December 18, 2024

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Sent via email to: scott@lassmanfdalaw.com

Re: Citizen Petition [Docket Number: FDA- 2020-P-1689]

Dear Mr. Lassman:

This letter responds to the Citizen Petition dated July 20, 2020 (Original Petition) and the Supplemental Information in Further Support of Citizen Petition (Supplement) dated December 5, 2022 (collectively, "Petition"), which you filed with the Food and Drug Administration (FDA, the Agency, or we) on behalf of a client under docket number FDA-2020-P-1689 regarding the Biologics License Application (BLA) for remestemcel-L-rknd (RYONCIL).

This letter responds to the Petition in full. We have reviewed these filings and other relevant information available to the Agency. In accordance with Title 21 CFR (Code of Federal Regulations) 10.30(e)(3), and for the reasons stated below, we deny the Petition's request that FDA refuse to issue a license to RYONCIL until certain conditions are met. In addition, we rule as moot the Petition's request to provide a copy of this Citizen Petition to members of any Advisory Committee scheduled to discuss the BLA for RYONCIL.

Here is an outline of our response:

I. PETITIONER'S REQUEST

Petitioner requests FDA "to take certain actions with respect to Biologics License Application ('BLA') 125706, for remestemcel-L (ex-vivo culture-expanded adult human mesenchymal stromal cells suspension for intravenous infusion), also known by the trade name RYONCIL, submitted by Mesoblast, Inc. ('Mesoblast') for treatment of pediatric patients with steroid-refractory acute graft-versus-host disease ('SR-aGVHD')."[1]

Specifically, the Petition requests FDA to:

(1) Refuse to issue a license to RYONCIL for the treatment of SR-aGVHD in pediatric patients unless and until the sponsor provides "substantial evidence" of effectiveness that consists of, at a minimum, at least one successful, pivotal clinical trial that is prospective, randomized, blinded, and uses an appropriate concurrent control; and
(2) Provide a copy of this Citizen Petition to members of any Advisory Committee scheduled to discuss the BLA for RYONCIL for the proposed indication for treatment of SR-aGVHD in pediatric patients.[2]

II. BACKGROUND

A. Remestemcel-L-rknd (RYONCIL)

Remestemcel-L-rknd, also known as remestemcel-L and by the trade name RYONCIL[3], is a cellular therapy product composed of allogeneic culture-expanded mesenchymal stromal cells (MSCs) that have been isolated from bone marrow aspirate collected from healthy human donors.

[1] Original Petition at 1.
[2] *Id.* at 2-3.
[3] In the Original Petition and Supplement, Petitioner refers to the product at issue as "remestemcel-L"; therefore, throughout the remainder of this response, FDA uses "remestemcel-L" and "RYONCIL" interchangeably to refer to the product.

In February of 2020, Mesoblast submitted a BLA seeking to market RYONCIL for the treatment of steroid-refractory acute graft-versus-host disease (SR-aGVHD) in pediatric patients. SR-aGVHD is a serious, life-threatening complication of hematopoietic stem cell transplantation (HSCT) characterized by immune-mediated damage to multiple tissues. The severity of SR-aGVHD is graded clinically by tabulating the extent of the involvement of three main target organs: the skin (the site of the most frequent and often the earliest clinical manifestation), the gastrointestinal tract (the second most common site), and the liver. SR-aGVHD is associated with a high degree of morbidity and mortality. Patients with SR-aGVHD have a dismal prognosis with an overall survival rate of only 5 to 30%; Grade IV SR-aGVHD is typically fatal.[4] There are currently no FDA-approved treatments for SR-aGVHD in children under twelve years of age.

In its initial BLA submission, Mesoblast included the results of Study MSB-GVHD001, a single-arm, multicenter study conducted in pediatric participants 2 months to 17 years of age with SR-aGVHD as the primary evidence of effectiveness to support licensure of RYONCIL for treatment of SR-aGVHD in pediatric patients. The study met its pre-specified primary endpoint, demonstrating a durable overall response rate at Day 28 (Day 28-ORR) of 70.4% (with a 95% Confidence Interval [CI]: 56.4, 82.0).

On August 13, 2020, FDA convened a meeting of FDA's Oncologic Drugs Advisory Committee (ODAC), to discuss the BLA for RYONCIL. At the conclusion of this meeting, the ODAC voted nine to one[5] that "the available data support the efficacy of remestemcel-L in pediatric patients with steroid-refractory aGVHD."[6] Subsequently, FDA's Office of Tissues and Advanced Therapies (OTAT)[7] issued a Complete Response Letter (CRL) to Mesoblast in September 2020.[8] The CRL recommended that Mesoblast conduct at least one additional randomized, controlled study to provide evidence of effectiveness. The CRL also identified

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[4] See David A. Jacobsohn et al., Acute graft versus host disease, Orphanet J Rare Dis., 2007 Sep 4, 2:35, doi: 10.1186/1750-1172-2-35; H. Joachim Deeg, How I Treat Refractory Acute GVHD, Blood, 2007 Jan 18, 109(10):4119–4126, doi: 10.1182/blood-2006-12-041889; Samantha M. Jaglowski et al., Graft-versus-Host Disease: Why Haven't We Made More Progress?, Curr Opin Hematol., 2014 Mar, ;21(2):141–147, doi: 10.1097/MOH.0000000000000026; Paul J. Martin et al., First- and Second-Line Systemic Treatment of Acute Graft-Versus-Host Disease: Recommendations of the American Society of Blood and Marrow Transplantation, Biol Blood Marrow Transplant., 2012 Apr 14, 18(8):1150–1163, doi: 10.1016/j.bbmt.2012.04.005.

[5] The vote at the meeting was recorded as eight "yes" to two "no," but, as noted in the meeting minutes, "one member who voted 'No', changed their vote due to the compelling medical information provided and nature of the unmet need in this condition." See FDA, Final Summary Minutes of the Oncologic Drugs Advisory Committee Meeting August 13, 2020 at 7, available at https://public4.pagefreezer.com/browse/FDA/04-03-2022T19:30/https:/www.fda.gov/advisory-committees/advisory-committee-calendar/august-13-2020-meeting-oncologic-drugs-advisory-committee-meeting-announcement-08132020-08132020.

[6] Although the FDA considers the recommendations of the ODAC, the final decision regarding the approval of the product is made by the FDA, and the recommendations by ODAC are non-binding.

