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VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2020-P-1689; Supplemental Information in Further Support of Citizen Petition Requesting FDA to Take Certain Actions with Respect to Licensure of RYONCIL™ (remestemcel-L)

Dear Sir or Madam:

On behalf of a client, and in accordance with 21 C.F.R. § 10.30(g), the undersigned hereby submits supplemental information in support of the above-referenced Citizen Petition requesting that the Food and Drug Administration ("FDA") 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"). This submission addresses new regulatory developments regarding the BLA for RYONCIL and provides further scientific support for the arguments in the Citizen Petition that the data submitted in the BLA to establish effectiveness – including data submitted in Mesoblast's most recent filing – fails to meet the rigorous standards necessary to qualify as "substantial evidence" of effectiveness under the Public Health Service Act ("PHS Act") and Food and Drug Administration ("FDA") policies.

Accordingly, approving RYONCIL based upon this inadequate data set not only threatens to expose pediatric patients suffering from SR-aGVHD to an unproven and potentially ineffective treatment, but also could impede many eligible pediatric patients from using Jakafi (ruxolitinib), the only medication approved by FDA for treatment of SR-aGVHD in pediatric patients 12 years and older. Because of the serious and progressive nature of SR-aGVHD, even minor delays in effective treatment pose a serious public health concern.

A. Factual Background

On February 3, 2020, Mesoblast submitted its BLA for RYONCIL for treatment of children with SR-aGVHD, which was accepted by the FDA on April 1, 2020, with a Prescription Drug User Fee Act ("PDUFA") action date set on September 30, 2020. RYONCIL is an investigational biological product comprising culture-expanded mesenchymal stem cells ("MSCs") derived from the bone marrow of an unrelated donor. RYONCIL previously has been studied for a number of other indications, including chronic obstructive pulmonary disease ("COPD"), acute coronary syndrome ("ACS"), Diabetes Mellitus Type I ("DMT1"), and Crohn's Disease, but none of these

development programs appear to have been successful. Likewise, RYONCIL was studied in a Phase 3, randomized clinical trial for the treatment of SR-aGVHD in adult and pediatric patients, but the study was unsuccessful and did not meet the primary endpoint for demonstrating the effectiveness of RYONCIL.[1]

A *post hoc* analysis of the failed Phase 3 trial was able to identify patient subpopulations for further research. Based upon the *post hoc* analysis suggesting that RYONCIL may have some activity in pediatric patients, Mesoblast conducted a single-arm, open-label, non-randomized trial of RYONCIL in a limited number of pediatric patients with SR-aGVHD. Although the trial was not randomized or concurrently controlled, Mesoblast used as a historical control a purported 45% overall response ("OR") rate at Day 28 for standard of care alone, which Mesoblast claims was supported by "historical age and disease severity-adjusted published findings and internal data showing an approximate 45% day 28 OR rate for aGVHD patients treated with steroids, second-line systemic agents, and supportive symptom management."[2] Mesoblast asserted that this non-randomized, single-arm study was successful and supports approval of RYONCIL because RYONCIL-treated patients achieved statistically superior OR compared with the prespecified, historical control rate (69% versus 45%, p=0.0003), demonstrating a greater than 20 percentage point difference in treatment effect.[3]

On October 1, 2020, Mesoblast announced it had received a Complete Response Letter ("CRL") from FDA.[4] A CRL is issued in cases where the Agency determines that "it will not approve the [BLA] or supplement in its present form." 21 C.F.R. § 601.3(a). In such cases, the CRL typically "will describe all of the deficiencies that the agency has identified in a [BLA] or supplement …." *Id.* § 601.3(a)(1). In its press release, Mesoblast cited two deficiencies with the BLA for RYONCIL identified by FDA. First, "the FDA recommended that Mesoblast conduct at least one additional randomized, controlled study in adults and/or children to provide further evidence of the effectiveness of remestemcel-L for SR-aGVHD." Second, "FDA also identified a

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[1] Kebriaei P, Hayes J et al. A Phase 3 Randomized Study of Remestemcel-L versus Placebo Added to Second-Line Therapy in Patients with Steroid-Refractory Acute Graft-versus-Host Disease. *Biol Blood Marrow Transplant*. 2020;26:835-844 (Exhibit 2 to Citizen Petition).

