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July 20, 2020

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: 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, the undersigned hereby submits this Citizen Petition pursuant to 42 U.S.C. § 262(a) and 21 C.F.R. §§ 10.25, 10.30, 601.2, and 601.4 to request the Commissioner of Food and Drugs 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").

The undersigned is concerned that the data submitted in the BLA to establish effectiveness – an open-label, single-arm, non-randomized study in pediatric patients and a failed, Phase 3 randomized study in adults and pediatric patients – fail 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 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.

I. Actions Requested

For the reasons set forth below, the undersigned respectfully requests the Commissioner of Food and Drugs 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.

The grounds for these requests are set forth in detail below.

II. Statement of Grounds

A. Background

1. SR-aGVHD and RYONCIL

Mesoblast is seeking FDA approval of RYONCIL (remestemcel-L) for treatment of children with SR-aGVHD. aGVHD is a potentially serious and life-threatening condition that often develops in patients following allogeneic hematopoietic stem cell transplantation ("HSCT"). aGVHD arises when donor T cells recognize alloantigens on the recipient patient's antigen-presenting cells, triggering an inflammatory response that damages target tissues, including the skin, gut, and liver. Depending on the severity of the inflammatory response and the number of organs involved, aGVHD can range from mild to severe (Grade 1-4) and is potentially life-threatening.

In view of the inflammatory nature of the disorder, corticosteroids (such as methylprednisolone) are the standard first-line treatment for grade 2-4 aGVHD. However, many patients with aGVHD do not experience sustained responses to corticosteroids, and these "steroid resistant" patients thus require second-line therapy. Until recently, there was no FDA approved treatment for patients with SR-aGVHD. In 2019, however, FDA approved Jakafi (ruxolitinib) tablets as the first second-line therapy for treatment of SR-aGVHD in adult and pediatric patients 12 years and older. At the time of this approval, Jakafi already was approved (since 2011) for other indications, including treatment of myelofibrosis and polycythemia vera, so the activity of the drug was well-established, and Jakafi had a substantial, pre-existing safety database upon which FDA could rely. Given this prior, relevant experience, FDA was able to approve Jakafi for treatment of SR-aGVHD based primarily upon a rigorous, open-label, single-arm, multicenter trial (REACH 1).[1] Subsequently, the results from this robust, single-arm trial were confirmed by a multicenter, randomized, and concurrently controlled Phase 3 trial demonstrating that ruxolitinib therapy led to significant improvements in efficacy outcomes versus control therapy (REACH 2).[2]

On April 1, 2020, Mesoblast announced that FDA had accepted for priority review its BLA for RYONCIL for treatment of children with SR-aGVHD. RYONCIL is an investigational biological product comprising culture-expanded mesenchymal stem cells ("MSCs") derived from the bone marrow of an unrelated donor. RYONCIL previously was studied for a number of other

[1] Przepiorka D, Luo L et al. FDA Approval Summary: Ruxolitinib for Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease. *The Oncologist* 2020;25:e328-e334 (Exhibit 1).

[2] Zeiser R, von Bubnoff N et al. Ruxolitinib for Glucocorticoid-Refractory Acute Graft-versus-Host Disease. *N Eng J Med*. 2020; 382:1800-1810.

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.[3]

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."[4] Mesoblast asserts 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.[5] Mesoblast thus is seeking FDA approval based primarily upon this single-arm study. Mesoblast has announced that the Prescription Drug User Fee Act ("PDUFA") action date for its BLA has been set as September 30, 2020.

2. Statutory and Regulatory Requirements

Under the PHS Act, a biological product cannot be licensed by FDA unless the sponsor demonstrates that it is "safe, pure, and potent." 42 U.S.C. § 262(a)(2)(C)(i)(I). FDA's implementing regulations have long interpreted the term "potency" to include "effectiveness." *See* 21 C.F.R. § 600.3(s). Accordingly, FDA has "generally considered substantial evidence of effectiveness to be necessary to support licensure of a biological product under section 351 of the PHS Act." FDA, *Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products [Draft]*, pp. 3-4 (Dec. 2019) ("Substantial Evidence Draft Guidance"). This is consistent with Congress's instruction that FDA take measures to "minimize

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[3] 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).

