrawal at 3.

[21] *See id*.

meeting.[22] On January 13, 2022, Oncopeptides rescinded its request for voluntary withdrawal of approval.[23]

After Oncopeptides rescinded its withdrawal request, CDER scheduled an ODAC meeting on September 22, 2022, to discuss Pepaxto and the OCEAN trial results.[24] The ODAC discussed, "the benefit-risk profile of [Pepaxto] for the currently indicated patient population considering the results of the confirmatory OCEAN trial."[25] As summarized in the ODAC meeting minutes:

> A majority of the Committee members shared a common concern when discussing the benefit-risk profile of [Pepaxto] for the currently indicated patient population. Specifically, there were concerns regarding the marginal PFS benefit and the potential detriment in [OS]. These Committee members agreed that the result of the confirmatory OCEAN trial did not confirm clinical benefit in the indicated patient population. Some Committee members noted that it would be challenging to explain the mild [PFS] and negative result in [OS] to their patients if [Pepaxto] was one of the treatment options. The Committee members further noted that the post-hoc analyses presented regarding the transplant subgroups should be used for hypothesis generation as opposed to labeling or as an indication for use. The Committee members acknowledged that there is a huge need in this heavily treated patient population, however, we should not use drugs that cause harm. Please see the transcript for details of the Committee's discussion.[26]

The ODAC then voted on the following question: "Given the potential detriment in [OS], failure to demonstrate a [PFS] benefit, and lack of an appropriate dose, is the benefit-risk profile of [Pepaxto] favorable for the currently indicated patient population?"[27] The ODAC voted 14 to 2 that the benefit-risk profile of Pepaxto was not favorable for the currently indicated patient population.[28] As summarized in the ODAC meeting minutes:

> The majority of the Committee members voted "No," indicating that the benefit-risk profile of [Pepaxto] is not favorable for the currently indicated patient population given the potential detriment in overall survival, failure to demonstrate a [PFS] benefit, and lack of an appropriate dose. A majority of the Committee members who voted no reiterated that post-hoc analyses should be considered merely hypothesis-generating and need to be tested in a prospectively designed trial. The Committee members who voted "Yes", noted that [Pepaxto] may be beneficial to some of the patient population, however, the members also

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[22] *See id*.
[23] *See id*.
[24] *See* https://www.fda.gov/advisory-committees/advisory-committee-calendar/september-22-23-2022-meeting-oncologic-drugs-advisory-committee-announcement-09222022 for all information related to the ODAC meeting.
[25] "Final Summary Minutes of the Oncologic Drugs Advisory Committee Meeting September 22-23, 2022 (Final ODAC Summary Minutes)," available at https://www.fda.gov/media/164048/download.
[26] Final ODAC Summary Minutes at 9.
[27] "Final Questions for the September 22-23, 2022 Meeting of the Oncologic Drugs Advisory Committee," available at https://www.fda.gov/media/161757/download.
[28] *See* Final ODAC Summary Minutes at 9.

[acknowledged] the post hoc nature of the analysis and that the results need to be confirmed in a prospective clinical trial.[29]

d. Procedural History from CDER's Proposal to Withdraw to the Appeal to the Commissioner's Designee

On July 7, 2023, CDER notified Oncopeptides of the proposal to withdraw approval of Pepaxto. In its proposal to withdraw approval, CDER stated that it was proposing to withdraw approval on the legal grounds that (1) the postapproval confirmatory trial required as a condition of Pepaxto's accelerated approval failed to verify clinical benefit, and (2) because available evidence demonstrates Pepaxto is not shown to be safe or effective under its conditions of use.[30] CDER further explained that, in OCEAN, median OS "was approximately five months shorter in the Pepaxto arm compared to the control arm."[31]

CDER also included additional considerations that it felt supported withdrawal, including that, as a policy matter, an approved drug product should only remain on the market if its benefits outweigh its risks, as is not the case for Pepaxto according to CDER.[32] Additionally, CDER stated that withdrawing Pepaxto's approval would uphold "the regulatory integrity of the accelerated approval pathway," noting that, "for the accelerated approval program to serve its purpose and not operate as a lower approval standard, FDA must be able to withdraw approvals when it determines… that the confirmatory trial(s) failed to verify the predicted clinical benefit and that the drug should be withdrawn."[33]

CDER's proposal gave Oncopeptides the opportunity to appeal the proposal and to request a meeting with the Commissioner or his designee regarding CDER's proposal.

On July 26, 2023, Oncopeptides submitted a letter indicating an intent to appeal the proposal to withdraw approval and requesting a meeting with the FDA Commissioner or his designee with respect to the proposed withdrawal of approval. On August 4, 2023, Oncopeptides submitted its written appeal of CDER's proposal to withdraw approval of Pepaxto.

In its written appeal, Oncopeptides made several arguments. Oncopeptides stated that the OCEAN trial met its primary clinical endpoint, PFS, and argued that the negative effect on OS is not relevant because of issues with the PomDex arm, particularly in older individuals for which it asserts there was a dissociation in the clinically relevant outcomes of PFS and OS.[34] Oncopeptides asserted that its post-hoc analyses of OCEAN support that "Study OP-103 was successful in terms of superiority vs pomalidomide on the primary endpoint of PFS. However, no safety conclusions can be made based on the differences between PFS and OS results from this study due to the lack of relationship between PFS and OS for the pomalidomide treatment effect."[35] Additionally, Oncopeptides set forth an alternative argument that Pepaxto should

[29] Final ODAC Summary Minutes at 9.
[30] CDER Proposed Withdrawal at 1.
[31] *See id*. at 4; *see generally* CDER Decisional Memorandum.
[32] *See* CDER Proposed Withdrawal at 4-5.
[33] *Id.* at 3-4.
[34] *See generally* Oncopeptides Written Appeal.
[35] *Id.* at 3; *see generally id.* at 5-11.

remain on the market for a subset of the currently indicated population based on the evidence it provided in its post-hoc analyses.[36]

By letter dated August 9, 2023, I notified both CDER and Oncopeptides that I would be the Commissioner's designee for this matter and outlined general procedures moving forward.[37] In addition, I requested that CDER submit a response to Oncopeptides' written appeal by September 8, 2023.[38] In its response, CDER reiterated that the topline results of OCEAN failed to verify the clinical benefit of Pepaxto and that the results indicate that the drug product is no longer shown to be safe or effective under its conditions of use.[39] CDER also challenged Oncopeptides' argument regarding the post-hoc analyses, stating that any post-hoc analyses are hypothesis-generating and not grounds for maintaining approval.[40]

On September 19, 2023, Oncopeptides replied to CDER's response and reiterated its position that Pepaxto should remain on the market—with either its current intended use or a narrower one—while additional clinical studies are conducted.[41]

On October 2, 2023, I held a virtual meeting with CDER and Oncopeptides at which both sides presented information and had the opportunity to ask questions regarding the other side's presentation.[42] I asked questions of both CDER and Oncopeptides and concluded the meeting by requesting additional information. CDER and Oncopeptides submitted additional information by the requested deadline.[43]

Separately, during these ongoing proceedings, Oncopeptides has declined to market Pepaxto in the US.[44]

3. Analysis

As I explain below, I find that Pepaxto's approval is subject to withdrawal based on the two separate, independent statutory grounds proposed by CDER: (1) that the confirmatory study failed to verify the clinical benefit of Pepaxto and (2) that the evidence demonstrates that Pepaxto is not shown to be safe or effective under its conditions of use. Additionally, Oncopeptides' policy arguments do not persuade me that FDA should decline to withdraw approval of Pepaxto.