[7] This office is now known as FDA's Office of Therapeutic Products (OTP). Therefore, we will refer to "OTP" throughout the remainder of this response.

[8] FDA will send a biologics license applicant or supplement applicant a CRL if the Agency determines that it will not approve the biologics license application or supplement in its present form. 21 CFR 601.3(a). Issuing a CRL is not a final decision on a BLA; after receiving a CRL, the applicant must either resubmit the application (addressing all deficiencies identified in the CRL) or withdraw the application (a withdrawal is without prejudice to a subsequent submission). 21 CFR 601.3(b).

certain chemistry, manufacturing, and controls (CMC) deficiencies, including deficiencies in the data and information provided to support the proposed approach to measuring product potency.[9] Following receipt of the September 2020 CRL, Mesoblast submitted a Formal Dispute Resolution Request (FDRR), asking that FDA reconsider the clinical data submitted in the BLA and find that they provide substantial evidence of effectiveness of RYONCIL for the treatment of SR-aGVHD in pediatric patients. The response to Mesoblast's FDRR explained that it would be premature to decide if Mesoblast's existing clinical data provided substantial evidence of effectiveness for the proposed indication in advance of resolving the outstanding CMC issues related to potency, which were relevant to evaluating the clinical data submitted in the BLA. However, the FDRR response indicated that FDA would be open to considering the adequacy of the clinical data in the BLA once Mesoblast had addressed the related CMC issues.

In January 2023, Mesoblast resubmitted the BLA for RYONCIL. FDA issued another CRL in August 2023, citing the need for more information to support Mesoblast's BLA submission.[10]

In July 2024, Mesoblast again resubmitted the BLA for RYONCIL, addressing the issues in the CRL received on August 1, 2023. In its July 2024 resubmission, Mesoblast provided sufficient CMC information to conclude that the investigational product for Study MSB-GVHD001 was standardized as to identity, strength, quality, purity and dosage form to give significance to the results of the investigation.[11] With this additional information, FDA carefully reconsidered Study MSB-GVHD001 and concluded that it represents an adequate and well-controlled clinical investigation that, together with other evidence in the BLA, provides substantial evidence of effectiveness. On December 18, 2024, following a thorough review of the resubmission, FDA approved Mesoblast's BLA for RYONCIL for the treatment of SR-aGVHD in pediatric patients 2 months of age and older.

B. Statutory and Regulatory Background

FDA approval of a BLA submitted under section 351(a) of the Public Health Service Act (PHS Act) (42 U.S.C.§ 262(a)) is based on a showing that the product is "safe, pure, and potent," a demonstration that the facility in which the product is manufactured, processed, packed, or held meets applicable standards, and the applicant's consent to inspection of the manufacturing facility.[12] Potency has long been interpreted to include effectiveness (21 CFR 600.3(s)). As FDA has noted in several guidance documents, FDA has also generally considered substantial evidence of effectiveness to be necessary to support licensure of a biological product under section 351(a) of the PHS Act.[13]

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[9] Mesoblast, Press Release: Mesoblast Receives Complete Response from the FDA for Biologics License Application for Steroid-Refractory Acute Graft Versus Host Disease in Children (Oct. 2, 2020), available at https://investorsmedia.mesoblast.com/static-files/1e259fcb-77ba-470c-91af-1c71e5fa32e0.

[10] Mesoblast, Press Release: Mesoblast Receives Complete Response from U.S. Food and Drug Administration for Biologics License Application for Steroid-Refractory Acute Graft Versus Host Disease in Children (Aug. 3, 2023), available at https://investorsmedia.mesoblast.com/static-files/422cd6da-a0b9-49cf-a177-7fd106f111f2.

[11] See 21 CFR 314.126(d).

[12] See section 351(a)(2)(C) of the PHS Act.

[13] In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would, with limited exceptions, consist of controlled clinical investigations as

i. Substantial Evidence of Effectiveness

Section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires an applicant to provide "substantial evidence" to establish a drug's effectiveness. The statute defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." FDA has interpreted the "substantial evidence" standard as generally requiring at least two adequate and well-controlled clinical investigations to establish effectiveness.[14] Under some circumstances, however, FDA has considered a trial that has certain characteristics to be the scientific and legal equivalent of evidence from two or more trials and to satisfy the legal requirement for substantial evidence of effectiveness.[15]

In addition, section 115(a) of Food and Drug Administration Modernization Act of 1997 (FDAMA) amended section 505(d) of the FD&C Act to provide that "[i]f [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence." This modification explicitly recognized the potential for FDA to find that one adequate and well-controlled clinical investigation with confirmatory evidence, including supportive data outside of a controlled trial, is sufficient to establish effectiveness. FDA exercises its scientific judgment to determine the nature and quantity of data and information an applicant must provide to demonstrate substantial evidence of effectiveness for a particular product.[16]

ii. Clinical Circumstances Where Additional Flexibility May Be Warranted

Although randomized superiority trials with a placebo- or active-control design generally provide the strongest evidence of effectiveness, there are circumstances where trials not using a

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defined in the provision for "adequate and well-controlled studies" for new drugs (21 CFR 314.126) (see former 21 CFR 601.25(d)(2) (2015) (revoked as no longer necessary, 81 FR 7445 (Feb. 12, 2016))). In section 123(f)) of the Food and Drug Administration Modernization Act of 1997, Congress also directed the Agency to take measures to "minimize differences in the review and approval" of products required to have approved BLAs under section 351 of the PHS Act and products required to have approved new drug applications (NDAs) under section 505(b)(1) of the FD&C Act. See also Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, at 4 (May 1998), available at https://www.fda.gov/media/71655/download ("1998 Guidance"); Guidance for Industry: Benefit-Risk Assessment for New Drug and Biological Products, at 3 (October 2023), available at https://www.fda.gov/media/152544/download ("Benefit-Risk Assessment Guidance").

[14] See 1998 Guidance at 3; *Warner-Lambert Co. V. Heckler,* 787 F. 2d 147 (3d Cir. 1986). See also Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products; Draft Guidance for Industry, at 4 (December 2019), available at https://www.fda.gov/media/133660/download ("Substantial Evidence of Effectiveness Draft Guidance"). When finalized, this draft guidance will represent FDA's current thinking on this topic.

[15] See 1998 Guidance at 12.

