FDA Session on Clinical Evidence

BLA 125706

Remestemcel-L

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Proposed Indication

- Treatment of steroid-refractory acute graft-versus-host disease (SR-aGvHD) in pediatric patients.

- One single-arm trial as the basis of efficacy
  - Study MSB-GVHD001*

*FDA's analyses use data pooled from Protocol MSB-GVHD001 and MSB-GVHD002; the results of these analyses are reported under Protocol MSB-GVHD001.

Outline

- Issue #1 - MSB-GVHD001: Trial Design Issues
  - Regulatory background on choice of controls
  - MSB-GVHD001: trial design
  - Justifying the null Day-28 overall response rate (ORR)
  - Summary
- Issue #2 - Remestemcel-L: Evidence of Effectiveness
  - Regulatory background on single trials
  - MSB-GVHD001: FDA Analysis
  - Supporting Evidence: FDA Analysis
  - Summary

ISSUE #1

PROTOCOL MSB-GVHD001: TRIAL DESIGN ISSUES

GVHD001 Design Elements

- Single-arm trial
- Pediatric patients
- Steroid-refractory Grades B-D aGVHD
- Treatment plan
- Primary efficacy endpoint
  - Day-28 ORR
  - Durability
- Success if Day-28 ORR is > 45%

GVHD001 Design Elements

- Single-arm trial
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- Primary efficacy endpoint
  - Day-28 ORR
  - Durability
- Success if Day-28 ORR is > 45%

Evidence of Effectiveness

- To obtain marketing approval, FDA requires that sponsors provide substantial evidence of safety and efficacy of their products based on the conduct of adequate and well-controlled studies.[1, 2, 3]
- Randomized superiority trials with a placebo- or active-control design generally provide the strongest evidence of effectiveness.
- No requirement to demonstrate superiority over other treatments.

[1] Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-392 Suppl

[2] Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. Guidance for Industry. (December 2019)

[3] Section 351 of the Public Health Service Act (PHS Act) (42 U.S.C.§ 262)

Limitations of Single-Arm Trials[1]

- Lack of randomization
  - Differences in patient characteristics or concomitant treatments in the trial population compared to the external control may lead to differences in outcomes that are unrelated to the investigational treatment.
- Lack of blinding
  - May introduce bias in concomitant treatment or endpoint assessment.
- For these reasons, external control designs are usually reserved for specific circumstances, such as trials of diseases with high and predictable mortality or progressive morbidity.

[1] Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. Guidance for Industry. (December 2019)

Applicability of Single-Arm Trials[1]

- Natural history of the disease is well-defined
- External control population is very similar ("exchangeable") to the study population
- The study endpoint is objective
- Concomitant treatments are consistent between the external controls and the study population
- Success based on compelling evidence of a change in the established disease progression

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External Controls[1]

- The International Conference on Harmonisation (ICH) E10 guidance describes the limitations when choosing an external control.
  - It is difficult to establish comparability of the treatment and control groups.
  - Groups can be dissimilar regarding a range of factors other than the study treatment affecting outcome.
  - Such dissimilarities can include important but unrecognized prognostic factors that have not been measured. As such, externally-controlled trials can be subject to bias and may overestimate efficacy of test therapies.
  - Tests of statistical significance carried out in such studies may be less reliable than in randomized trials.

[1] E10 Choice of Control Group and Related Issues in Clinical Trials. (May 2001)

MSB-GVHD001 Design

Choosing the Null Rate for the Primary Endpoint

- The primary efficacy endpoint was Day-28 overall response rate (ORR) = complete response + partial response (CR + PR)
- Ideally, the null rate would have been based on the expected Day-28 ORR in patients who are untreated (or treated with a standard-of-care (SOC) comparator)
  - The target treatment effect is based on a clinically meaningful improvement from the null rate.

MSB-GVHD001 Design

Choosing the Null Rate for the Primary Endpoint

- Ideal approach not used by Applicant
- In MSB-GVHD001,
  - The Day-28 ORR for treatment with remestemcel-L was anticipated to be 65% based on the rate seen in Protocol 275 and for the remestemcel-L-treated pediatric subgroup of Protocol 280.
  - An effect size of 20% was deemed clinically meaningful.
  - The null hypothesis using 45% ORR was calculated as a rate that was 20 points lower than the anticipated 65% ORR rate.
- Therefore additional justification was needed

Proposed Justification for Null Rate

Data from Prior Trials

- In the SOC + placebo arm of Protocol 280, the ORR was 74% for patients with "standard risk" SR-aGVHD and 37% for those with "high-risk" SR-aGVHD. Assuming accrual of "standard risk" to "high risk" patients at 3:1 in GVHD001, the risk-adjusted null rate would be 46% for a study of 60 patients.