[4] 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).

[5] Mesoblast, Press Release: Primary Endpoint Successfully Achieved in Mesoblast's Phase 3 Cell Therapy Trial for Acute Graft Versus Host Disease (Feb. 21, 2018) (Exhibit 4), *available at* https://www.globenewswire.com/news-release/2018/02/21/1373001/0/en/Primary-Endpoint-Successfully-Achieved-in-Mesoblast-s-Phase-3-Cell-Therapy-Trial-for-Acute-Graft-Versus-Host-Disease.html. 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%.

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 Federal Food, Drug, and Cosmetic Act. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 123(f), 111 Stat. 2296 (1997).

The "substantial evidence" of effectiveness standard refers to both the quality and quantity of the evidence provided. 21 U.S.C. § 355(d). With respect to quality, FDA typically requires sponsors to demonstrate effectiveness via "adequate and well-controlled" clinical investigations. 21 U.S.C. § 355(d). "Reports of adequate and well-controlled investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs[,]" Including biological products. 21 C.F.R. § 314.126(a). With respect to quantity, "FDA has interpreted the law as generally requiring at least two adequate and well-controlled clinical investigations, each convincing on its own, to establish effectiveness …." FDA, Substantial Evidence Draft Guidance, p. 4. In certain, limited circumstances, however, FDA will accept one adequate and well-controlled clinical investigation plus confirmatory evidence to establish effectiveness. 21 U.S.C. § 355(d). A second adequate and well-controlled clinical investigation or, in some cases, confirmatory evidence, is intended to provide substantiation of experimental results in accordance with widely accepted scientific principles.

FDA's regulations describe the characteristics of an adequate and well-controlled clinical investigation. *See* 21 C.F.R. § 314.126. Generally, an adequate and well-controlled trial must incorporate: (a) a control; (b) a method of patient assignment to treatment (e.g., randomization); (c) adequate measures to minimize bias (e.g., blinding); (d) well-defined and reliable assessments of individuals' responses (e.g., meaningful efficacy endpoint); and (e) adequate analysis of the clinical investigation's results to assess the effects of the drug (i.e., statistical methods). 21 C.F.R. § 314.126(b)*; see also* FDA, Substantial Evidence Draft Guidance, p. 5. These safeguards, particularly the requirement for a control group, are necessary because the primary purpose of adequate and well-controlled clinical trials "is to distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation." 21 C.F.R. § 314.126(a).

FDA typically requires at least one randomized, concurrently controlled trial to support traditional approval of a drug or biological product. This is because the main purpose of control groups is "to allow discrimination of patient outcomes (for example, changes in symptoms, signs, or other morbidity) caused by the test treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatment." FDA, *Guidance for Industry: Choice of Control Group and Related Issues in Clinical Trials (ICH E10)*, p. 3 (May 2001) ("ICH E10 Guidance"). Although FDA regulations permit the use of external controls (such as historical controls), in most situations, "a concurrent control group is needed because it is not possible to predict outcome with adequate accuracy and certainty." *Id*. Moreover, the "inability to eliminate systematic differences between treatment groups is a major problem of studies without a concurrent randomized control …" *Id*. In historically controlled trials, the "groups can be dissimilar with respect to a wide range of factors, other than use of the study treatment, that could affect outcome, including demographic characteristics, diagnostic criteria, stage or severity of disease, concomitant treatments, and observational conditions (such as methods of assessing outcome, investigator expectations)." *Id*. at 26-27.

Because of this inability to control bias, external control designs typically are restricted to situations "in which the effect of treatment is dramatic and the usual course of the disease highly predictable." *Id*. at 27. In other words, "[a]n externally controlled trial 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 and the disease or condition to be treated has a well-documented, highly predictable course." *Id*. at 28. "In addition, use of external controls should be limited to cases in which the endpoints are objective and the impact of baseline and treatment variables on the endpoint is well characterized." *Id*. at 27. Because of these significant disadvantages, FDA has warned that it is "well documented that externally controlled trials tend to overestimate efficacy of test therapies. It should be recognized that tests of statistical significance carried out in such studies are less reliable than in randomized trials." *Id*. at 29.