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[36] *See id.* at 11-13.
[37] August 9, 2023, letter from Dr. Marks to CDER and Oncopeptides.
[38] *Id.*
[39] *See generally* CDER September Response at 3.
[40] *See id.*
[41] *See generally* Oncopeptides Reply, dated September 19, 2023 (Oncopeptides Reply), at 2.
[42] For more information on what was presented as well as an outline of the meeting, please refer to the meeting minutes posted to the docket as well as CDER and Oncopeptides' PowerPoint presentations, which are also posted to the docket.
[43] For more information on the requested information, please refer to my October 4, 2023, letter to both parties, which is posted in the docket. CDER and Oncopeptides' subsequent responses are also available in the docket.
[44] Press release: Oncopeptides provides update on Pepaxto US marketing authorization (December 7, 2022), available at https://oncopeptides.com/en/media/press-releases/oncopeptides-provides-update-on-pepaxto-us-marketing-authorization/ (stating that "At the FDA's request, Oncopeptides stopped marketing Pepaxto in the US on October 22, 2021, and Pepaxto is currently not commercially available for US patients").

A. FDA Has Multiple Grounds for Withdrawing the Approval of Pepaxto

i. OCEAN Failed to Confirm the Expected Clinical Benefit of Pepaxto

A product's accelerated approval is subject to withdrawal if, among other reasons, "a study required to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical benefit of the [approved] product fails to verify and describe such effect or benefit."[45] I find that the confirmatory study—OCEAN—failed to verify the expected clinical benefit of Pepaxto. Therefore, I conclude that this ground for withdrawing approval has been satisfied.

In broad terms, when Oncopeptides conducted a large, randomized trial, it failed to show a statistically significant improvement in PFS or OS with Pepaxto.[46] I discuss this failure to confirm clinical benefit in greater detail below.

As previously explained, the accelerated approval of Pepaxto relied on evidence generated by HORIZON, which was a single-arm, open-label trial.[47] Of the 157 individuals enrolled in the trial, Pepaxto's efficacy was "assessed in 97 patients who had received four or more prior lines of therapy and were refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed antibody (i.e., triple class refractory)."[48] As described in CDER's memorandum, the ORR was "23.7% (95% CI: 15.7, 33.4) with a median DOR of 4.2 months (95% CI: 3.2, 7.6). In other words, 23.7% of the 97 participants evaluated exhibited reduction in disease markers specified in the ORR endpoint."[49] Thus, less than a quarter of participants in HORIZON had a reduction in disease markers. None exhibited stringent complete response or complete response.[50] PFS and OS were secondary endpoints in HORIZON, but those endpoints were not interpretable due to "the absence of a control arm and did not contribute to the assessment of efficacy."[51] While HORIZON provided adequate support for accelerated approval given the benefit-risk analysis of the evidence available at the time, it did not provide specific evidence of PFS or OS, which is needed to verify the clinical benefit.

Unlike HORIZON, OCEAN was a large, randomized, controlled trial. It enrolled 495 participants.[52] Under the prespecified statistical analysis plan for OCEAN, the median PFS was 6.9 months (95% CI: 5.1, 8.5) for the MelDex arm and 4.9 months (95% CI: 4.2, 5.9) for the PomDex arm. The Hazard Ratio (HR) was 0.817 (95% CI: 0.659, 1.012).[53] The p-value for PFS was $p = 0.0644$, showing that MelDex did not demonstrate statistical superiority to PomDex.[54] Even if FDA were to disregard the p-value for PFS, the OS data indicated a concerning safety finding, which is tied to the agency's overall view of the clinical benefit. Regarding OS, a

[45] Section 506(c)(3)(A)(ii) of the FD&C Act.
[46] *See*, *e.g.*, CDER Decisional Memorandum at 3-4, 10, 12.
[47] *See id.* at 6.
[48] *Id.*
[49] *Id.* at 7.
[50] *See id*.
[51] *Id*.
[52] *See id.* at 6, 10.
[53] A hazard ratio is a measure of relative risk: it compares the risk over a period of time that patients in the treatment arm will experience a negative event, against the risk that the same event will happen to patients in the control arm.
[54] *See* CDER Decisional Memorandum at 10.

secondary endpoint, the median was 19.7 months (95% CI: 15.1, 25.6) in the MelDex arm compared to 25.0 months (95% CI: 18.1, 31.9) in the PomDex arm, and the HR for OS was 1.104 (95% CI: 0.846,1.441).[55] OS is an important, if not a central, clinical endpoint, and that showed a 5-month deficit for those using MelDex compared to PomDex. Even if FDA were inclined to consider the potential 2-month PFS improvement with MelDex, despite its lack of statistical significance, the possibility of that supporting Pepaxto's continued approval is negated by the concerning OS data.

As Dr. Gormley explained at the Advisory Committee meeting:

> [CDER doesn't] agree that a PFS statistical significance was demonstrated, but please note, even if we did, we would have significant concerns and . . . this trial would not provide demonstration of safety and effectiveness because of the [OS] results.
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> So we've had multiple instances throughout oncology -- and, unfortunately, particularly multiple myeloma -- where we've seen discordance between [PFS] and [OS]. [OS] is the paramount endpoint that is needed for determination of clinical benefit. When we have a primary endpoint of [PFS], we still require data from [OS] to ensure that it is favorable and that there's not a potential for harm.[56]

As noted by CDER, an independent review committee, which analyzed the data based upon the pre-specified statistical analysis plan, found that OCEAN failed to demonstrate superiority, i.e., statistically significant improvement, in the primary endpoint of PFS.[57] Further, as previously described, the ODAC likewise agreed that the result of OCEAN did not confirm clinical benefit in the indicated patient population.[58]

On appeal, Oncopeptides states that, based upon its post-hoc analyses, OCEAN shows that Pepaxto has a superior PFS endpoint, while attempting to separate that finding from the inferior OS finding.[59] Oncopeptides argues that the control regimen for OCEAN, PomDex, was the cause of the "dissociation" between PFS and OS.[60] Although Oncopeptides does not deny that OCEAN did not show statistically significant improvement in the primary endpoint of PFS as analyzed according to the pre-specified statistical analysis plan, they submitted a post-hoc analysis, in which 29 individuals who had unconfirmed progression on the PomDex arm were included as having had their cancer progress while on study, rather than being censored as previously agreed upon in the statistical analysis plan, and concluded from those data that the trial met its primary endpoint. In other words, the sponsor reassessed 29 patients after the

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[55] *See id.*
[56] Oncology Drugs Advisory Committee Transcript from September 22, 2022 (ODAC Transcript), available at https://www.fda.gov/media/164050/download, at 128.
[57] *See* CDER September Response at 4.
[58] *See* ODAC Summary Minutes at 9; *see generally* ODAC Transcript at 178-200.
[59] *See* Oncopeptides Written Appeal at 5-6; *see generally* Oncopeptides PowerPoint Presentation from the October 2, 2023 meeting (Oncopeptides PowerPoint).
[60] Oncopeptides Written Appeal at 3. *See also* Oncopeptides Written Appeal at 6, 23.

primary database lock.[61] The sponsor also provided additional post-hoc analyses arguing that specific subpopulations benefitted from MelDex, such as those who had not undergone autologous HSCT within the prior 36 months.[62] The findings of various CDER and sponsor analyses of PFS are summarized in Table 1 below. Regardless of the rules used for analysis by CDER or the sponsor, the difference in median improvement in PFS was at most 2 months.