Limitations: adult patients, additional salvage therapy

- In the steroids + placebo arm of Protocol 265, there were 33 adults identified as not responding to steroids by Day 7 who continued on study. Of these 33 adults, 14 (42%; 95% CI: 26% – 61%) achieved CR or PR at the Day 35 assessment (28 days later).

Limitation: subgroup analysis, adult patients

Proposed Justification for Null Rate

Data from Prior Trials

- In the SOC + placebo arm of Protocol 280, the Day-28 ORR was 36% for the 14 pediatric patients accrued.

Limitation: small number, subgroup analysis, additional salvage therapies, patients were not randomized by age

- In the Mount Sinai Acute GVHD International Consortium (MAGIC) database, there were 30 pediatric patients transplanted 2005 - 2019 who received salvage therapy for grades B-D SR-aGVHD (excluding grade B skin alone as in MSB-GVHD001). The Day-28 ORR for pediatric patients after first salvage therapy was 43%.

Limitations: post hoc analysis, data does not inform the null, patients not matched to GVHD001

Background Historic Rates
Data from Literature

- In a retrospective analysis from Day-28 ORR for second-line therapy for SR-aGVHD for the 61 pediatric patients was 34%. Notably, the pediatric subgroup had the lowest Day-28 ORR (34% for patients < 18 years; 36% for patients 18-40 years, and 43% for patients > 40 years).*

Limitation: question of whether these patients are exchangeable with the study population.

*Rashidi A, DeFor TE, et al (2019) Outcomes and predictors of response in steroid-refractory acute graft-versus-host disease. **BBMT 25:2297-2302**

Background Historic Rates
Data from Literature

- A prospective study evaluating etanercept in 25 children with grade II-IV SR-aGVHD observed an ORR of 68% (17/25) at Day 7.[1]
- A retrospective analysis from the Pediatric Blood and Marrow Transplant Consortium (PBMTC) evaluated infliximab in 22 children with SR-aGVHD. The ORR, defined as the maximal response with 56 days of starting treatment was 82%.[2]
- A single-center, prospective study of alemtuzumab as a 2nd- line agent for SR aGVHD in pediatric and young adults with grades II to IV aGVHD. The ORR was 67% at 4 weeks (CR 40%, PR 27%).[3]

Limitations: Small studies, varied endpoints, varied definitions of steroid refractoriness

[1]Faraci M, Calevo MG, et al. (2019) Etanercept as treatment of SR-aGVHD in pediatric patients. **BBMT;25(4):743-748.**
[2]Sleight, B., Chan, K., et al. (2007) Infliximab for GVHD therapy in children. **BMT 40, 473–480.**
[3] Khandelwal P, Emoto C, et al. A prospective study of alemtuzumab as a second-line agent for SR-aGVHD in pediatric and young adult alloHSCT. (2016) **BBMT22:2220-2225.**

Confounding Factors for the Justification for Null Rate / Historic Controls

- The ORRs observed are highly variable
  - Potential for publication bias
  - Confidence interval wide with small numbers of patients
- Limited ability to ensure population exchangeability
  - Baseline disease definition
  - Baseline prognostic factors, both known and unknown
  - Concomitant immunosuppressive drugs
  - Supportive care measures that could influence efficacy outcomes
- Limited ability to ensure that the reported endpoint is the same
  - Endpoint definition
  - Endpoint measurement

GVHD001 Study Design Issues

Summary

- MSB-GVHD001 was a single-arm trial designed to determine if the Day-28 ORR exceeded 45% for pediatric patients with SR-aGVHD grades B-D treated with remestemcel-L.
- Although the null rate and hypothesis were prespecified in the Statistical Analysis Plan (SAP), there were some limitations with regard to how 45% was chosen for the null rate.
- It is uncertain as to whether the data cited for use as historical controls are applicable for establishing the null hypothesis for the purposes of quantitating a treatment effect in a single-arm trial of a new therapy for SR-aGVHD in pediatric patients.

GVHD001 Study Design Issues

For Discussion

- Given these limitations, please discuss the strengths and weaknesses of the design of Study MSB GVHD001?

ISSUE #2

REMESTEMCEL-L: EVIDENCE OF EFFECTIVENESS?