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

As discussed above, 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. Remestemcel-L's Mechanism of Action Is Poorly Defined

As an initial matter, the lack of understanding regarding remestemcel-L's mechanism of action underscores the need for robust clinical data in support of efficacy. Of particular concern, remestemcel-L lacks a prospectively defined hypothesis for why the drug modulates cytokines, which Mesoblast claims leads to a clinically meaningful benefit in aGVHD.

In fact, remestemcel-L's mechanism of action is poorly defined. At an aGVHD doctor panel that financial services firm Cantor Fitzgerald held on June 8, 2020 with Drs. Jonathan Gutman (Director of Allogeneic Transplant, University of Colorado) and James Ferrara (Professor and Director of Hematology and Medical Oncology at Mount Sinai Hospital in New York), Dr. Ferrara remarked:

> [T]the mechanism of action of this is -- seems to be multiple. You can't -- this isn't like a drug. It's a cellular therapy. But when -- in the animal models when they did this, well, where are the cells going and what precisely are they doing? The data weren't particularly clear, so it's a little bit fuzzy around some what we would have called the harder science, and now you've got -- and now you've got this

> previous phase 3 that didn't work. Now you've got a really strong phase 2, but is that the luck of small numbers?[6]

Given Dr. Ferrara's prominence in the field of GVHD, in general, and pediatrics, in particular, it is unlikely that remestemcel-L's mechanism of action is well-understood if his experience and review of the literature was unable to identify one. This conclusion is consistent with an independent review of the scientific literature, which also fails to support a rational mechanism of action. For instance, a 2018 paper reviewing MSC's for treatment of SR-GVHD that specifically mentions remestemcel-L notes: "Although numerous clinical studies using MSCs for the treatment of GVHD have been conducted, *the mechanisms by which MSCs mediate their immunosuppressive effect against GVHD in humans is still unknown*."[7]

This lack of a mechanistic understanding of how MSC's can modulate pathophysiology appears to have led to a "shotgun" approach regarding the development of remestemcel-L. Prior to Mesoblast's submission of the current BLA for treatment of SR-aGVHD in pediatric patients, remestemcel-L had been investigated as a potential treatment for a number of different diseases with the hopes that it might work somewhere. Specifically, clinical trials in remestemcel-L have been conducted in a variety of different diseases, including COPD, ACS, and DMT1. According to third party research sources, each of these programs were suspended, suggesting an apparent lack of efficacy.

In addition, a fourth program in Crohn's disease was suspended in 2009 due to what the sponsor called a "design flaw" in the trial, which the sponsor claimed led to a significantly higher placebo response than expected.[8] The sponsor purportedly fixed the design flaw and resumed the trial in 2010, but the results were never published or reported publicly on ClinicalTrials.gov. Moreover, it does not appear the sponsor ever sought approval of remestemcel-L for treatment of Crohn's disease.

Given that lead programs for drugs and biological products tend to follow the most promising indications, it is sensible to believe that the GVHD indication represents a "4th string" probability of success for remestemcel-L. As described further below, remestemcel-L has already failed to demonstrate efficacy in a broad aGVHD indication that includes both adults and pediatric patients, and there is little reason to believe it would perform better in pediatric patients alone. This history of failed clinical trials in (a) other indications and (b) a broad GVHD indication raises significant doubts as to whether stem cell therapy makes mechanistic sense for treatment of SR-aGVHD in pediatric patients.

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[6] Transcript of Cantor Fitzgerald Panel, pp. 42-43 (June 8, 2020) ("Transcript") (Exhibit 5).

[7] Galipeau, J. Mesenchymal Stromal Cells. *Hematology (Seventh Edition)*. 2018 (emphasis added). Available at https://www.sciencedirect.com/topics/medicine-and-dentistry/remestemcel-l.