[2] Kurtzberg J, Abdel-Azim H, 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. *Biol Blood Marrow Transplant*. 2020;26:845-854 (Exhibit 3 to Citizen Petition).

[3] Mesoblast, Press Release: Primary Endpoint Successfully Achieved in Mesoblast's Phase 3 Cell Therapy Trial for Acute Graft Versus Host Disease (Feb. 21, 2018), *available at* Primary Endpoint Successfully Achieved in Mesoblast's Phase (globenewswire.com). Although Mesoblast's 2018 press release announced a 69% 28-day OR for remestemcel-L, the Kurtzberg article cited above reports that the 28-day OR for remestemcel-L was 70.4%.

[4] Mesoblast, Press Release: Mesoblast Receives Complete Response Letter from the FDA for Biologics License Application for Steroid-Refractory Acute Graft Versus Host Disease In Children (Oct. 1, 2020 (USA)), *available at* https://www.globenewswire.com/news-release/2020/10/01/2102679/0/en/Mesoblast-Receives-Complete-Response-Letter-From-the-FDA-for-Biologics-License-Application-for-Steroid-Refractory-Acute-Graft-Versus-Host-Disease-in-Children.html.

need for further scientific rationale to demonstrate the relationship of potency measurements to the product's biologic activity."

On October 3, 2022, Mesoblast announced it had submitted "substantial new information on clinical and potency assay items" to FDA to address the deficiencies identified in the Agency's CRL.[5] Although Mesoblast states that the new information was submitted to its IND file "as guided by FDA," it appears that this filing is intended to constitute a resubmission of the BLA in accordance with 21 C.F.R. § 601.3(b)(1). Based on Mesoblast's public comments, it appears that the resubmission consists largely of a new, *post hoc* analysis conducted by the company on a potency assay. There is no indication that Mesoblast conducted or submitted information from "at least one additional randomized, controlled study in adults and/or children to provide further evidence of the effectiveness of remestemcel-L for SR-aGVHD[,]" as requested in the CRL.

B. Mesoblast Continues to Fail to Provide "Substantial Evidence" of Effectiveness in Treating SR-aGVHD in Pediatric Patients

As discussed in the July 20, 2020, Citizen Petition, a demonstration of efficacy must account for many factors. Most importantly, it requires robust clinical data using a design that minimizes bias and distinguishes the effect of the test drug from other influences. In remestemcel-L's case, reliance on a single-arm, historically controlled trial as the primary evidence of efficacy is inappropriate because, among other things: (1) remestemcel-L's mechanism of action is poorly defined; (2) prior, concurrently-controlled clinical trials have failed to support efficacy in a broad aGVHD population, and there is little reason to believe remestemcel-L would perform significantly better in pediatric patients alone; and (3) Mesoblast's use of a historical control in its pivotal single-arm efficacy trial is problematic.

1. New Information Confirms That Remestemcel-L's Historical Control Cohort Is Severely Confounded

The Citizen Petition explained in detail why the historical control cohort relied upon by Mesoblast is severely confounded. Among other things, the Citizen Petition exposed significant problems with Mesoblast's use of a 45% historical OR rate to assess efficacy, which Mesoblast claimed is supported by "historical age and disease severity-adjusted published findings and internal data showing an approximate 45% day 28 OR rate for aGVHD patients treated with steroids, second-line systemic agents, and supportive symptom management."[6] However, the Citizen Petition demonstrated that the references cited by Mesoblast do not appear to support its historical control.[7] For example, the only study conducted solely in pediatric patients – the 2019 MacMillan article – appears to show a day 28 OR rate of 65%, which is 20 percentage points

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[5] Mesoblast: Press Release: Mesoblast Submits New Information to FDA IND File in Response to Items in the CRL to the Remestemcel-L BLA for SR-aGVHD (Oct. 2, 2022 (USA)), *available at* 4ea53823-b66a-466b-83a2-a91a0f8f8ea3 (mesoblast.com).

[6] Kurtzberg et al., *supra* note 2.