[16] See, e.g., 1998 Guidance at 8, 13; see also Substantial Evidence of Effectiveness Draft Guidance at 14.

placebo control, superiority design, or randomization may be acceptable to provide substantial evidence of effectiveness.[17] These circumstances include when the disease is life-threatening or severely debilitating with an unmet medical need and when the disease is rare. For a life-threatening disease, for example, without any available treatment, FDA might accept the results of adequate and well-controlled investigations with less rigorous designs, such as a historically controlled study. When evaluating trials in these circumstances, FDA will consider trial design, trial endpoints, number of trials, and statistical considerations, among other things.[18]

iii. Benefit-Risk Assessment

Because all drugs, including drugs regulated as biological products, can have adverse effects, the demonstration of a drug's safety requires a showing that the benefits of the drug outweigh its risks. As such, a benefit-risk assessment is integrated into FDA's regulatory review of marketing applications for new drugs and biological products. As FDA has noted in its guidance, "[the] benefit-risk assessment in FDA's drug regulatory context is making an informed judgment as to whether the benefits (with their uncertainties) of the drug outweigh the risks (with their uncertainties and approaches to managing risks) under the conditions of use described in the approved product labeling."[19] In the case of drugs intended to treat serious diseases for which there are few or no approved therapies, FDA has recognized that greater uncertainty or greater risks may be acceptable provided that the standard for substantial evidence of effectiveness has been met.[20]

III. DISCUSSION

A. Petitioner's Request That FDA Not Issue a License to RYONCIL Until Certain Specified Conditions Are Met Regarding a Successful Pivotal Clinical Trial

Throughout the Petition, Petitioner makes several arguments asserting that the data submitted in the BLA for RYONCIL "fail to meet the rigorous standards necessary to qualify as 'substantial evidence' of effectiveness…."[21] The Agency disagrees.

In its BLA, Mesoblast submitted the results of Study MSB-GVHD001, a single-arm, multicenter study conducted in pediatric participants 2 months to 17 years of age with SR-aGVHD. The study protocol specified study objectives, enrollment criteria, outcome measures, and an analysis plan to evaluate outcomes. Mesoblast compared the effects of RYONCIL to a historical overall response rate (ORR) benchmark of 45% at Day 28. As noted above, Study MSB-GVHD001 met its primary endpoint and demonstrated a durable Day-28 ORR of 70.4% (with a 95% Confidence Interval [CI]: 56.4, 82.0).

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[17] See Substantial Evidence of Effectiveness Draft Guidance at 3 and 14.
[18] See 21 CFR 312.80 (calling for FDA to exercise its broad scientific judgment in applying the evidentiary approval standards to drugs "intended to treat persons with life-threatening and severely debilitating diseases, especially where there is no satisfactory alternative therapy"); see also Substantial Evidence of Effectiveness Draft Guidance at 15-16.
[19] Benefit-Risk Assessment Guidance, at 3-4.
[20] *Id.* at 12.
[21] Original Petition at 1.

Substantial evidence of effectiveness is supported with *in vivo* pharmacodynamic data from biomarker analyses of participants treated with RYONCIL in Study MSB-GVHD001 and/or Study MSB-GVHD002.[22] Specifically, treatment with RYONCIL resulted in a 54% reduction of circulating CD3+CD4+CD25+HLA-DR+ T cells (which represent activated T cells). Additionally, reduction in two biomarkers released by activated T cells in aGVHD, TNFR1 (decreased by 76%) and ST2 (decreased by 72%) was observed at Day 180 compared to the baseline level. Given that aGVHD is driven by alloreactive T cells and that its pathophysiology is well understood,[23] these data provide compelling evidence of RYONCIL'S immunomodulatory effects.

Acute GVHD is a serious and potentially fatal condition that physicians do not leave untreated. In Study MSB-GVHD001, treatment with RYONCIL demonstrated durable ORR in individuals who are refractory to systemic corticosteroid therapy, the standard treatment for this condition. Taken together, as detailed in the Remestemcel-L-rknd BLA Clinical and Clinical Pharmacology Review and Evaluation (Clinical Review Memo for RYONCIL) [24], the clinical data from Study MSB-GVHD-001, an adequate and well-controlled clinical investigation, along with confirmatory evidence provided by the pharmacodynamic data, form the basis for our determination that there is substantial evidence of effectiveness of this product for treatment of SR-aGVHD in pediatric patients 2 months and older. The Agency's determination was informed by science, medicine, policy, and scientific judgment, in accordance with applicable regulatory requirements and was made after a thorough evaluation of the scientific data.

We address below the Petition's specific arguments in support of its request that FDA refuse to approve a BLA for "RYONCIL for the treatment of SR-aGVHD in pediatric patients unless and until the sponsor provides 'substantial evidence' of effectiveness that consists of, at a minimum, at least one successful, pivotal clinical trial that is prospective, randomized, blinded, and uses an appropriate concurrent control."[25]

i. Petitioner's Argument That RYONCIL's Mechanism of Action is Poorly Defined

Petitioner asserts that "[i]n remestemcel-L's case, reliance on a single-arm, historically controlled trial as the primary evidence of efficacy is inappropriate because, among other things… remestemcel-L's mechanism of action is poorly defined…."[26] Petitioner further claims "the lack of understanding regarding remestemcel-L's mechanism of action underscores the need for robust clinical data in support of efficacy."[27] FDA disagrees with these assertions. While the

[22] Study MSB-GVHD002 provided for additional follow-up of participants in Study MSB-GVHD001 through 180 days from the start of treatment with RYONCIL.
[23] Florent Malard et al., Acute graft-versus-host disease, Nat Rev Dis Primers, 2023 Jun 8;9(1):27. doi: 10.1038/s41572-023-0CI0438-1.
[24] FDA, Remestemcel-L-rknd BLA Clinical and Clinical Pharmacology Review and Evaluation (Dec. 18, 2024). This memorandum will be posted on fda.gov.
[25] Original Petition at 2.
[26] *Id.* at 5.
[27] *Id.*

precise mechanism of action for RYONCIL is not currently understood, that does not prevent FDA from approving Mesoblast's BLA.[28]