Table 1. Original and Post hoc PFS Analysis Results

PFS Analyses	HR (95% CI)	Difference in Medians	p-value
Applicants original ITT analysis	0.817 (0.659, 1.012)	2.0	0.0644
FDA's original ITT analysis	0.833 (0.665, 1.044)	1.7	0.1122
Applicant's Post hoc Reassessment	0.793 (0.640, 0.981)	1.9	0.0322
FDA Re-adjudicated Post hoc Analysis using Applicant's censoring rules	0.796 (0.642, 0.985)	1.9	0.0359
FDA Re-adjudicated Post hoc Analysis using FDA's censoring rules	0.820 (0.654, 1.027)	1.8	0.0837

Source: FDA analysis; *FDA's censoring rules-censor all unconfirmed PD [progressive disease];
Post hoc analyses do not have alpha allocation and p-values are considered to be nominal
**3 patients from Applicant's updated results were not confirmed by FDA and reverted to the original analysis results, 1 patient change in date (FDA Appendix 10.6)
[ITT, intent to treat]

Source of Table: Oncologic Drugs Advisory Committee (ODAC) Meeting, Combined FDA and Applicant ODAC Briefing Document, September 22, 2022, Table 1

It is noted that even under the sponsor's post-hoc analysis suggesting a very modest benefit in PFS of just under 2 months, there was still a notable detrimental effect of MelDex on OS, with a HR of 1.10 (95% CI 0.846, 1.441). This difference was also present after nearly three years of follow up with an HR of 1.14 (95% CI: 0.91, 1.42). This latter hazard ratio is associated with a decrease in median OS of 3.8 months with MelDex as of an updated data cutoff of February 3, 2022.

Additionally, MelDex was found to have notably more hematologic toxicity in some respects than PomDex. There was a higher rate of Grade 3-4 neutropenia, anemia, and thrombocytopenia with MelDex compared to PomDex (56%, 42%, 63% versus 41%, 18%, 10%, respectively).[63] The finding of greater hematologic toxicity, indicated by low white blood cell, red blood cell,

[61] CDER Decisional Memorandum at 3. As Dr. Gormley explained at the Advisory Committee meeting, "the censoring rules that we shared are the typical censoring rules that we use in multiple myeloma, but even though we can discuss the SAP and other analyses planned, it did not include for the reassessment that occurred. That obviously was outside of the SAP." ODAC Transcript at 189.
[62] *See generally* Oncopeptides PowerPoint; Oncopeptides Response to October 4, 2023, Request for Information (Oncopeptides October Response).
[63] *See generally* CDER Decisional Memorandum at 7. *See also* CDER October 2, 2023, PowerPoint Presentation (CDER PowerPoint) at 15 (discussing "Toxicities that may explain detrimental effect on OS").

and platelet counts, with Pepaxto is consistent with the known toxic effects of melphalan on the bone marrow, which produces these cells.[64]

As part of its explanation for the observed dissociation of effects between PFS and OS (following the reanalysis including the 29 individuals with unconfirmed progression), Oncopeptides argues that immunomodulatory drugs such as pomalidomide do not show a correlation between PFS and OS.[65] This argument does not appear to be supported by the multiple myeloma literature or real world observations, which indicate a reasonable correlation between PFS and real-world OS in multiple myeloma following the introduction of immunomodulatory agents into the standard of care.[66] Additionally, as discussed at the Advisory Committee meeting, [67] this argument should not apply to OCEAN in which OS was measured in the two arms and indicated a detrimental effect of MelDex for OS.

An alternative explanation for the finding of a modest PFS benefit on reanalysis along with the OS detriment is that Pepaxto interfered with the effective administration of subsequent lines of chemotherapy because of its hematologic toxicity. This latter hypothesis is indeed supported by the observation that the MelDex caused more grade 3/4 hematologic toxicity than PomDex. This proposed explanation is also consistent with published literature on the effect of melphalan and is specifically why melphalan, an agent also associated with an increased risk of acute leukemia, is avoided in individuals who might ultimately be candidates for autologous HSCT, as it can adversely affect stem cell mobilization.[68]

In general, FDA considers post-hoc analyses of clinical data of the type offered by Oncopeptides to be sufficient only for generating hypotheses suitable for testing in subsequent clinical trials.[69] Therefore, even if I found such post-hoc analyses to be persuasive, I would consider them inadequate from a scientific perspective to verify the clinical benefit of Pepaxto for the labeled indication and maintain its approval.[70] For the reasons detailed above, however, I believe there

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[64] *See, e.g.*, Barlogie B. Advances in therapy of multiple myeloma: lessons from acute leukemia. Clin Cancer Res. 1997 Dec;3(12 Pt 2):2605-13. PMID: 10068262; Knudsen LM, Rasmussen T, Jensen L, Johnsen HE. Reduced bone marrow stem cell pool and progenitor mobilisation in multiple myeloma after melphalan treatment. Med Oncol. 1999 Dec;16(4):245-54. doi: 10.1007/BF02785870. PMID: 10618687.

[65] *See, e.g.*, Oncopeptides October Response at 2-3.

[66] *See, e.g.*, Richter J, Singh E, Rice MS. Real-World Multiple Myeloma Treatment Patterns By Patient Characteristics and Outcomes in the United States. Blood 2021; 138:4114-4116.

[67] *See, e.g.*, Dr. Gormley's comments that "when we make any assessment for a product, there's a requirement that there's demonstration of safety and effectiveness. So we don't look in an isolated fashion at just one endpoint; we look at the entire clinical picture of the data that's presented. So as stated previously, we would never rely on a positive PFS value if there was evidence of detriment of overall survival. And when we've used subgroups in the past, the ITT result has been positive. We have not and do not use subgroup analyses to find a population that has a favorable benefit when the overall is negative." ODAC Transcript at 189.

[68] *See, e.g.*, Jonsdottir G, Björkholm M, Turesson I, Hultcrantz M, Diamond B, Porwit A, Landgren O, Kristinsson SY. Cumulative exposure to melphalan chemotherapy and subsequent risk of developing acute myeloid leukemia and myelodysplastic syndromes in patients with multiple myeloma. Eur J Haematol. 2021 Aug;107(2):275-282. doi: 10.1111/ejh.13650. Epub 2021 May 28. PMID: 33966293; Knudsen et al., 1999, *op cit*.