[7] Supplementary materials to Kurtzberg et al. (Exhibit 7 of Citizen Petition).

higher than Mesoblast's preferred historical control rate of 45%.[8] This raised significant questions about whether Mesoblast's historical control is biased and/or whether the results of the single-arm study overestimate the efficacy of remestemcel-L, as is often seen with historically controlled, non-randomized, single-arm studies.

Now that Mesoblast apparently has decided to resubmit its BLA without conducting any additional randomized, controlled clinical trials, Petitioner has identified additional information that raises further concerns about Mesoblast's reliance on a single clinical trial with historical controls. Specifically, a review of the literature for second-line treatment in pediatric aGVHD patients has been conducted and finds eleven (11) clinical trials and prospective and retrospective studies that show a wide range of overall response rates, ranging from 34 to 100% (citations provided in Appendix). The mean across the studies is 67.7% and the sample size weighted average is 65.2%. Given the wide range of ORs (18.6% standard deviation), 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.

SUMMARY TABLE: Response Rates in Clinical Trials for Pediatric Patients with aGVHD

Treatment	28 day response rate (%)	Sample Size
Antithymocyte globulin, etanercept, or mycophenolate mofetil*	34.4	61
Ruxolitinib	45.5	11
Ruxolitinib	76.9	13
Ruxolitinib	87.5	8
Ruxolitinib	80.0	5
CellEx Photopheresis System	55.2	29
Basiliximab	85.0	100
Etanercept	64.0	25
Alemtuzumab	66.7	15
Alemtuzumab	100.0	3
Alemtuzumab	73.7	19
Daclizumab**	61.5	13
Mycophenolate mofetil	50.0	14

Average	**67.7**
Sample size weighted average	**65.2**
Standard Deviation	**18.6**

*Mesoblast cited - note that it has the lowest response rate of any of these studies
** 30 day response rate (not 28 days)

[8] MacMillan et al. Pediatric acute GVHD: clinical phenotype and response to upfront steroids. *Bone Marrow Transplant.* 2020; 55(1): 165-171 (Exhibit 8 of Citizen Petition).

In sum, given the confounding nature of the patient population and evolving outcomes for patients over time, the data comparison between the treatment and historical control arms in Mesoblast's single arm, historically controlled trial is severely confounded. Consequently, Mesoblast has failed to provide "substantial evidence" from adequate and well-controlled trials that remestemcel-L is effective for treatment of SR-aGVHD in pediatric patients.

2. <u>Mesoblast Has Made No Efforts to Conduct a Randomized, Controlled Study In Adults and/or Children to Provide Further Evidence of the Effectiveness of Remestemcel-L for SR-aGVHD</u>

It has been more than two years since the FDA issued the CRL for Mesoblast's BLA wherein it recommended "at least one randomized, controlled study in adults and/or children to provide further evidence of the effectiveness of remestemcel-L for SR-aGVHD." Yet, Mesoblast apparently has made little to no efforts to conduct another trial to support its recent resubmission.

In fact, 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 Mount Sinai Acute GVHD International Consortium.[9] These *post hoc* analyses do not meet the rigorous standards necessary to qualify as substantial evidence of effectiveness.

Nevertheless, during the two years since issuance of the CRL, Mesoblast did have time to conduct a randomized, concurrently controlled study for remestemcel-L for a *different* indication: COVID-19 induced acute respiratory distress syndrome (ARDS).[10] That trial, like the prior Phase 3 trials in GVHD, did not meet its primary endpoint, having been stopped early for futility.[11] This is now the second randomized, concurrently controlled study that remestemcel-L has failed. The first failed study was the SR-aGVHD study,[12] which should be considered as evidence *against* the efficacy of remestemcel-L for the treatment of SR-aGVHD.

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[9] Kasikis S, Baez J, 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; see also Mesoblast, Press Release: Remestemcel-L Improves Survival of Children With Biomarkers for Highest Mortality in Steroid Refractory Acute GVHD (Oct. 18, 2021), *available at* https://www.globenewswire.com/news-release/2021/10/18/2315632/0/en/Remestemcel-L-Improves-Survival-of-Children-With-Biomarkers-for-Highest-Mortality-in-Steroid-Refractory-Acute-GVHD.html.