Cellular therapy products often have a complex mechanism(s) of action, and as FDA has previously explained in guidance, many cellular therapy products have mechanisms of action that are not fully characterized.[29, 30] Although the precise mechanism of action for RYONCIL for the treatment of SR-aGVHD is unclear, it is thought be related to immunomodulatory effects. Acute GVHD occurs when alloreactive donor-derived T cells within the donated tissue (graft) trigger an immunological response, and alloreactive donor-derived T cells play a role in mediating the systemic inflammation, cytotoxicity and potential end organ damage associated with acute GVHD. As discussed above, Mesoblast's BLA included *in vivo* pharmacodynamic data derived from participants in Study MSB-GVHD001/002. Specifically, treatment with RYONCIL resulted in a 54% reduction of circulating CD3+CD4+CD25+HLA-DR+ T cells (which represent activated T cells). Reduction in two biomarkers released by activated T cells in aGVHD, TNFR1 (decreased by 76%) and ST2 (decreased by 72%) was also observed at Day 180 compared to the baseline level. These data provide compelling evidence of RYONCIL's immunomodulatory effects that are relevant to the pathophysiology of aGVHD and suggest that the treatment effect observed in Study MSB-GVHD001 is more likely attributable to the action of the product than to chance. In approving the BLA for RYONCIL, FDA appropriately determined that a complete understanding of the product's mechanism of action was unnecessary to conclude that the BLA provided substantial evidence of effectiveness for the approved indication.

ii. Petitioner's Arguments Regarding Other Trials of RYONCIL

The Petition argues that "[i]n assessing the appropriateness of relying upon a single arm, open-label, historically controlled trial as the primary evidence of efficacy, FDA must consider the two failed, randomized, placebo-controlled, phase 3 trials of remestemcel-L for the treatment of

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[28] In support of the proposition that RYONCIL's mechanism of action is not well understood, Petitioner cites statements made during a financial institution's panel discussion on GVHD ("GVHD Q&A") by Dr. James Ferrara, emphasizing "Dr. Ferrara's prominence in the field of GVHD, in general, and pediatrics, in particular[.]" *Id.* at 5-6 (citing the Original Petition's Exhibit 5, Transcript of Cantor Fitzgerald Panel, pp. 42-43 (June 8, 2020)). We note that Dr. Ferrara was subsequently listed as an author of a correspondence to the editor (Stelios Kasikis et al., Mesenchymal stromal cell therapy induces high responses and survival in children with steroid refractory GVHD and poor risk biomarkers, *Bone Marrow Transplantation*, 2021 Sept. 1, available at https://www.nature.com/articles/s41409-021-01442-3), which concluded that findings from the authors' analyses "support and extend the recently published results that showed that children with severe, SR acute GVHD benefit from remestemcel-L therapy."

[29] See Potency Tests for Cellular and Gene Therapy Products; Guidance for Industry, at 6 (January 2011), available at https://www.fda.gov/media/79856/download.

[30] In its briefing materials for the 2020 ODAC meeting on RYONCIL, FDA expressly recognized the challenges to developing adequate potency assays for MSC-based product and noted that "[t]he *in vivo* activity of cell-based products can be multimodal and difficult to characterize, and as a result the mechanism of action may not be clearly established." FDA, Oncologic Drugs Advisory Committee Aug. 13, 2020 Meeting FDA Briefing Document-AM Session, at 5, available at https://public4.pagefreezer.com/content/FDA/04-03-2022T19:30/https://www.fda.gov/media/140988/download. FDA's briefing document went on to describe two potential approaches for potency assays to support licensure in situations where a biological product's mechanism of action is not completely understood, clearly indicating that it is possible for such products to meet the licensure standard, including with respect to effectiveness. *Id.* at 5-6.

GVHD, i.e., studies 265 and 280."[31] Regarding these studies, Petitioner states: "[i]n both randomized, concurrently controlled trials, remestemcel-L failed to demonstrate efficacy as assessed by the primary endpoints."[32]

In 2013, Mesoblast purchased remestemcel-L from Osiris Therapeutics.[33] Prior to Mesoblast's purchase, Osiris conducted two randomized, concurrently controlled trials of remestemcel-L in populations with aGVHD (Study 265[34] and Study 280[35]).

- Study 265 was a randomized, double-blind, placebo-controlled study with a primary endpoint of complete response (CR) lasting greater than or equal to 28 days. It enrolled adults with newly diagnosed aGVHD grades B-D.
- Study 280 was a randomized, double-blind placebo-controlled trial with a primary endpoint of CR lasting greater than or equal to 28 days. It enrolled adult and pediatric individuals with SR-aGVHD grades B-D and evaluated the efficacy of remestemcel-L plus the investigator's choice of additional salvage therapy.

As Petitioner notes, both of these studies failed to meet their primary efficacy endpoints. However, post-hoc analyses of the pediatric subgroup in Study 280 indicated a substantial numerical difference between the treatment arms for Day-28 ORR, although the treatment effect had a large confidence interval. FDA does not consider the results of these analyses to be evidence of a treatment effect but advised the sponsor prior to the initiation of Study MSB-GVHD001 that these analyses may be used to inform a hypothesis for the design of a prospective trial.

FDA carefully considered the results of Study 265 and Study 280 as part of its review of the RYONCIL BLA and presented information regarding these studies at the August 2020 ODAC meeting. In comparison to Study MSB-GVHD001, studies 265 and 280 have substantial differences, including in the study populations, trial design, treatment regimens, and primary endpoint evaluations. For example, Study 265 evaluated the effectiveness of remestemcel-L in combination with systemic corticosteroid therapy in patients with newly diagnosed aGVHD (rather than steroid-refractory patients), and Study 280 evaluated the effectiveness of remestemcel-L plus the investigator's choice of additional salvage therapy in patients with SR-aGVHD. This contrasts with Study MSB-GVHD001, where no additional salvage immunosuppressive agent was allowed under the protocol. In addition, different versions of the product that were not demonstrated to be comparable to the remestemcel-L product used in Study MSB-GVHD001 were used in these studies. Due to these differences, FDA does not view the negative efficacy results of Study 265 and Study 280 as relevant to the effectiveness of the commercial remestemcel-L product for treatment of SR-aGVHD in pediatric patients.