[69] *See, e.g.*, U.S. Food and Drug Administration. E8(R1) General Considerations for Clinical Studies: Guidance for Industry (April 2022), available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e8r1-general-considerations-clinical-studies.

[70] This point was also noted by the Chairperson of the ODAC. Dr. Jorge Garcia, MD, FACP, Chief, Division of Solid Tumor Oncology, Case Western University, made the following comment during the September 2022 ODAC

are alternative explanations for the findings generated by Oncopeptides' post-hoc analyses and thus do not find those analyses persuasive relative to the clinical benefit of Pepaxto in the patient population for which the drug is intended. Therefore, after reviewing the evidence, with a focus on the pre-specified statistical analysis plan and the evidence generated under that review, I conclude that OCEAN failed to show statistical superiority in PFS or OS and thus failed to verify Pepaxto's clinical benefit. Thus, the first independent ground for withdrawal has been met.

Oncopeptides' remaining arguments regarding whether OCEAN confirmed the clinical benefit of Pepaxto do not directly address my finding, or CDER's finding in the proposal for withdrawal, that OCEAN did not verify the clinical benefit of Pepaxto as currently approved. Rather, Oncopeptides argues that OCEAN verified Pepaxto's clinical benefit with respect to certain subpopulations. In my view, these arguments raise policy issues related to the agency's discretion under section 506(c)(3) to maintain a drug on the market even if a statutory ground for withdrawal has been satisfied. I thus address those arguments below in a section devoted to such policy issues.

ii. The Available Evidence Demonstrates that Pepaxto Is Not Shown to Be Safe or Effective Under Its Conditions of Use

A product's accelerated approval is subject to withdrawal if, among other reasons, "other evidence demonstrates that the [approved] product is not shown to be safe or effective under the conditions of use."[71] Here, the evidence demonstrates that Pepaxto is not shown to be safe or effective for its approved use.[72]

I have discussed in the preceding section how the efficacy data from OCEAN failed to confirm the expected clinical benefit of Pepaxto. OCEAN also yielded important other evidence. In broad terms:

- safety data from OCEAN presents cause for concern,
- the results of HORIZON and OCEAN together fall short of showing Pepaxto is safe and effective for its approved use, and
- the evidence now available does not indicate a favorable risk-benefit ratio for patients with RRMM who have received at least four prior lines of therapy and whose disease is triple-class refractory.

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meeting: "I am not a multiple my[e]loma expert; I'm a drug developer in GU oncology. But when I see the data, after I review the docket, based upon the FDA presentation, based upon the applicant presentation, it's hard for me to understand how we use subset analysis to try to tease out true benefit for a treatment. That goes against everything that I have actually been taught for statistics for clinical trial design and for drug development." ODAC Transcript at 184.

[71] Section 506(c)(3)(A)(iii) of the FD&C Act.

[72] Pepaxto's approved indication is for the treatment of adult patients with RRMM who have received at least four prior lines of therapy and whose disease is triple-class refractory, as stated in the Pepaxto prescribing information, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214383s000lbl.pdf. "PEPAXTO is an alkylating drug indicated in combination with dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody."

I discuss the evidence in greater detail below.

First and foremost, the OCEAN results showed a potential decline in OS and higher rate of death for MelDex as compared PomDex. Specifically, at the time of primary PFS analysis, "the observed median OS was 5.3 months shorter in the [MelDex] arm compared to that of the PomDex arm (19.7 months vs. 25.0 months; HR 1.104 (95% CI: 0.846, 1.441)). There were higher rates of death in the [MelDex] arm (117/248; 47.6%) than in the PomDex arm (108/249; 43.4%)."[73] As CDER explained in its decisional memorandum supporting withdrawal,

> The five-month lower median OS and increased deaths in the [MelDex] arm from the randomized Phase 3 OCEAN trial suggests a potential for harm for patients treated with MelDex. Although not statistically significant, the OS results suggest an increased risk of death in patients receiving MelDex compared to PomDex, raising the potential for harm in patients treated with melphalan flufenamide.[74]

Moreover, while the topline results on OS were not statistically significant, they persisted across more extended lengths of follow-up and across multiple subgroups. More precisely, the reduction in OS appeared in analyses with a median follow-up duration of nearly three years. In CDER's words:

> OS results updated (data cut-off date February 2, 2022) to include a median follow-up duration of nearly three years (31.8 months in MelDex and 29.8 months in PomDex) were consistent with the initial OS results with a HR >1; HR 1.14 (95% CI: 0.91, 1.42). The rates of death in the ITT population with extended follow-up were also higher in the MelDex arm compared to the PomDex arm; 65.9% (162/246) and 59% (147/249) respectively.[75]

In terms of subgroups, as CDER noted in its proposal to withdraw, "the concerning [overall survival] result with an HR greater than 1 was also noted in multiple subgroups evaluated in OCEAN."[76] Although Oncopeptides has advanced multiple alterative explanations of this OS and death rate data,[77] CDER has convincingly highlighted flaws in their arguments, ranging from the scientific limitations of subgroup analyses and failure to control for multiplicity to confidence intervals crossing 1 in even the subgroups Oncopeptides identified.[78] As CDER also noted:

> There were higher rates of deaths in the MelDex arm (47.6%) compared to the PomDex arm (43.4%) in the intention-to-treat (ITT) population. The higher [Pepaxto] death rate was most notable in events that occurred beyond 60 days after the last dose; 31% of deaths in the MelDex arm occurred beyond 60 days compared to 25% in the PomDex arm. This raises concerns that treatment with

[73] CDER Decisional Memorandum at 11.
[74] *Id.* at 12.
[75] *Id.* at 11.
[76] *Id.* at 10. Figure 1 from page 11 is reproduced below.
[77] *See generally* Oncopeptides Written Appeal; Oncopeptides PowerPoint, *e.g*, at 2-4.
[78] *See, e.g.*, CDER Decisional Memorandum at 12; CDER PowerPoint at 8-21; CDER Response to October 4, 2023, Request for Information (CDER October Response) at 3-6.