Single Trial Requirements

- Reliance on a single trial to establish effectiveness is generally limited to situations in which the trial has
  - demonstrated a clinically meaningful effect on a potentially serious outcome, and
  - confirmation of the results in a second trial would be practically or ethically impossible*

*Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Draft Guidance for Industry, 2019

Study GVHD001 Primary Efficacy Endpoint: Day 28 ORR, FDA Analysis

Analysis Set	N	Day-28 CR n, %	Day-28 PR n, %	Day-28 ORR n, %	Day-28 ORR 95% CI
Full Analysis Set	55	16 29.1%	22 40.0%	38 69.1%	(55.2, 80.9)
Treated Set	54	16 29.6%	22 40.7%	38 70.4%	(56.3, 82.0)
Sensitivity Set 1	45	15 33.3%	19 42.2%	34 75.6%	(60.5, 87.1)
Sensitivity Set 2	55	15 27.3%	19 34.5%	34 61.8%	(47.8, 74.6)

Source: FDA analysis

Abbreviations: CI, confidence interval; CR, complete response; ORR overall response rate; PR, partial response

- Despite the positive outcome of this trial, the clinical meaningfulness is unclear in the setting of the uncertainties and limitations in determining the null for this population

Study GVHD001 Duration of Response: Duration of Day-28 ORR, FDA Analysis

Definition Used	Duration of ORR days (n=38)		Duration of CR days (n=16)		Duration of PR days (n=22)	
	Median	Range	Median	Range	Median	Range
Applicant-defined DOR[a]	70.5	1, 171	N/A	N/A	N/A	N/A
FDA-defined DOR[b]	54	7, 159+	50.5	10, 158+	57.5	7, 159+
FDA-defined alternative measure of durability[b]	111.5	9, 182+	112+	16, 172+	111.5	9, 182+

Abbreviations: CI, confidence interval; CR, complete response; DOR, duration of response; N/A, not available, ORR overall response rate; PR, partial response

- FDA's DOR is shorter than the Applicant's based on definitions provided in the FDA Briefing Document (Table 3: Computation of DOR)

Remestemcel – L: aGVHD Pediatric Clinical Trials

	Protocol 001	Protocol 280	Protocol 275
Phase	Phase 3	Phase 3	Expanded access
Ages	Pediatric	Adult and pediatric	Pediatric
Population	SR-aGVHD grade B-D aGVHD (no skin only grade B)	SR-aGVHD grade B-D aGVHD (skin only grade B allowed)	SR-aGVHD grade B-D aGVHD (skin only grade B allowed)
Design	Single arm, multi-center	Randomized, double-blind, placebo- controlled, multicenter	Single arm
Primary Endpoint	Day-28 ORR	CR $\geq$ 28 days duration	Day-28 ORR
Control Arm	-	SOC + Placebo	-
Treatment Arm	Remestemcel-L 2×10^6 cells/kg x 2 infusions/week x Weeks 1-4, then 1 infusion/week x Weeks 5-8 (continuation)	SOC + remestemcel-L 2×10^6 cells/kg x 2 infusions/ week x Weeks 1-4, then 1 infusion/week x Weeks 5-8	SOC + remestemcel-L 2×10^6 cells/kg x 2 infusions/ week x Weeks 1-4, then 1 infusion/week x Weeks 5-8

Abbreviations: CR, complete response; EAP, expanded access protocol; ORR, overall response rate; SOC, standard care salvage therapy.

Remestemcel –L aGVHD Clinical Trials: Pediatric Day 28 ORR

	Protocol 001	Protocol 280 (Pediatric subgroup)		Protocol 275
Arm	Rem-L	SOC + Rem-L	SOC + Placebo	SOC + Rem-L
Number of treated patients	54	14	13	241
Day-28 ORR[b] (95% CI)	69.1% (55.2, 80.9)	64.3% (35.1,87.2)	38.5% (13.9, 68.4)	65.1% (58.8, 71.1)

Issues with cross-study comparison:

- Studies 280 and 275 allowed new salvage therapy for aGVHD
- Small numbers of patients
- The 280 subgroup analysis not persuasive (large CI)