[8] Forbes, Placebo Effect Drags Down Osiris (March 27, 2009), *available at* https://www.forbes.com/2009/03/27/osiris-therapeutics-crohns-markets-equity-pharmaceuticals.html#5ecb18dd5e3f.

2. Remestemcel-L's Failed Phase 3, Concurrently Controlled Trials in GVHD Must Be Considered As Evidence Against Efficacy

In 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 GVHD,[9] i.e., studies 265[10] and 280.[11] In both randomized, concurrently controlled trials, remestemcel-L failed to demonstrate efficacy as assessed by the primary endpoints. The first phase 3 trial, Study 265, enrolled 192 patients ages 18-70 years with aGVHD grades B-D across 52 transplant centers. The second trial, Study 280, enrolled 260 patients ages 6 months to 60 years with SR-aGVHD grades B-D across 72 transplant centers.

In 2009, the two trials definitively failed to show benefit in the intent-to-treat ("ITT") population for their primary endpoints[12]:

- There was no statistical difference between remestemcel-L and placebo on the primary endpoints for the ITT populations in either the steroid-refractory (35% vs. 30%, n=260) or the first-line (45% vs. 46%, n=192) GvHD trials;

- The primary endpoint for the steroid-refractory GvHD trial (durable complete response) for the per-protocol population approached statistical significance (40% vs. 28%, p=0.087, n=179), but still was not statistically significant;

- In patients with steroid-refractory liver GvHD, treatment with remestemcel-L significantly improved response (76% vs. 47%, p=0.026, n=61) and durable complete response (29% vs. 5%, p=0.046);

- Remestemcel-L significantly improved response rates in patients with steroid-refractory gastrointestinal GvHD (88% vs. 64%, p=0.018, n=71); and

- In pediatric patients, remestemcel-L showed a trend of improvement in response rates (86% vs. 57%, p=0.094, n=28), but did not reach statistical significance.

It appears that the last three findings, including the findings regarding pediatric patients, are derived from a *post hoc* analysis of data from the two trials.

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[9] These clinical trials were conducted by Osiris Therapeutics, Inc. ("Osiris"), the previous owner of remestemcel-L, which was then being developed under the trade name "Prochymal."

[10] NIH, ClinicalTrials.gov, *available at* https://clinicaltrials.gov/ct2/show/NCT00562497.

[11] NIH, ClinicalTrials.gov, *available at* https://www.clinicaltrials.gov/ct2/show/NCT00366145.

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

The study's sponsor subsequently performed *post hoc* subgroup analyses of Study 280 in which it claimed to have identified a subset of patients who benefitted from remestemcel-L:

- Children receiving remestemcel-L had an overall response rate of 64% compared to 36% of patients receiving placebo;

- Treatment with remestemcel-L resulted in a 29-point improvement in 100-day survival compared to placebo (79% vs. 50%); and

- There was no infusional toxicity reported, no evidence of remestemcel-L leading to ectopic tissue, and no adverse events leading to discontinuation of therapy.[13]

In 2013, Mesoblast purchased remestemcel-L from the prior study sponsor, Osiris. Based on the findings in the two failed, phase 3 trials, Mesoblast conducted an open label, single arm, phase 3 trial with remestemcel-L in 55 SR-aGVHD patients ages two months to 17 years.[14] Patients enrolled had grades B-D aGVHD excluding grade B, skin only. The trial excluded patients who received systemic agents other than steroids for aGVHD. Planned treatment was eight bi-weekly intravenous ("IV") infusions of 2 × 10^6 hMSCs/kg for four weeks, with four additional weekly infusions after day +28 for patients who achieved a partial or mixed response. The primary endpoint was the rate of overall response (partial response + complete response) at Day 28 ± two days, and the key secondary endpoint was overall survival at Day 100 ± seven days.[15]

Mesoblast claimed that the primary endpoint was met with a Day 28 overall response rate of 69%, which it claims was statistically significantly superior to the protocol-defined historical control rate of 45% (p=0.0003).[16] Additionally, patients who received at least one treatment infusion were followed up for 100 days (n=50), with a mortality rate of 22%. The company contrasted this against a Day 100 mortality rate of 70% in patients who failed to respond to initial steroid therapy based upon historical rates it derived from literature. As discussed further below, the comparisons between the remestemcel-L treatment group and historical control groups appear to be "apples to oranges" given the age differences of patients in Mesoblast's trial compared to the referenced trials.