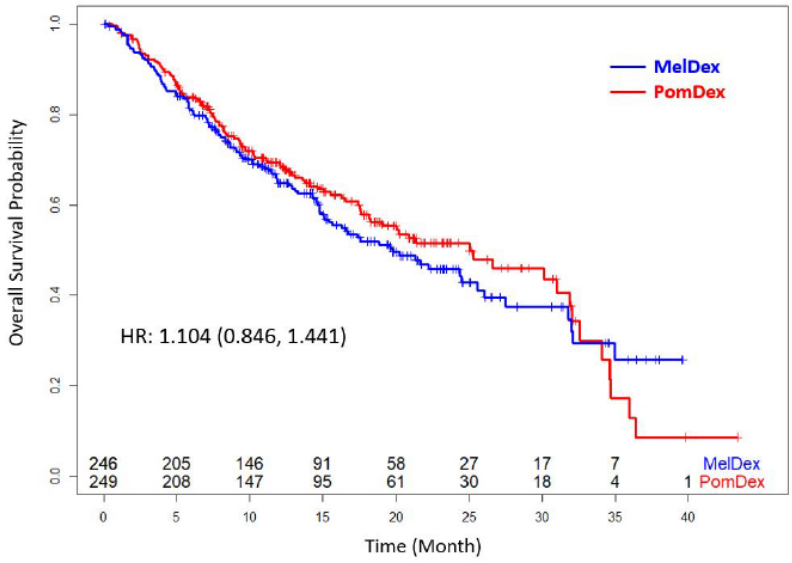
MelDex may impact the ability to tolerate subsequent lines of therapy. Therefore, although the rate of receipt of subsequent therapies was similar across the arms, patients may not be able to tolerate the other therapies due to their treatment with MelDex.[79]

Thus, the OS and death rate results from OCEAN remain cause for concern. Advisory Committee members shared this concern. As noted by Dr. Garcia, Chairperson of the ODAC, "every single point, data, that I see here, really leads me to believe, without confidence, even if the PFS is real, I cannot tell a patient I'm going to actually be able to put you in a therapy that may delay your progression free survival, but it may have the chance of actually harming you and cause detrimental outcome by shortening your survival."[80]

These key OS results are presented in Figure 1 and Figure 2 below.

Figure 1. Kaplan-Meier Curve OS Results – OCEAN Trial, Data Cut-Off date February 3, 2021

Figure 1 Kaplan-Meier Curve OS Results- OCEAN Trial

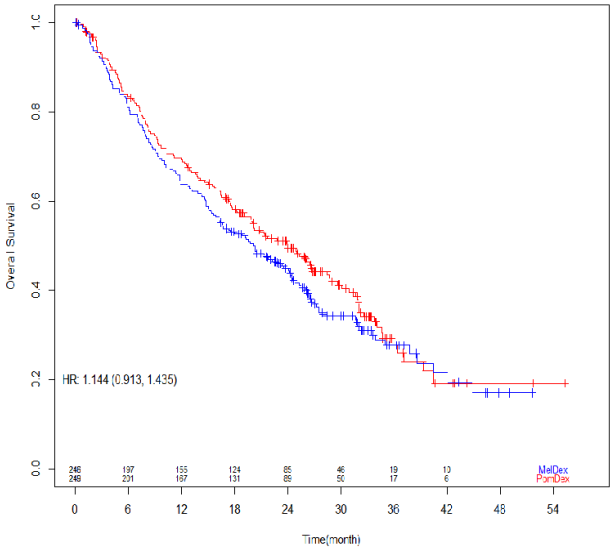


FDA analysis; Data Cut-off date February 3, 2021

Source: Figure 1 from CDER Decisional Memorandum at 11.

[79] CDER September Response at 5.
[80] ODAC Transcript at 185.

Figure 2. Kaplan-Meier Curve for OS (ITT Population) Data Cut-Off date February 2, 2022



Source: FDA Analysis, Figure 5 presented at ODAC September 22, 2022.

Safety data on measures beyond OS and death rate are also troubling. For example, as CDER explained in its discussion of Pepaxto's safety profile:

> There were higher rates of severe adverse events (Grade 3-4) in the MelDex arm (90%) compared to the control arm (74%). There was a higher rate of Grade 3-4 thrombocytopenia in the MelDex arm (81%) compared to the PomDex arm (14%). These high rates of thrombocytopenia led to higher rates of all grade (16% vs. 6.5%) and Grade 3-4 hemorrhage (2.2% vs. 0.4%) in the MelDex arm compared to the PomDex arm.[81]

In addition to thrombocytopenia, there were also higher rates of Grade 3-4 neutropenia and anemia) with MelDex compared to PomDex (56% and 42% versus 41% and 18%, respectively).[82] Furthermore:

> A higher rate of dose modifications was observed in the MelDex arm compared to PomDex control arm indicative of significant safety and tolerability concerns with MelDex. In study OP-103, a total of 78% of patients experienced at least one adverse event leading to dose modification, 60% of patients experienced at least one adverse event leading to dose delay, 47% of patients experienced at least one adverse event leading to dose reduction, and 26% of patients experienced at least one adverse event leading to drug discontinuation. These rates were substantially

[81] CDER September Response at 6-7.
[82] *See generally* CDER Decisional Memorandum at 7. *See also* CDER PowerPoint at 15.

higher in the MelDex arm as compared to the PomDex arm; this indicates that the 40 mg dose may not be appropriate for the indicated population.[83]

As previously described, the results ultimately led CDER to put a partial clinical hold on Pepaxto-related clinical trials and issue a public safety alert. CDER has also noted that in a nonclinical, non-human study, melphalan flufenamide was also associated with an increased risk of mortality compared to melphalan at dosages higher than the recommended dosage.[84] In short, safety measures showed higher rates of certain adverse events and higher rates of dose modifications needed for patients taking the Pepaxto-containing MelDex regimen, which contribute to significant questions about the safety profile of the drug.

As described elsewhere in this decision, the now-available efficacy data, taken together, falls short of demonstrating efficacy for the approved use.[85] Overall, OCEAN indicated potentially shorter OS, potentially higher risk of death, higher rates of certain adverse events, and higher rates of dose modifications needed for patients taking the Pepaxto-containing MelDex regimen. For both safety and efficacy, the OCEAN results are particularly noteworthy because OCEAN had a comparator arm, unlike the single-arm HORIZON study that supported the accelerated approval in 2021.

Based on my review of the record, I find that the available evidence demonstrates that Pepaxto is not shown to be safe and effective for its conditions of use, and therefore, an additional ground for withdrawal has been met. Echoing the concerns raised at the ODAC meeting, and those described by CDER, these safety concerns have serious implications for patients. Pepaxto's potential toxicity could lead to a patient's lesser ability to tolerate future treatments, and therefore, have a lower OS rate due to this course of treatment. Even if the observation of a modest improvement in PFS were to be true, the finding of a detriment in OS outweighs this finding because patients generally place a higher value on OS than PFS.[86]

Oncopeptides is not able to adequately address the concerning OS findings in the context of the original study design and tries to redirect the focus to post-hoc PFS analyses.[87] Oncopeptides states that "the heterogenous pomalidomide treatment effect in terms of survival invalidates any scientific interpretation of the ITT OS HR result in OP-103 since this pomalidomide

[83] CDER September Response at 6.
[84] *See* CDER Decisional Memorandum at 7.
[85] *See, e.g.*, the discussion of PFS and OS measures in the section of this document on failure to confirm expected benefit, and the discussion on whether Pepaxto should remain on the market while additional data are generated.
[86] *See also* CDER September Response at 4-5 where CDER states, "A modest improvement in PFS in the setting of substantial toxicities may result in OS decrement. Even non-fatal toxicities, by limiting the ability to receive adequate exposure of the investigational treatment or subsequent therapies, can result in OS decrement in the overall population. Conversely, significant improvement in OS has been demonstrated with minimal or no improvement in PFS or ORR in some trials. As such, FDA relies on an OS analysis, even if descriptive, to assure there is no decrement in OS when PFS or other early endpoints are the primary endpoint. This principle is articulated in a position paper by Amatya et al., referenced by the Sponsor. The paper states that '[a]n anti-cancer therapy that prolongs PFS is not considered safe and effective if the therapy results in a detrimental effect on OS.'" (citing to Amatya et al., "Subgroup Analyses in Oncology Trials: Regulatory Considerations and Case Examples," *Clinical Cancer Research*, pp. 5753-5756, 2021).
[87] *See, e.g.,* Oncopeptides PowerPoint.

phenomenon was not accounted for in the study design, in accordance with ICH E9 guideline."[88] However, Oncopeptides cannot now discard OCEAN's results merely because they did not bear out data to support Pepaxto's safety and effectiveness under the approved conditions of use. This is particularly true since the hematologic toxicity of melphalan, the primary metabolite of their product, is well understood, and an understanding of this toxicity in other settings could reasonably support an alternative explanation for the decrement in OS.