Petitioner further asserts that the rate of complete response (CR) among studies 265, 280, and MSB-GVHD001 was similar, speculating that this casts doubt on whether Study MSB-

[31] Original Petition at 7 (internal citations omitted).
[32] *Id.* at 7.
[33] Mesoblast, Remestemcel-L For Treatment of Steroid Refractory Acute Graft Versus Host Disease in Pediatric Patients- FDA Oncologic Drugs Advisory Committee Briefing Document (Aug. 13, 2020), at 50, available at https://public4.pagefreezer.com/browse/FDA/04-03-2022T19:30/https://www.fda.gov/media/140996/download.
[34] See NIH, ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT00562497.
[35] See NIH, ClinicalTrials.gov, https://www.clinicaltrials.gov/ct2/show/NCT00366145.

GVHD001 would have been successful with a concurrent control arm. Specifically, the Petition states that in Study 265, "45% of patients survived at least 90 days to achieve a complete response, and in the 280 study, 35% of patients achieved a durable complete response. By comparison, in the phase 3 single-arm study, only 29% achieved CR at day 28 and 44% at day 100." [36] However, the Petition does not address differences in study design when making this comparison, and FDA disagrees with Petitioner's assertions regarding the conclusions that can be drawn from this information on CR rates.

FDA has generally interpreted cross-trial comparisons with caution even when the trials are very similar, and especially when the trials are different. Our determination that study MSB-GVHD001 demonstrated effectiveness is primarily based on the endpoint of Day-28 ORR, defined as CR plus partial response (PR) at 28 days after initiation of remestemcel-L. FDA considers Day-28 ORR with durability to be an acceptable primary endpoint as a measure of clinical benefit to support approval of drugs intended to treat aGVHD, and Day-28 ORR was the primary endpoint of the study that supported the 2019 approval of ruxolitinib (JAKAFI) for treatment of SR-aGVHD in adult and pediatric patients 12 years and older.[37,38] In addition to the difference in endpoints, there were other substantial differences between Study MSB-GVHD001 and the prior studies 265 and 280, as described above. Given these differences, FDA does not consider Petitioner's comparison of the CR rates among these three studies to be an appropriate way to evaluate the effectiveness of RYONCIL. FDA's assessment of the evidence submitted in the BLA determined that Study MSB-GVHD001 demonstrated a clinically meaningful effect on an endpoint that FDA considers to represent clinical benefit.

Petitioner also argues that because RYONCIL has been investigated "as a potential treatment for a number of different diseases" for which it has not been approved, this raises doubts about the probability of RYONCIL's success in treating a GVHD indication.[39] However, Petitioner does not explain why the results of any particular trial of RYONCIL for another indication demonstrate that RYONCIL is unlikely to "make[]mechanistic sense for treatment of SR-aGVHD" in pediatric patients.[40] The results of trials investigating the effectiveness of a product

[36] Original Petition at 8.
[37] See Donna Przepiorka et al., FDA Approval Summary: Ruxolitinib for Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease, Oncologist. 2020;25(2):e328-e334. doi:10.1634/theoncologist.2019-0627; Graft-versus-Host Diseases: Developing Drugs, Biological Products, and Certain Devices for Prevention or Treatment; Draft Guidance for Industry, at 18 (September 2023), available at https://www.fda.gov/media/172524/download. When finalized, this draft guidance will represent FDA's current thinking on this topic.
[38] The definition of this endpoint and its acceptability as an endpoint that denotes clinical benefit in certain trials of products to treat aGVHD was discussed in a public workshop on Clinical Trial Endpoints for Acute Graft-vs-Host Disease after Allogeneic Hematopoietic Stem Cell Transplantation that was co-sponsored by FDA. 74 FR 10944 (March 13, 2009), https://www.federalregister.gov/documents/2009/03/13/E9-5496/clinical-trials-endpoints-for-acute-graft-versus-host-disease-after-allogeneic-hematopoietic-stem; SZ Pavletic, Response as an endpoint in treatment trials for acute GVHD, Bone Marrow Transplant 2012;47:161–163, available at https://www.nature.com/articles/bmt201159.
[39] Original Petition at 6. Additionally, in the Supplement, Petitioner states that Mesoblast sponsored a randomized, concurrently controlled study for remestemcel-L for COVID-19 induced acute respiratory distress syndrome and cites a Mesoblast press release indicating that the Data Safety Monitoring Board (DSMB) performed an interim analysis and "noted that the trial [was] not likely to meet the 30-day mortality reduction endpoint at the planned 300 patient enrolment. The DSMB recommended that the trial complete with the currently enrolled 223 patients, and that all be followed-up as planned." Supplement at 5.
[40] Original Petition at 6.

for one indication may have varying relevance to determining the effectiveness of the product for another indication, and a product's lack of an observed treatment effect in unrelated diseases or conditions may have little or no relevance to its effectiveness for the target indication. FDA considered information regarding trials of remestemcel-L for other diseases during its review of this BLA[41] and ultimately concluded that efficacy information from clinical trials of remestemcel-L in conditions other than aGVHD, particularly in the context of clinical data derived from previous versions of product with no demonstrated comparability, had little relevance to review of the BLA for RYONCIL.

iii. Petitioner's Arguments Regarding Use of a Historical Control

Petitioner notes that FDA guidance has previously stated concerns about use of historical controls, including with respect to minimizing bias and properly controlling for differences between the test and control groups.[42] According to the Petition, these potential concerns are "operative" with respect to Study MSB-GVHD001 and undermine the validity of that study's results.[43]

FDA is aware of the potential challenges and disadvantages associated with use of a historical control described in its guidance documents and factored those considerations into its evaluation of Study MSB-GVHD001. However, the Agency has also long recognized that study designs that may involve more uncertainty than a randomized, placebo-controlled trial, such as those that use a historical control, can serve as adequate and well-controlled clinical investigations that provide substantial evidence of effectiveness.[44]

In addition to describing the types of concerns that may be presented by studies that use a historical control generally, Petitioner asserts that there are "significant problems with Mesoblast's use of a 45% historical [ORR] to assess efficacy" in Study MSB-GVHD001.[45] Specifically, Petitioner argues that references cited in an article by Kurtzberg et al. describing the results of Study MSB-GVHD001[46] "do not appear to support" use of Mesoblast's historical 45%

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[41] See, e.g., FDA, Oncologic Drugs Advisory Committee Aug. 13, 2020 Meeting FDA Briefing Document-PM Session, at 35-36, available at https://public4.pagefreezer.com/browse/FDA/02-10-2021T03:58/https://www.fda.gov/advisory-committees/advisory-committee-calendar/august-13-2020-meeting-oncologic-drugs-advisory-committee-meeting-announcement-08132020-08132020.