[10] NIH, ClinicalTrials.gov, MSCs in COVID-19 ARDS (NCT04371393), *available at* https://clinicaltrials.gov/ct2/show/NCT04371393.

[11] Mesoblast, Press Release: Mesoblast Update on COVID-19 ARDS Trial (Dec. 17, 2020), *available at* https://www.globenewswire.com/news-release/2020/12/17/2147472/0/en/Mesoblast-Update-on-COVID-19-ARDS-Trial.html.

[12] Bioprocess Online, Osiris Therapeutics Announces Preliminary Results for Prochymal Phase III GvHD Trials (Sept. 8, 2009) (Exhibit 6 to Citizen Petition), *available at* https://www.bioprocessonline.com/doc/osiris-therapeutics-announces-preliminary-res-0001.

3. FDA Should Continue to Require At Least One Additional Successful, Randomized, Concurrently Controlled Clinical Trial

In light of the series of failed randomized, placebo-controlled phase 3 trials and a confounded, non-randomized, historically controlled trial, FDA should continue to refuse to approve RYONCIL unless and until Mesoblast conducts and submits data from a successful randomized, concurrently controlled, phase 3 clinical trial. FDA has explained that, even for trials involving rare diseases, "[r]andomized, placebo-controlled trials with equal allocation are generally the most efficient designs to assess effectiveness." FDA, *Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products [Draft]*, p. 16 (Dec. 2019) ("Substantial Evidence Draft Guidance"). Moreover, 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." Substantial Evidence Draft Guidance at 14.

In this case, as explained in the July 20, 2020, Citizen Petition, a randomized, concurrently controlled clinical trial appears to be possible. Indeed, FDA has explained that an "externally controlled trial should generally be considered only when prior belief in the superiority of the test therapy to all available alternative is so strong that alternative designs appear unacceptable …." FDA, *Guidance for Industry: Choice of Control Group and Related Issues in Clinical Trials (ICH E10)*, p. 28 (May 2001). In this case, especially given the string of failed prospective, concurrently controlled clinical trials in GVHD and other diseases, there is no objective evidence to support a "prior belief in the superiority of [remestemcel-L] to all available alternatives." Quite the contrary. Consequently, as was previously communicated to Mesoblast in the CRL, FDA should require the sponsor to conduct at least one randomized, controlled trial to provide "substantial evidence" of the effectiveness of remestemcel-L (plus confirmatory evidence).

C. Conclusion

In conclusion, remestemcel-L's ill-defined mechanism of action in combination with a pair of prior, failed, phase 3 trials and a third trial featuring a confounded and uncontrolled historical control arm does not constitute "substantial evidence" of RYONCIL's effectiveness. It is particularly important for FDA to be confident in remestemcel-L's efficacy given alternative, approved therapies on the market and potential development-stage therapies that could be delayed or passed over altogether, possibly causing harm to patients who have potentially life-threatening aGVHD.

As noted above, remestemcel-L has failed in every randomized, concurrently controlled trial in which it has been investigated, regardless of indication. In the October 2020 CRL, the FDA recommended that Mesoblast "conduct at least one additional randomized, controlled study in adults and/or children to provide further evidence of the effectiveness of remestemcel-L for SR-aGVHD." Mesoblast has seemingly refused to do that, despite choosing to run a large, randomized, concurrently controlled trial for remestemcel-L in COVID-19-induced ARDS, which subsequently failed to meet its primary endpoint. Given this consistent history of disappointing and failed clinical studies, it would be inconsistent with the Public Health Service Act, the Federal Food, Drug, and Cosmetic Act, and the Agency's commitment to the public health to approve

remestemcel-L without at least one successful randomized, controlled study in adults and/or children to provide "substantial evidence" of the effectiveness of remestemcel-L for SR-aGVHD.

Thank you for your consideration of these supplemental comments, and please do not hesitate to contact me directly if you have any questions.