In sum, I conclude that the available evidence demonstrates that Pepaxto is not shown to be safe or effective for its approved use and that a second ground for withdrawal is met.

Meeting either of these two grounds would be sufficient for FDA to withdraw approval of Pepaxto.[89] Thus, it is not legally required for me to discuss Oncopeptides' arguments about subpopulations or generating additional data in order for FDA to withdraw Pepaxto's approval. I do so below in the interest of completeness and transparency.

b. Oncopeptides' Additional Policy Arguments on Appeal that Pepaxto Should Remain on the Market Are Unpersuasive

Oncopeptides crystallized its main positions in the October 2, 2023, meeting, where it argued that (1) Pepaxto should remain on the market while further studies are conducted and/or (2) Pepaxto should remain on the market with a narrower indication. The former argument, that Pepaxto should remain on the market while further studies are conducted, follows a similar argument made by Genentech, Inc., in response to CDER's proposal to withdraw accelerated approval for Avastin's breast cancer indication.[90] Specifically, Genentech argued that Avastin should retain its breast cancer indication so long as "there is uncertainty about whether Avastin may confer clinical benefit."[91] In that decision, FDA explained that:

> This is not what Congress intended in establishing the accelerated approval program, and it is not consistent with the protection of public health. Before FDA may grant accelerated approval, it must make a risk-benefit determination on the basis of evidence provided by the applicant. The labeling that is approved reflects what is known at the time, and it is conditioned on confirmatory studies to verify benefit. When those studies are received, FDA must review them and determine whether, in light of the new information they provide, the risk-benefit determination still favors approval. Where, as here, the studies do not verify the clinical benefit, and the available evidence does not show the drug to be safe and effective, in the absence of unusual circumstances the accelerated approval should not be continued.[92]

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[88] Oncopeptides Written Appeal at 21; *see also* Oncopeptides Reply at 6.
[89] *See* section 506(c)(3)(B) of the FD&C Act.
[90] *See* Decision of the Commissioner on the Proposal to Withdraw Approval for the Breast Cancer Indication for Avastin (Bevacizumab) (Avastin Decision), at 8, dated November 11, 2011. Available at Docket No. FDA-2010-N-0621, document number 0544.
[91] Avastin Decision at 53.
[92] Avastin Decision at 53-54.

Consistent with this precedent, and for the reasons described below, I find Oncopeptides' policy arguments along these same lines to be unpersuasive. Specifically, I conclude that it would not be in the interest of public health to exercise the agency's discretion under section 506(c)(3) of the FD&C Act to decline to withdraw approval of Pepaxto even though Pepaxto is subject to withdrawal under two separate statutory grounds and the benefit-risk balance favors withdrawal.

i. Pepaxto Should Not Remain on the Market While Additional Data Are Generated

As noted above, Oncopeptides argues that the agency should exercise its discretion under section 506(c)(3) of the FD&C Act to decline to withdraw approval of Pepaxto from the market while Oncopeptides collects additional data regarding the drug's clinical benefit. But I have concluded that doing so is not in the interest of public health.

As explained above, the results of OCEAN disclosed a concerning safety finding for Pepaxto—namely a potential increased risk of death. Even standing alone, this safety finding outweighs many of Oncopeptides' arguments regarding the benefits to public health if FDA declined to withdraw approval of Pepaxto.

Furthermore, OCEAN not only failed to verify the clinical benefit of Pepaxto but also, as determined above, provided information the agency did not have at the time of approval with respect to safety and effectiveness for the drug's intended use. My assessment of the safety and effectiveness of Pepaxto hinges largely on balancing the benefits and risks of the drug in light of both HORIZON and OCEAN. In short, taken together, HORIZON and OCEAN do not support that Pepaxto's benefits outweigh its risks. Ignoring the current data and allowing time for "more studies on the chance that they might confirm benefit . . . would be inconsistent with the statute and protection of public health."[93] As further described in the Commissioner's decision in the Avastin proceeding:

> Withdrawal here is the essential counterpart to accelerated approval. When the accelerated approval pathway was established, it was done with full recognition of the risk that drugs might be approved and later found not to confer clinical benefits to patients. FDA deemed this a risk worth taking for life-threatening illnesses in need of additional therapies, but also found it essential to mitigate that risk by providing for follow-up studies and withdrawal when benefit is not confirmed. . . When follow up studies fail to confirm benefit, it is essential that approval be withdrawn in order to protect patients.[94]

Separately, there are several alternative regimens available for the treatment of patients with triple-class refractory multiple myeloma using FDA-approved agents.[95] These include combination chemotherapy regimens and single agent products having received traditional

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[93] *See* Avastin Decision at 54.
[94] Avastin Decision at 55 (citing to 57 Fed. Reg. 13234, 13238 (April 15, 1992)).
[95] *See* CDER Powerpoint at 22-23. *See also* Stalker ME, Mark TM. Clinical Management of Triple-Class Refractory Multiple Myeloma: A Review of Current Strategies and Emerging Therapies. Curr Oncol. 2022 Jun 23;29(7):4464-4477. doi: 10.3390/curroncol29070355.

approval, including the chimeric antigen receptor T cell (CAR T cell) therapies idecabtagene vicleucel and ciltacabtagene autoleucel. Additionally, Selinexor, an XPO-1 inhibitor, and Teclistamab, a bispecific monoclonal antibody, have received accelerated approval by FDA for use in this setting.

Given the other treatment options that are currently available for triple-class refractory disease, which have been determined to be safe and effective for their indications, Oncopeptides' arguments that Pepaxto should remain on the market while additional data are gathered are even less persuasive. In the current situation, the patients for whom Pepaxto is indicated potentially have other options for non-investigational treatments that have been found to have the necessary benefit-risk ratio to support their approvals.

FDA is supportive of sponsors trying to gain more information about drug products, especially those treating an unmet need related to a serious of life-threatening condition, but not at the expense of patient health. If Oncopeptides believes that there is a route forward for Pepaxto, as further discussed below, it can later work with CDER to complete clinical research studies that explore whether there are data to support a different indication.