Significantly, the two prior remestemcel-L trials used a variation of complete response ("CR") as the primary endpoints. It is important to note that the rate of CR between these two prior, failed trials and the new, single-arm trial were similar. In the 265 study, 45% of patients

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[13] Health Canada, Product Monograph for PROCHYMAL, *available at* https://pdf.hres.ca/dpd_pm/00024994.PDF.

[14] Kurtzberg J et al., *supra* note 4.

[15] NIH, ClinicalTrials.gov, *available at* https://clinicaltrials.gov/ct2/show/NCT02336230.

[16] Mesoblast Press Release, *available at* https://www.globenewswire.com/news-release/2018/05/08/1498184/0/en/mesoblast-phase-3-trial-results-for-acute-graft-versus-host-disease-presented-at-2018-international-society-for-cell-and-gene-therapy-annual-meeting.html.

survived at least 90 days to achieve a complete response,[17] and in the 280 study, 35% of patients achieved a durable complete response.[8] By comparison, in the phase 3 single-arm study, only 29% achieved CR at day 28 and 44% at day 100.[18] This casts substantial, additional doubt as to whether the single-arm study would have been successful with a concurrent control arm.

3. Remestemcel-L's "Successful" Historical Control Cohort Is Severely Confounded

FDA has recognized that the use of historical control cohorts in trials often leads to errant conclusions and thus should be used only sparingly in "unusual circumstances." ICH E10 Guidance, p. 4. In particular, it is frequently very difficult to ensure that a comparative control arm is selected without bias and properly controls for differences in patient selection criteria, clinical trial environments, concurrent medication use, changes in time to diagnosis, and improvements in standard of care treatment over time. ICH E10 Guidance, pp. 26-27. As a result, "[i]t is well documented that externally controlled trials tend to overestimate efficacy of test therapies." ICH E10 Guidance, p. 29. In this case, there are strong reasons to believe that these concerns are operative and serve to undercut the validity of the results of Mesoblasts single-arm, non-randomized clinical study in pediatric patients with SR-aGVHD.

In fact, while discussing remestemcel-L, Dr. Gutman highlighted the dangers of relying on uncontrolled trials to make conclusions in this patient population, especially given approved agents that could be used as active controls:

> But I think the gold standard for really understanding how well things work is generally going to be a randomized trial where we're – and I think we're now maybe getting to a place in GVHD where we have enough agents that might have efficacy that we could start thinking about that in more meaningful ways. But I think there's a long history in GVHD studies of phase 2 studies looking quite promising and when further efforts are undertaken to maybe more robustly or rigorously study the drug, their efficacy may not be quite as high as it appears up front.[19]

Dr. Ferrara added his skepticism of the historical control cohort used by Mesoblast to assess efficacy, commenting that the age of the historical control data was likely to result in an uninterpretable comparison:

> The patients were sick, but the problem is, if you'll notice, the data that they show for I think it was grades 3 and 4 and Grades C and D,

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[17] Bioprocess Online, *supra* note 12, *available at* https://www.bioprocessonline.com/doc/osiris-therapeutics-announces-preliminary-res-0001.

[18] Mesoblast Press Release, *supra* note 5, *available at* https://www.globenewswire.com/news-release/2018/02/21/1373001/0/en/Primary-Endpoint-Successfully-Achieved-in-Mesoblast-s-Phase-3-Cell-Therapy-Trial-for-Acute-Graft-Versus-Host-Disease.html.

[19] Transcript, p. 32, *supra* note 6.