Remestemcel – L: aGVHD
Randomized, Placebo-Controlled Trials

	Protocol 001	Protocol 265	Protocol 280
Phase	Phase 3	Phase 3	Phase 3
Ages	Pediatric	Adult	Adult and pediatric
Population	SR-aGVHD grade B-D aGVHD (no skin only grade B)	Newly-diagnosed grade B-D aGVHD (skin only grade B allowed)	SR-aGVHD grade B-D aGVHD (skin only grade B allowed)
Design	Single arm, multi-center	Randomized, double-blind, placebo-controlled, multicenter	Randomized, double-blind, placebo-controlled, multicenter
Primary Endpoint	Day-28 ORR	CR $\geq$ 28 days duration	CR $\geq$ 28 days duration
Control Arm	-	Steroids + Placebo	SOC + Placebo
Treatment Arm	Remestemcel-L 2×10^6 cells/kg x 2 infusions/week x Weeks 1-4, then 1 infusion/week x Weeks 5-8 (continuation)	Steroids + remestemcel-L 2×10^6 cells/kg x 2 infusions/ week x Weeks 1-2, then 1 infusion/week x Weeks 3-4	SOC + remestemcel-L 2×10^6 cells/kg x 2 infusions/ week x Weeks 1-4, then 1 infusion/week x Weeks 5-8

Abbreviations: CR, complete response; EAP, expanded access protocol; ORR, overall response rate; SOC, standard care salvage therapy.

aGVHD Clinical Trials: Efficacy Results Randomized, Placebo-Controlled Trials

	Protocol 001	Protocol 265		Protocol 280	
	Rem- L	Steroids + Rem-L	Steroids + Placebo	SOC + Rem-L	SOC + Placebo
Number of patients	54	97	95	173	87
CR lasting ≥ 28 days	-	45%	46%	35%	30%
Day-28 ORR[b] (95% CI)	70.4% (56.3, 82.0)	60% (49.3, 69.6)	61% (50.5, 70.9)	54% (46.0, 61.3)	47% (36.3, 58.1)
Day-28 CR	29.6%	41%	49%	25%	23%
Day-28 PR	40.7%	19%	12%	29%	24%

Issues with cross-study comparison:

- Differences in patient populations
  - Adults, newly diagnosed aGVHD on Study 265
- Allowance for salvage aGVHD therapies on study 280

aGVHD Clinical Trials: Efficacy Results Randomized, Placebo-Controlled Trials

	Protocol 001	Protocol 265		Protocol 280	
	Rem- L	Steroids + Rem-L	Steroids + Placebo	SOC + Rem-L	SOC + Placebo
Number of patients	54	97	95	173	87
CR lasting ≥ 28 days	-	45%	46%	35%	30%
Day-28 ORR[b] (95% CI)	70.4% (56.3, 82.0)	60% (49.3, 69.6)	61% (50.5, 70.9)	54% (46.0, 61.3)	47% (36.3, 58.1)
Day-28 CR	29.6%	41%	49%	25%	23%
Day-28 PR	40.7%	19%	12%	29%	24%

Issues identified in efficacy evaluation:

- No treatment effect in the randomized trials
- ORR in the remestemcel treatment arms ranged from 54-70% with wide confidence intervals

Do Trials 265, 275, 280 Provide Additional Supportive Evidence?

- Difference in primary endpoints CR sustained > 28 days versus ORR at Day 28
- Differences in populations
  - ages (pediatric versus adult subjects)
  - disease state (newly diagnosed aGVHD versus SR-aGVHD)
  - disease stage (allowing grade B skin-only disease)
- Difference in treatment regimens
- Impact of concomitant medications (positive or negative) on outcomes in Studies 280 & 275, in light of the unknown mechanism of action
- Limitations in reporting of DOR and variability in duration of follow-up

Evidence of Effectiveness

Summary

- The primary endpoint results in MSB-GVHD001 were statistically significant, the measured response was durable (median 54 days), and the study results were consistent across subpopulations and secondary efficacy endpoints.
- However, the results of Protocols 265 and 280, the two randomized trials, did not provide evidence of a treatment effect for remestemcel-L in aGVHD even when reanalyzed using the efficacy endpoint of Day-28 ORR.
- In fact, a treatment effect has not been identified in any of the previous clinical trials conducted in various disease entities, including: type 1 diabetes mellitus, Crohn's Disease, myocardial infarction, or severe chronic obstructive pulmonary disease.

EVIDENCE OF EFFECTIVENESS
FOR DISCUSSION

- Please discuss whether the results of Studies 265 and 280 are relevant to the effectiveness of remestemcel-L for the treatment of pediatric SR-aGVHD.

- FDA may require an additional clinical trial to support the effectiveness of the remestemcel-L in pediatric SR-aGVHD. If so, what are your recommendations regarding the design of such a trial?

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Voting Question

Do the available data support the efficacy of remestemcel-L in pediatric patients with steroid-refractory aGVHD?


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