In light of the foregoing, I decline to exercise the agency's discretion to allow Pepaxto to remain on the market on the basis of Oncopeptides' arguments that I should do so to allow it to conduct additional clinical studies to verify clinical benefit or to otherwise establish the safety and effectiveness of the drug.

ii. Oncopeptides' Policy Arguments Regarding a Narrower Indication Are Unpersuasive

Oncopeptides further argues that FDA should exercise its discretion under section 506(c)(3) of the FD&C Act to maintain approval of Pepaxto because, in its view, OCEAN suggests clinical benefit for a subgroup of study subjects.[96] Oncopeptides has argued that its post-hoc subgroup analyses indicate that those individuals who did not undergo autologous HSCT and those who were aged 75 years and older appeared to benefit the most from MelDex and that both of these groups—particularly those under the age of 75 who did not undergo autologous HSCT—had an improved PFS and OS, even if not statistically significant.[97] Oncopeptides thus effectively maintains that Pepaxto should remain on the market with a narrower indication, i.e., one reflecting an intent for use in patients matching the criteria used to identify a subgroup in its post-hoc analyses.

As noted above with respect to this argument, whether Pepaxto is safe and effective for a narrower indication is outside the scope of the statutory basis for withdrawing accelerated approval under section 506(c)(3)(A). Indeed, even as a policy matter, the question before me is not whether Pepaxto has been shown to be safe and effective for a narrower indication than reflected in the approved labeling but whether Pepaxto should remain on the market as currently approved and labeled. For reasons stated above, I have determined that declining to withdraw the approval of Pepaxto as it is currently indicated and labeled is not in the interest of public

[96] *See, e.g.,* Oncopeptides PowerPoint at 51.
[97] *See, e.g.*, Oncopeptides Reply at 26.

health or consistent with FDA's regulatory mission. If Oncopeptides believes that it has substantial evidence of the safety and effectiveness of Pepaxto for a narrower indication, it should work with CDER to seek approval of that narrower indication under section 505 or 506 and the implementing regulations.

However, to specifically address the sponsor's submissions, I find the post-hoc analyses provided by Oncopeptides with respect to Pepaxto's safety and effectiveness for a narrower indication to be unpersuasive. As noted previously, from the perspective of a formal statistical analysis of a randomized, controlled clinical trial, post-hoc analyses of the type offered by Oncopeptides in a relatively small subpopulation of patients enrolled in a clinical trial are, at best, only hypothesis-generating. With that caveat in mind, I find that the specific post-hoc analyses submitted by Oncopeptides do not support its interpretation of the data from OCEAN in terms of Pepaxto's potential effect on PFS and OS in the identified subgroup to support a regulatory action.

A review of the data from OCEAN sheds additional light on the Oncopeptides' proposed findings with respect to MelDex's effectiveness in a subgroup highlighted during the October 2 meeting. Following the October 2, 2023, meeting, at my request, Oncopeptides provided a breakdown of the OCEAN data for those individuals who had not undergone autologous HSCT by age groups: less than age 75 versus 75 years and older.[98] This data revealed notable differences in the population aged 75 years and older randomized to the MelDex and PomDex arms. Specifically, although the post-hoc analysis indicated a 4.33-month improvement in PFS and a 3.87-month improvement in OS on the MelDex arm, review of demographic and historical data revealed that the 33 individuals in this age category randomized to MelDex were treated a median 3.2 years after diagnosis following a median of 2 prior lines of chemotherapy, whereas the 37 individuals randomized to the PomDex were treated a median 4.0 years after diagnosis following a median of 3 prior lines of chemotherapy (Table 2). These data indicate that those randomized to the PomDex arm in this subgroup had more advanced disease progression than those randomized to the MelDex arm. Additionally, patient history data indicated that a greater number these of individuals randomized to PomDex were melphalan refractory, had poor-risk cytogenetics, and had notably decreased renal function, all consistent with more advanced disease. Based on historical data available in the literature, the approximately 4-month differences in PFS and OS reported by Oncopeptides could readily be explained by treatment of more individuals with MelDex in the third-line versus the fourth-line treatment setting of those in the PomDex arm.[99]

[98] *See generally* Oncopeptides October Response.

[99] *See, e.g.*,Verelst SGR, Blommestein HM, De Groot S, Gonzalez-McQuire S, DeCosta L, de Raad JB, Uyl-de Groot CA, Sonneveld P. Long-term Outcomes in Patients With Multiple Myeloma: A Retrospective Analysis of the Dutch Population-based HAematological Registry for Observational Studies (PHAROS). Hemasphere. 2018 May 4;2(4):e45. doi: 10.1097/HS9.0000000000000045. PMID: 31723779; PMCID: PMC6746001.

Table 2. OCEAN Data for Individuals 75 years of age and older with no prior ASCT

(from data submitted 10/4/2023 and 10/18/2023)

Parameter	MelDex (N=33)	PomDex (N=37)
Median age, years (range)	77 (75-91)	79 (75-87)
Male (%)	16 (48)	22 (59)
Race, white (%)	30 (90.9)	37 (100)
Race, unknown (%)	3 (9.1)	0 (0)
Region, Europe (%)	32 (97.0)	31 (83.8)
Region, US (%)	1 (3.0)	3 (8.1)
Region, rest of world (%)	0 (0)	3 (8.1)
Years from diagnosis, median (ranges)	3.2 (0.5-7.8)	4.0 (0.6-25.2)
Prior treatment regimens, median (ranges)	2 (2-4)	3 (2-4)
Previous stem cell transplant, n (%)	0 (0)	0 (0)
Refractory status, lenalidomide, n (%)	33 (100)	37 (100)
Refractory status, pomalidomide, n (%)	0 (0)	0 (0)
Refractory status, alkylator, n (%)	9 (27)	11 (30)
Melphalan exposed, n (%)	18 (55)	20 (54)
Melphalan refractory, n (%)	2 (6)	7 (19)
High risk cytogenetics, n (%)	9 (27)	17 (46)
Creatinine clearance < 60, n (%)	13 (41)	24 (65)
Overall response rate, % (95% CI)	45.5 (28.1-63.6) (p-0.0034)	13.5 (4.5-28.8)
Duration of response, months (95% CI)	17.31 (5.78-NA) HR: 0.356 (p=0.2449)	11.01 (6.47-NA)
Progression free survival, months (95% CI)	9.26 (4.96-NA) HR: 0.446 (p=0.0063)	4.93 (2.43-6.64)
Overall survival, months (95% CI)	20.30 (12.88-26.68) HR: 0.881 (p=0.6469)	16.43 (6.47-30.85)

Sources: Oncopeptides PowerPoint at 54-56 (supplemental slides submitted 10/4); Oncopeptides October Response at 10-13.

The finding of a randomization imbalance in these individuals aged 75 and older favoring MelDex once again illustrates the danger of post-hoc subgroup analyses. The PomDex regimen was given to a group of individuals who were on average sicker, treated with an additional prior regimen, and about 8 months more advanced in their disease trajectory, which could explain any potential benefit in PFS and OS observed in this post-hoc subgroup. The finding in this post-hoc subgroup also tends to undermine other post-hoc analysis arguments from the randomized clinical trial, including the assertion of potential clinical benefit of Pepaxto in those younger than age 75 who had not received autologous HSCT. Beyond those just described, other potential confounding factors may have resulted in Oncopeptides' finding in younger individuals in the post-hoc analysis that was conducted.