> that paper was published, was published in 2005,[20] and that means that the data of those patients is between 18 and 20 years old. So that's – I don't know what – 3 to 4s these days don't have disease that is that bad. You don't see – all of those patients died. And grade 4 is still bad disease, but it's not 100 percent fatal. So I think that that's another grain of salt to put in there. And just one final thing, Dr. Gutman's absolutely right. In general, GVHD occurs less frequently in children and is more easy to treat in children in general.[21]

Dr. Ferrara's concerns regarding use of a historical control in this case echo FDA's concerns regarding historical controls generally. As FDA has warned, external controls are often biased because, *inter alia*, "[c]ritical patient disease characteristics may not have been assessed or may have been assessed differently based on historical approaches, resulting in a lack of comparability (e.g., disease definitions, diagnostic techniques, and approaches to safety monitoring may have evolved)." FDA, *Rare Diseases: Natural History Studies for Drug Development* [Draft], p. 5 (March 2019) ("Rare Diseases Draft Guidance").

There are also significant problems with Mesoblast's use of a 45% historical OR rate to assess efficacy, which it claims 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."[22] However, the references cited by Mesoblast do not appear to support its historical control.[23] 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 higher than Mesoblast's preferred historical control rate of 45%.[24] While this study included some grade I patients, this appears to have made little difference: "Initial GVHD grade did not predict overall response at day 28 being 68% for grade I, 67% for grade II, 59% for grade III, and 43% for grade IV (p=0.21)."[25] Because it is well-known that GVHD is easier to treat in pediatric patients, these higher day 28 OR rates in pediatric patients appear to be a more appropriate historical comparator than the 45% OR rate used by Mesoblast. At the very least, it raises significant questions about whether Mesoblast's historical control is biased and/or whether the results of the single-arm study

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[20] Dr. Ferrara was likely referring to the 2002 trial relied on (in part) by Mesoblast to derive the historical OR rate of 45% used in its single-arm, pivotal efficacy study. *See* MacMillian ML, Weisdorf DJ, Wagner JE et al. Response of 443 patients to steroids as primary therapy for acute graft-versus-host-disease: comparison of grading systems. *Biol Blood Marrow Transplant*. 2002;8:387-394.

[21] Transcript, pp. 48-49, *supra* note 6.

[22] Kurtzberg et al., *supra* note 4.

[23] Supplementary materials to Kurtzberg et al. (Exhibit 7).

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

[25] MacMillan et al., *supra* note 24.

overestimate the efficacy of remestemcel-L, as is often seen with historically controlled, non-randomized, single-arm studies.

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.

4. FDA Should Require a Randomized, Concurrently Controlled Clinical Trial

In light of a series of failed randomized, placebo-controlled phase 3 trials and a confounded, non-randomized, historically controlled trial, FDA should 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." Substantial Evidence Draft Guidance, p. 16. 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." *Id*. at 14.

In this case, a randomized, concurrently controlled clinical trial appears to be possible. Mesoblast claims to have chosen a single-arm design based on feedback from investigators and key experts in pediatric aGVHD indicating that a randomized, controlled study design would be "challenging" and "potentially unfeasible" because patients "might be reluctant to consent to participate in the study" if they were not assured of receiving study drug.[26] But just because a clinical study may be "challenging" does not mean it is impossible. 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 …." ICH E10 Guidance, p. 28. In this case, even before the approval of Jakafi, there was no objective evidence to support a "prior belief in the superiority of [remestemcel-L] to all available alternatives." Quite the contrary, although there were some promising signals regarding efficacy in pediatric patients, the data were, at best, mixed. Following the approval of Jakafi, however, there is even less reason to believe remestemcel-L is superior to all available alternatives.

Moreover, although FDA approved Jakafi in 2019 for treatment of SR-aGVHD in adult and pediatric patients 12 years and older based primarily upon the results of a pivotal, single-arm clinical trial, this precedent cannot be applied to remestemcel-L. FDA accepted the results from the single-arm clinical trial as the sole basis of efficacy only after considering several regulatory factors regarding SR-aGVHD and prior clinical experience with Jakafi. Specifically, the FDA reviewers explained that such reliance was appropriate "where the disease is life-threatening, there are no approved therapies and no optimal therapy identified, the efficacy endpoint is objective, the

[26] Kurtzberg et al., *supra* note 4.

activity of the drug is established in other diseases, and there is a substantial safety database ….”[27] Significantly, several of these factors clearly do not apply to remestemcel-L.