Sincerely,

Scott M. Lassman

APPENDIX
Pediatric Study Citations

TREATMENT	STUDY
Antithymocyte globulin, etanercept, or mycophenolate mofetil	Rashidi A, DeFor T, et al. Outcomes and predictors of response in steroid-refractory acute graft-versus-host disease: single-center results from a cohort of 203 patients. *Biol Blood Marrow Transplant*. 2019; 25(11): 2297-2302. doi:10.1016/j.bbmt.2019.07.017.
Ruxolitinib (45.0 OR rate)	Khandelwal P, Teusink-Cross A, et al. Ruxolitinib as Salvage Therapy in Steroid-Refractory Acute Graft-versus-Host Disease in Pediatric Hematopoietic Stem Cell Transplant Patients. *Biol Blood Marrow Transplant*. 2017; 23: 1122-1127. doi:10.1016/j.bbmt.2017.03.029.
Ruxolitinib (77.0 OR rate)	Vicent MG, Molina B, et al. Ruxolitinib treatment for steroid refractory acute and chronic graft vs host disease in children: Clinical and immunological results. *Amer Journal Hematology*. 2019; 94(3):319-326. doi: 10.1002/ajh.25376.
Ruxolitinib (87.5 OR rate)	Mozo Y, Bueno D, et al. Ruxolitinib for steroid-refractory graft versus host disease in pediatric HSCT: high response rate and manageable toxicity. *Pediatr Hematol Oncol.* 2021; 38(4): 331-345. doi: 10.1080/08880018.2020.1868637.
Ruxolitinib (80.0 OR rate)	EMA Assessment Report for Jakavi, Procedure No. EMEA/H/C/002464/II/0053 (March 24, 2022), available at Jakavi; INN-ruxolitinib (europa.eu).
CellEx Photopheresis System	Kitko CL, Abdel-Azim H, et al. A Prospective, Multicenter Study of Closed-System Extracorporeal Photopheresis for Children with Steroid-Refractory Acute Graft-versus-Host Disease. *Transplant Cell Ther*. 2022; 28(5):261.e1-261.e7. doi: 10.106/j.jtct.2022.01.025.
Basiliximab	Tang F, Cheng Y, et al. Basiliximab as Treatment for Steroid-Refractory Acute Graft-versus-Host Disease in Pediatric Patients after Haploidentical Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2019; 26(2): 351-357. doi:10.1016/j.bbmt.2019.10.031.
Etanercept	Faraci M, Calevo MG, et al. Etanercept as Treatment of Steroid-Refractory Acute Graft-versus-Host Disease in Pediatric Patients. *Biol Blood Marrow Transplant*. 2018; 25(4): 743-748. doi:10.1016/j.bbmt.2018.11.017.
Alemtuzumab (66.7 OR rate)	Khandelwal P, Emoto C, et al. A Prospective Study of Alemtuzumab as a Second-Line Agent for Steroid-Refractory Acute Graft-versus-Host Disease in Pediatric and Young Adult Allogeneic Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant*. 2016; 22(12): 2220-2225. doi:10.1016/j.bbmt.2016.09.016.
Alemtuzumab (100.0 OR rate)	Gomez-Almaguer D, Ruiz-Arguelles GJ, et al. Alemtuzumab for the treatment of steroid-refractory acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2008; 14(1): 10-15. doi:10.1016/j.bbmt.2007.08.052.
Alemtuzumab (73.7 OR rate)	Khandewal P, Lawrence J, et al. The successful use of alemtuzumab for treatment of steroid-refractory acute graft-versus-host disease in pediatric patients. *Pediatr Tranplant*. 2014; 18(1):94-102. doi: 10.1111/petr.12183.
Daclizumab	Miano M, Cuzzubbo D, et al. Daclizumab as useful treatment in refractory acute GVHD: a paediatric experience. *Bone Marrow Transplant*. 2009; 43(5): 423-427. doi: 10.1038/bmt.2008.331.
Mycophenolate mofetil	Inagaki J, Kodama Y, et al. Mycophenolate mofetil for treatment of steroid-refractory acute graft-versus-host disease after pediatric hematopoietic stem cell transplantation. Pediatr Transplant. 2015; 19(6): 652-658. doi: 10.1111/petr.12545.