Given the foregoing analysis, I cannot support Pepaxto's staying on the market with a narrowed indication. Allowing Pepaxto to remain on the market with a narrower indication would convey that FDA believes that there is substantial evidence of effectiveness for that indication and that

the benefit-risk ratio supports continued approval, which is not reflective of the data before me. Furthermore, I cannot overlook the safety finding of potentially reduced survival with Pepaxto, which—based on what is known regarding the hematologic toxicity profile of the drug melphalan (an active metabolite of Pepaxto)—must be taken seriously and requires further explanation. If FDA were to leave Pepaxto on the market with a narrower indication, the agency would potentially place patients at a greater risk for harm, and such a decision would undermine the agency's mission to protect public health.

In short, I do not believe that Pepaxto has been shown to be safe and effective according to the agency's standards, either in the currently indicated population, or in the more limited population(s) proposed by Oncopeptides.

iii. FDA's Consideration of Whether Pepaxto's Approval Should be Withdrawn is Independent from Any Determinations Made by the European Medicines Agency (EMA) or other Regulatory Bodies

Oncopeptides has pointed to the European Medicines Agency, which, rather than withdrawing Pepaxti (the EMA-marketed name for Pepaxto), was contemplating expanding its labeling to include treatment as a third-line or later chemotherapy for multiple myeloma.[100] I note that the European labeling for Pepaxti states that it is indicated "in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least three prior lines of therapies, whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on or after the last therapy" and that "For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation."[101] By contrast, the indication in the United States is "for use in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma [RRMM] who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory drug, and one CD38-directed monoclonal antibody (triple class refractory)."[102] Beyond these differing indications, regulatory frameworks vary between governments, and my determination in this matter is based on the application of the FDA statutory framework to the evidence included in the record before me. Therefore, while it may lead to varying determinations between the EMA and FDA, I can only address the proposed withdrawal within the context of FDA's standards, as the agency did in the Avastin proceeding.[103] As explained above, under FDA's statutory framework, I find that

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[100] Oncopeptides Reply at 1-2; *See also* https://www.ema.europa.eu/en/medicines/human/variation/pepaxti (describing the 14 September 2023 recommendation of the Committee for Medicinal Products for Human Use on Pepaxti); https://www.ema.europa.eu/en/medicines/human/EPAR/pepaxti#ema (listing an indication that is not expanded)" (Last updated 29/11/2023). More recently, on December 15, 2023, Oncopeptides noted that it would be withdrawing its request to extend its indication and would be working with EMA and the European Commission to remove the extended indication from the labeling. *See* https://oncopeptides.com/en/media/press-releases/update-on-the-type-ii-application-process/.

[101] *See* https://www.ema.europa.eu/en/medicines/human/EPAR/pepaxti#ema (Last updated 29/11/2023).

[102] *See* Pepaxto prescribing information, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214383s000lbl.pdf.

[103] *See* Avastin Decision at 8.

the two separate, independent grounds for withdrawal have been met in this matter and that other policy considerations weigh in favor of withdrawal. Therefore, withdrawal is appropriate.

c. Summary of Public Comments

FDA received four comments related to CDER's proposal to withdraw approval of Pepaxto. One comment came from the International Myeloma Foundation (IMF); one from a private company, Arnold Ventures (AV); and two from individuals.

The IMF expressed support for keeping Pepaxto on the market due to the limited number of available treatment options for those patients in need of third-line and later therapies. IMF stated that "it is very reasonable to limit approval to a subgroup demonstrating excellent efficacy with the proviso that a new confirmatory study be performed to adjust the indication."

AV described itself as a "philanthropy dedicated to investing in evidence-based policy solutions that maximize opportunity and minimize injustice." AV supported the proposal to withdraw approval "given the totality of evidence, lack of clinical benefits for patients, and increased risk of adverse events." AV stated that withdrawal ensures patients are not using ineffective drugs and allows "health care dollars" to be directed to other products that have more evidence documenting safety and efficacy.

The two comments from individuals expressed support for keeping Pepaxto on the market. One was submitted by a multiple myeloma patient and founder of HealthTree Foundation for Multiple Myeloma. She stated that, while Pepaxto did not meet its primary endpoint in OCEAN, there were positive findings that FDA should consider, particularly for patients who have not been previously exposed to melflufen. She maintained that Pepaxto should remain on the market to allow patients to determine, on an individual basis, whether Pepaxto's benefits are worth the potential risks. The other individual comment echoed that melflufen may be valuable in certain situations and stated that Pepaxto fulfills an unmet need for "well-selected patients" and should be available for patients with little or no other options.

The foregoing analysis discussing Oncopeptides' arguments addresses the public comments. As explained above, the evidence provided does not show that Pepaxto would be both safe and effective for a narrower population. If FDA were to leave Pepaxto on the market with a narrower indication, FDA would potentially place patients at a greater risk for harm, and such a decision would undermine the agency's mission to protect public health. If, at a later time, Oncopeptides has sufficient evidence to support a narrower indication or wishes to begin a new clinical trial involving Pepaxto, Oncopeptides may engage with CDER to determine a viable path forward.

4. Conclusion

I very much recognize that multiple myeloma is a serious disease and share the desire to see more effective treatment options available. As highlighted above, options are currently available for triple-class refractory multiple myeloma patients using FDA-approved products, and at this time all these options currently appear to have a more favorable benefit-risk profile than Pepaxto.

FDA is always striving to approve drugs that treat serious conditions and fill an unmet medical need. However, the desire to have more available treatment options cannot be the sole driving consideration, especially when the data show that Pepaxto is lacking in evidence of both effectiveness and safety. While I share the desire to have as many drug products as possible available to those suffering from multiple myeloma, exposing patients to this treatment that is no longer shown to be effective for its intended use and that has known safety concerns, particularly an increased potential for death, is not a viable solution. I thus agree with the ODAC members who acknowledged that there is a huge need in this heavily treated patient population but that we should not use drugs that cause harm.[104]

I recognize that the decision to withdraw Pepaxto might be upsetting for patients who have exhausted all their options among drugs approved for their condition, for their loved ones and providers as well. However, I also believe that patients deserve FDA-approved treatments that are safe and effective. I share the disappointment that the randomized trial designed to confirm Pepaxto's clinical benefit instead failed to confirm it. My hope is that today's decision ultimately helps protect patients, underscores the standards for what it means for a product to be FDA approved, and helps direct efforts and resources towards areas of future benefit.

Based on my review of the record, including relevant scientific literature and the discussion with CDER and Oncopeptides described above, I find that the grounds for withdrawing approval have been met and that it is appropriate to withdraw approval of Pepaxto. CDER should take all necessary actions to implement this decision.

Peter Marks, M.D., Ph.D.
Director
Center for Biologics Evaluation
and Research

[104] *See* Final ODAC Summary Minutes at 9.