First, now that Jakafi has been approved for treatment of SR-aGVHD – including in pediatric patients 12 years and older – the regulatory landscape is materially different than when FDA reviewed and approved the Jakafi NDA. Specifically, there is now an approved therapy that has been proven safe and effective for the treatment of SR-aGVHD, including in certain pediatric patients. Accordingly, the “unmet need” for therapies for patients with SR-aGVHD is not nearly as acute now in light of Jakafi’s 2019 approval.

Second, the “activity” of remestemcel-L has not been established in any other diseases – or even any other GVHD patient populations. As noted above, when Jakafi was approved for SR-aGVHD in 2019, it had been on the market for nearly eight years for other indications, including treatment of myelofibrosis and polycythemia vera. Moreover, its mechanism of action as an inhibitor of Janus Associated Kinases JAK1 and JAK2 was well-established.[28] In this case, remestemcel-L’s mechanism of action is poorly defined and not well understood. Moreover, remestemcel-L has never been approved for treatment of any other disease and in prior clinical trials has even failed to demonstrate efficacy *for the treatment of aGVHD*. Indeed, in the two randomized, concurrently controlled clinical trials described above, remestemcel-L failed to meet the primary endpoints for efficacy in a broad population of aGVHD patients. To the best knowledge and understanding of the undersigned, Mesoblast has not released or published any explanation for why remestemcel-L would perform differently and/or better in pediatric patients than in adult patients.

Because remestemcel-L’s regulatory situation differs markedly from Jakafi’s, the Jakafi approval cannot be used to justify relying upon a single-arm, open-label trial as the primary basis for demonstrating effectiveness of RYONCIL. Instead, Mesoblast should be required to conduct at least one randomized, controlled trial to provide “substantial evidence” of the effectiveness of remestemcel-L (plus confirmatory evidence).

5. Approval of Remestemcel-L Without Definitive Efficacy Data Risks Harm to Pediatric Patients with Potentially Life-Threatening SR-aGVHD

Finally, 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. Because of the serious and progressive nature of SR-aGVHD, even minor delays in effective treatment pose a serious public health concern.

Moreover, although there currently is no FDA-approved treatment for pediatric patients younger than 12 years old, FDA would actually do such patients a disservice by approving an unproven and potentially ineffective treatment based upon an inadequate dataset. Doing so not

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[27] Przepiorka D et al., *supra* note 1.

[28] Jakafi Approved Labeling, § 12.1 (Rev. 01/2020) (Exhibit 9), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202192Orig1s019Rpllbl.pdf.

only could make it more difficult to conduct rigorous, concurrently controlled trials to determine with a high degree certainty whether or not remestemcel-L is effective but also could impede the development of other promising therapies for treatment of pediatric patients with SR-aGVHD.

Finally, to the extent remestemcel-L holds any promise for such pediatric patients younger than 12 years old, such patients would not be without treatment options if FDA refuses to approve remestemcel-L based upon the current, inadequate dataset. To the contrary, such patients could continue to access remestemcel-L via: (1) adequate and well-controlled clinical trials designed to assess its effectiveness, (2) expanded access protocols, and (3) a request submitted pursuant to the Right to Try Act, Pub. L. No. 115-176 (2018). Significantly, these avenues would provide access to remestemcel-L for pediatric patients suffering from SR-aGVHD while preserving the ability of Mesoblast and FDA to assess, through adequate and well-controlled clinical investigations, whether remestemcel-L is actually effective for treating SR-aGVHD in pediatric patients even though it showed no statistically significant evidence of effectiveness in a previous, randomized, concurrently controlled clinical trial in adults and pediatric patients suffering from SR-aGVHD.

C. Conclusion

In conclusion, the undersigned believes that 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. Accordingly, FDA should refuse to approve BLA 125706 for RYONCIL unless and until Mesoblast 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.

III. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

IV. Economic Impact

Petitioner will submit economic information upon request of the Commissioner.

V. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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Exhibits