[42] See Original Petition at 9.

[43] In support of this argument, Petitioner cites a statement made by Dr. Jonathan Gutman in response to questions from market analysts during the GVHD Q&A. Original Petition at 9. However, the quoted comment from Dr. Gutman about randomized trials being the "gold standard for really understanding how well things work" was made regarding challenges seen in the "history of GVHD and GVHD therapy" generally and was not specific to remestemcel-L or Study MSB-GVHD001, as Petitioner suggests. See Original Petition, Exhibit 5 at 31:9-32:14. Further, Dr. Gutman's comment was made during discussion of reported data about a different product ("KD025"). *Id*. at 26:8-32:24.

[44] See, e.g., 21 CFR 314.126(b)(2)(v).

[45] Original Petition at 10.

[46] Joanne Kurtzberg et al., A Phase 3, Single-Arm, Prospective Study of Remestemcel-L, Ex Vivo Culture-Expanded Adult Human Mesenchymal Stromal Cells for the Treatment of Pediatric Patients Who Failed to Respond to Steroid Treatment for Acute Graft-versus-Host Disease, Biology of blood and marrow transplantation, Journal of the American Society for Blood and Marrow Transplantation, 2020, 26(5): 845-854, doi:10.1016/j.bbmt.2020.01.018.

Day-28 ORR as a control.[47] For example, the Petition notes that "the only study [cited by Kurtzberg et al.] conducted solely in pediatric patients – the 2019 MacMillan article – appears to show a day 28 [ORR] of 65%. . . ."[48] According to Petitioner, because "GVHD is easier to treat in pediatric patients, these higher day 28 [ORRs] in pediatric patients appear to be a more appropriate historical comparator than the 45% [ORR] used by Mesoblast."[49, 50] Petitioner further indicates that "a review of literature for second-line treatment in pediatric aGVHD patients" found "eleven . . . studies that show a wide range of overall response rates" with a "mean across the studies [of] 67.7% and [a] sample size weighted average [of] 65.2%."[51] According to the Petitioner, "[g]iven the wide range of ORs . . . it is not possible to predict how a control population would behave until there is a true control population, one that should be established in a prospective, randomized, concurrently controlled clinical study."[52]

During its review, FDA evaluated the appropriateness of the 45% Day-28 ORR benchmark used in Study MSB-GVHD001. As part of this evaluation, the Agency considered analyses of data from Study 265 and Study 280, as well as from an expanded access protocol for treatment of pediatric patients with SR-aGVHD (Study 275), information on pediatric patients from the Mount Sinai Acute GVHD International Consortium (MAGIC) database, and published reports of prospective studies and retrospective analyses involving pediatric patients with SR-aGVHD. Therefore, to the extent the Petition suggests that the information provided to support use of the 45% Day-28 ORR benchmark is limited to the literature referenced in the 2020 Kurtzberg et al. publication regarding RYONCIL, that suggestion is inaccurate.

With respect to Petitioner's arguments specific to the 2019 MacMillan article, we disagree that the article indicates that a 65% Day-28 ORR (rather than 45%) was appropriate to use as benchmark in Study MSB-GVHD001. This article retrospectively describes response to upfront steroid therapy in pediatric patients, whereas Study MSB-GVHD001 measured Day-28 ORR in individuals who were steroid refractory (i.e. refractory or progressed after steroid therapy). Therefore, FDA does not view this publication as relevant to its evaluation of the 45% benchmark.

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[47] Original Petition at 10. Petitioner points to comments from Dr. Ferrara during the GVHD Q&A regarding RYONCIL, which reference "that paper . . . published in 2005[.]" *Id.* at 9-10. Dr. Ferrara went on to comment that "the data of those patients is between 18 and 20 years old" and that "[grades] 3 to 4s these days don't have disease that bad." While Petitioner hypothesizes that Dr. Ferrara was referring to a study published in ***2002*** that was referenced in Kurtzberg et al., *supra* note 46, the transcript of the GVHD Q&A does not identify the ***2005*** study Dr. Ferrara referenced, and according to the transcript, Dr. Ferrara did not make comments on the appropriateness of the 45% Day-28 ORR benchmark used in Study MSB-GVHD001.

[48] The "2019 MacMillan article" refers to mean the following article: M.L. MacMillan et al., Pediatric acute GVHD: clinical phenotype and response to upfront steroids, Bone Marrow Transplant, Jan. 2020, 55(1):165-171, doi: 10.1038/s41409-019-0651-9. Epub 2019 Sep 2, available at https://www.nature.com/articles/s41409-019-0651-9. See Original Petition at 10 n. 24

[49] Original Petition at 10.

[50] The Petition does not explain why, under Petitioner's line of reasoning, a 45% Day 28-ORR is an inappropriately low benchmark to use for a trial of RYONCIL in pediatric participants with SR-aGVHD, while a 40% Day-28 ORR benchmark was appropriately used in the REACH-1 study that supported approval of JAKAFI for treatment of SR-aGVHD, including in pediatric patients as young as 12 years old. We note that Petitioner describes the REACH-1 trial as a "robust" and "rigorous, open-label, single-arm, multicenter trial[.]" *Id.* at 2.

[51] Supplement at 4.

[52] *Id.*

Regarding the studies[53] Petitioner identified as showing a "wide range" of ORRs, the cited papers describe experience with use of various second-line agents in pediatric individuals with SR-aGVHD. The publications Petitioner cites have various design limitations, such as retrospective observations, very small numbers of participants, single-institution enrollment, and diverging definitions of steroid refractoriness. The cited studies also report response rates to a variety of different therapies (e.g., JAKAFI, daclizumab, mycophenolate mofetil, alemtuzumab, and closed-system extracorporeal photopheresis), including with use of a second therapy in some cases. These issues make their findings difficult to interpret and of limited value in informing the appropriateness of the 45% Day-28 ORR benchmark used in Study MSB-GVHD001. After considering the totality of the information reviewed related to the pre-specified 45% Day 28-ORR null rate, FDA concluded that 45% was an adequate historical ORR benchmark.

iv. Petitioner's Argument That It Is Possible for Mesoblast to Conduct a Concurrently Controlled Trial

Petitioner asserts that "FDA should refuse to approve RYONCIL unless and until Mesoblast conducts and submits data from a successful randomized, concurrently controlled, phase 3 clinical trial."[54] Citing the Substantial Evidence of Effectiveness Draft Guidance, Petitioner notes that "FDA has stated that it would not 'find it responsible' to rely on study designs that produce less certainty, such as externally controlled trials, 'where designs providing more certainty are possible.'"[55] According to Petitioner, it "appears to be possible" for Mesoblast to conduct a concurrently controlled clinical trial to support its BLA for remestemcel-L, even if conducting a concurrently controlled trial would be "challenging."[56]

The Substantial Evidence of Effectiveness Draft Guidance, which, when finalized, will represent FDA's current thinking on that topic, explains that the "substantial evidence" standard incorporates an element of expert judgment.[57] The standard requires that the adequate and well-controlled investigations be such that "it could fairly and responsibly be concluded by [qualified] experts that the drug will have the effect it purports or is represented to have," and permits approval on the basis of one trial and confirmatory evidence only "[i]f [FDA] determines, based on relevant science, that data . . . are sufficient to establish effectiveness."[58] Accordingly, the draft guidance describes examples of situations in which FDA experts may "fairly and responsibly" rely on study designs that produce less certainty but does not prescribe FDA's conclusion with regard to whether the data in a particular application provide substantial evidence effectiveness. The draft guidance also expressly acknowledges that "the degree of certainty supporting such a conclusion may differ, depending on clinical circumstances (e.g.,

[53] We note that the Appendix of "Pediatric Study Citations" that Petitioner provided to identify these studies included a reference to an "EMA Assessment Report for Jakavi." However, the link provided for this reference was to a 2012 European Medicines Agency, Committee for Medicinal Products for Human Use assessment report of "Jakavi" (ruxolitinib) for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis—not for treatment of SR-aGVHD.
[54] Original Petition at 11.
[55] *Id.* (citing Substantial Evidence of Effectiveness Draft Guidance at 14).
[56] Original Petition at 11.
[57] Substantial Evidence of Effectiveness Draft Guidance at 14.
[58] Section 505(d) of the FD&C Act.

severity and rarity of the disease and unmet medical need)."[59] Therefore, to the extent Petitioner reads FDA's draft guidance to mean that an applicant cannot rely on data from a clinical study that uses a historical control to demonstrate substantial evidence of effectiveness if it is theoretically possible to conduct a randomized, concurrently controlled clinical trial, we disagree.

Petitioner also cites a statement from FDA guidance indicating that trials using an external or historical control "should generally be considered only when prior belief in the superiority of the test therapy to all available alternatives is so strong that alternative designs appear unacceptable …."[60] The Petition then asserts that "although there were some promising signals regarding efficacy [for remestemcel-L] in pediatric patients, the data were, at best, mixed" and with approval of JAKAFI, "less reason to believe that remestemcel-L is superior to all available alternatives."[61]

First, we note that guidance providing recommendations on when a study design using a historical or external control should generally be considered does not preclude sponsors from justifying use of such study designs in other circumstances. In addition, the relevance of Petitioner's contentions about "available alternatives" to RYONCIL is unclear. At the time that Study MSB-GVHD001 was designed and conducted there were no approved therapies for treatment of SR-aGVHD in pediatric patients. Specifically, with respect to JAKAFI, Study MSB-GVHD001 was completed in 2018, and FDA approved JAKAFI for treatment of SR-aGVHD in adult and pediatric patients 12 years and older on May 24, 2019. It would be illogical to determine that Study MSB-GVHD001 was inappropriately designed on the grounds that a different product was approved *after* the study was conducted.

FDA has concluded that Study MSB-GVHD001 represents an adequate and well-controlled clinical investigation that, together with confirmatory evidence, provides substantial evidence of effectiveness.[62] Accordingly, FDA does not consider it necessary for Mesoblast to conduct a randomized, concurrently controlled trial of remestemcel-L for treatment of SR-aGVHD in pediatric patients to support approval of the BLA. Moreover, given the high Day-28 ORR and favorable safety profile observed in Study MSB-GVHD001, FDA believes there would be

[59] Substantial Evidence of Effectiveness Draft Guidance at 14.
[60] Original Petition at 11.
[61] *Id.*
[62] Petitioner also asserts that rather than conducting a randomized, concurrently controlled trial, "the only 'new' data generated by Mesoblast have been additional *post hoc* analyses of the single-arm trial, such as the investigator-initiated historical control study where physicians from Mt. Sinai compared outcomes in 25 children from Mesoblast's Phase 3 trial of remestemcel-L in SR-aGVHD with 27 closely matched children from the [MAGIC database]." Supplement at 5 (citing Stelios Kasikis et al., Mesenchymal stromal cell therapy induces high responses and survival in children with steroid refractory GVHD and poor risk biomarkers, Bone Marrow Transplant. 2021; 56: 2869-2870, available at https://www.nature.com/articles/s41409-021-01442-3). Petitioner asserts that these "*post hoc* analyses do not meet the rigorous standards necessary to qualify as substantial evidence of effectiveness." *Id.* We interpret this to be an assertion that the study described in the Kasikis et al. publication—the only "*post hoc* analys[i]s" that Petitioner identifies—is not an adequate and well-controlled clinical investigation. As noted above, FDA has concluded that Study MSB-GVHD001 represents an adequate and well-controlled clinical investigation that, together with other evidence in the BLA, provides substantial evidence of effectiveness for RYONCIL. In reaching this conclusion, FDA did not rely on the study described by Kasikis et al. as an adequate and well-controlled clinical investigation or as confirmatory evidence.

significant challenges associated with attempting to conduct a trial that randomized subjects to a control arm due to a high risk of patient dropout.

v. Petitioner's Argument That FDA Should Require a Randomized, Concurrently Controlled Trial of RYONCIL for Treatment of SR-aGVHD Although FDA Did Not Require Such a Trial for Approval of JAKAFI

As Petitioner is aware, in 2019, FDA approved ruxolitinib (marketed as JAKAFI) for SR-AGVHD in adult and pediatric patients 12 years and older.[63] JAKAFI's approval was based primarily on Study INCB18424-271 (REACH-1),[64] an open-label, single-arm, multicenter study with similarities to Study MSB-GVHD001 in key design elements. REACH-1 did not have a concurrent control; the primary endpoint was Day-28 ORR, and the statistical analysis plan prespecified that a positive result would be concluded if the lower limit of the 95% confidence interval of the ORR was above the prespecified threshold of 40%.[65]

In attempting to explain why its arguments regarding the evidence of effectiveness for RYONCIL do not also apply to FDA's approval of JAKAFI, the Petition contends that with the approval of JAKAFI, the regulatory landscape for RYONCIL is different and that the "unmet need" for a treatment for patients with SR-aGVHD is no longer as acute.[66] However, we disagree that there is no longer an acute "unmet need" in light of JAKAFI's approval.

SR-aGVHD is a serious, life-threatening condition with high unmet need. No approved therapy exists for pediatric patients less than 12 years old, as JAKAFI is only approved in patients 12 years of age and older. With respect to pediatric patients 12 years of age and older with SR-aGVHD, RYONCIL may also address a remaining unmet need in this population. For example, JAKAFI's approved labeling notes that treatment with the drug can cause thrombocytopenia, anemia, and neutropenia, as well as the risk of serious bacterial, mycobacterial, fungal, and viral infections, which may affect the ability of some patients to safely initiate or continue treatment with JAKAFI.[67] The FDA-approved labeling for RYONCIL does not include these same risks in the Warnings and Precautions section. Thus, RYONCIL may represent a treatment option for those pediatric patients 12 years of age and older unable to tolerate JAKAFI. Accordingly, the Petition has not demonstrated that the regulatory landscape for treatment of SR-aGVHD has changed because of JAKAFI's approval such that there is no longer an unmet need for patients within the population for which RYONCIL is approved. SR-aGVHD is still a life-threatening condition with potentially fatal outcomes, and there is an unmet need for pediatric populations afflicted with SR-aGVHD.

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[63] FDA, FDA approves ruxolitinib for acute graft-versus-host disease, (May 24, 2019), https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-ruxolitinib-acute-graft-versus-host-disease.

[64] The approval of JAKAFI in adult and pediatric patients 12 years and older was based on an open label single-arm study of 49 patients considered as the primary efficacy population with grades 2-4 SR aGVHD. Donna Przepiorka et al., FDA Approval Summary: Ruxolitinib for Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease, Oncologist, Feb. 2020, 25(2):e328-e334, doi: 10.1634/theoncologist.2019-0627.

[65] *Id.*

[66] Original Petition at 12.

[67] https://www.jakafi.com/jakafi-prescribing-information.

The Petition further asserts that other factors supporting approval of JAKAFI are not present with respect to RYONCIL: Petitioner argues that (1) activity of RYONCIL has not been established in other diseases, unlike JAKAFI, which was approved for other indications prior to its approval for SR-aGVHD; and (2) JAKAFI's mechanism of action is well-established. Therefore, the Petition asserts that FDA should require Mesoblast to conduct a randomized, concurrently controlled trial to provide substantial evidence of effectiveness of RYONCIL for treatment of SR-aGVHD, even though such a trial was not conducted to support the JAKAFI approval.[68]

The specific scientific considerations and evidence regarding each individual product are unique. FDA thus reviews products on a case-by-case basis while working to ensure consistent regulatory approaches to similarly situated products and scenarios. As Petitioner notes, there are differences between JAKAFI and RYONCIL, such as the fact that JAKAFI was approved in other indications before it was approved to treat SR-aGVHD in patients 12 years and older.[69] But these are not the only differences. JAKAFI and RYONCIL are, for example, different kinds of products (kinase inhibitor vs. cellular therapy) with different toxicity profiles, among other things. FDA's approval of JAKAFI does not mandate approval of RYONCIL. But the specific differences Petitioner identifies also do not preclude approval of RYONCIL. As explained above, FDA found that Study MSB-GVHD001 was a well-controlled investigation that, together with confirmatory evidence submitted in Mesoblast's BLA, provides substantial evidence of effectiveness.

vi. Petitioner's Arguments Regarding Potential Harm to Pediatric Patients

Finally, the Petition asserts that "the approval of remestemcel-L without substantial evidence of efficacy risks harming patients, particularly pediatric patients 12 years and older, by potentially delaying or preventing treatment with Jakafi, the only FDA-approved treatment of SR-aGVHD in certain pediatric patients."[70] FDA disagrees with this assertion. As detailed in the Clinical Review Memo for RYONCIL, the Agency has determined RYONCIL is safe and effective for the treatment of SR-aGVHD in pediatric patients 2 months of age and older.[71] FDA considers patient access to a variety of safe and effective treatment options beneficial to public health. RYONCIL, a cellular therapy, may offer important benefits to patients, including those who may prefer not to use JAKAFI, and as Petitioner acknowledges, JAKAFI is not approved in individuals under 12 years of age. Ultimately, the decision of whether to prescribe RYONCIL or JAKAFI is one that rests with the prescriber and patient and will depend on factors such as the patient's history, goals for treatment, and tolerability.

B. Petitioner's Request That FDA Provide the Citizen Petition to Members of Any Advisory Committee Scheduled to Discuss the BLA for RYONCIL

[68] Original Petition at 12.
[69] *Id.*
[70] *Id.*
[71] Petitioner notes that if the FDA granted its request to refuse to approve RYONCIL, then patients could still access the product through clinical trials, expanded access, or a request submitted pursuant to the Right to Try Act. *Id.* at 13. Regardless of the extent to which patients would ultimately be able to access RYONCIL through these mechanisms, such access is not a basis on which FDA may withhold approval of a BLA that meets the standard for licensure. See 42 U.S.C. 262(a)(2); 21 CFR 601.4.

The Petition also requests that FDA "[p]rovide a copy of [the Citizen Petition] to members of any Advisory Committee scheduled to discuss the BLA for RYONCIL for the proposed indication for treatment of SR-aGVHD in pediatric patients."[72] Petitioner submitted a copy of the Original Petition as a comment to the docket for the August 2020 ODAC meeting. FDA provided a copy of the Original Petition and exhibits submitted to that docket to the members of ODAC in advance of the August 13, 2020 ODAC meeting. Because the Petition was provided to ODAC members at the August 13, 2020 meeting held to discuss the BLA submission of RYONCIL and FDA did not hold additional advisory committee meetings on the BLA for RYONCIL, FDA finds the second request of the Petition moot.

IV. CONCLUSION

FDA has considered Petitioner's requests as they relate to RYONCIL. For the reasons given above, FDA denies the first request of the Petition in its entirety and finds the second request of the Petition moot.

Sincerely,

Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research

[72] *Id*. at 2.