Supplemental methods:

Safety monitoring

Failure of sirolimus therapy by day 42 post-randomization, defined as the addition of a systemic immune suppressive therapy beyond prednisone among those patients originally treated with sirolimus, was monitored using a sequential probability ratio test (SPRT) for binary data, contrasting a 25% and 50% 42-day rate of sirolimus failure. Day 56 mortality was monitored in both study arms using a censored exponential SPRT contrasting a 10% and 25% rate of overall mortality.

Research was IRB-approved, and conducted in accordance with the Declaration of Helsinki.

Adjudication of GVHD response data

GVHD organ scores were recorded by the study site investigators. From these serial organ scores, responses were computed using the standard definitions reported in the manuscript. For Endpoint Review Committee (ERC) adjudications, reviewers were provided with data listings containing pertinent data including acute GVHD symptoms, etiologies, biopsies, and treatment as well as other relevant outcomes such as infections and adverse events. These listings were blinded to participant/center identifiers and Ann Arbor (AA) Score. Two reviewers were assigned to perform independent reviews of endpoints for each patient. If there were any discrepancies among the two reviewers, the case was assigned to a third reviewer. Once a consensus was reached among reviewers, the results represented the ERC adjudicated endpoints for the participant under review.

Supplemental tables:

Supplemental table 1: Detailed response categories at day 28 and 56 for the prednisone vs. sirolimus study arms

Acute GVHD Response				
Assessment Time	**Response Category**	**Prednisone (N=64) N (%)**	**Sirolimus (N=58) N (%)**	**p-value***
Day 28	Complete Response (CR)	39 (61.9%)	30 (55.6%)	0.320
	Partial Response (PR)	7 (11.1%)	5 (9.3%)	
	Mixed Response (MR)	5 (7.9%)	1 (1.9%)	
	No Response (NR)	11 (17.5%)	16 (29.6%)	
	Progression	1 (1.6%)	2 (3.7%)	
	Not Evaluable[1]	1	4	
Day 56	Complete Response (CR)	48 (76.2%)	30 (56.6%)	0.014
	Partial Response (PR)	2 (3.2%)	4 (7.5%)	
	Mixed Response (MR)	0 (0.0%)	0 (0.0%)	
	No Response (NR)	10 (15.9%)	19 (35.8%)	
	Progression	3 (4.8%)	0 (0.0%)	
	Not Evaluable[2]	1	5	

* Fisher's exact test

[1] Five participants were deemed unevaluable due to their withdrawal from the study prior to day 28.

[2] Six participants were deemed unevaluable. One participant on the prednisone arm withdrew from the study prior to day 56. On the sirolimus arm, four participants withdrew from the study prior to day 56 and one had a missing GVHD staging evaluation at day 56.

Supplemental table 2: (a) Grade 3-5 toxicities, (b) serious grade 3-5 adverse events, and (c) causes of death according to study arm

(a)

	Treatment Arm		
	Prednisone (N=64) N (%)	**Sirolimus (N=58) N (%)**	**Total (N=122) N (%)**
Maximum Toxicity Grade			
Grade 0 - 2	25 (39.1%)	31 (53.4%)	56 (45.9%)
Grade 3	27 (42.2%)	19 (32.8%)	46 (37.7%)
Grade 4	9 (14.1%)	7 (12.1%)	16 (13.1%)
Grade 5	3 (4.7%)	1 (1.7%)	4 (3.3%)
Oral Mucositis			
Grade 0 - 2	63 (98.4%)	54 (93.1%)	117 (95.9%)
Grade 3	1 (1.6%)	4 (6.9%)	5 (4.1%)
Cystitis Non-infective			
Grade 0 - 2	61 (95.3%)	58 (100.0%)	119 (97.5%)
Grade 3	3 (4.7%)	0 (0.0%)	3 (2.5%)
Acute Kidney Injury			
Grade 0 - 2	60 (93.8%)	54 (93.1%)	114 (93.4%)
Grade 3	4 (6.3%)	3 (5.2%)	7 (5.7%)
Grade 4	0 (0.0%)	1 (1.7%)	1 (0.8%)
Chronic Kidney Disease			
Grade 0 - 2	62 (96.9%)	56 (96.6%)	118 (96.7%)
Grade 3	1 (1.6%)	2 (3.4%)	3 (2.5%)
Grade 4	1 (1.6%)	0 (0.0%)	1 (0.8%)
Received Dialysis			
Yes	4 (6.3%)	2 (3.4%)	6 (4.9%)
No	60 (93.8%)	56 (96.6%)	116 (95.1%)
Hemorrhage			
Grade 0 - 2	59 (92.2%)	54 (93.1%)	113 (92.6%)
Grade 3	3 (4.7%)	2 (3.4%)	5 (4.1%)
Grade 4	2 (3.1%)	2 (3.4%)	4 (3.3%)
Hypotension			
Grade 0 - 2	55 (85.9%)	44 (75.9%)	99 (81.1%)
Grade 3	6 (9.4%)	10 (17.2%)	16 (13.1%)
Grade 4	2 (3.1%)	4 (6.9%)	6 (4.9%)
Grade 5	1 (1.6%)	0 (0.0%)	1 (0.8%)
Hypertension			
Grade 0 - 2	50 (78.1%)	47 (81.0%)	97 (79.5%)
Grade 3	14 (21.9%)	11 (19.0%)	25 (20.5%)
Cardiac Arrhythmia			
Grade 0 - 2	62 (96.9%)	56 (96.6%)	118 (96.7%)
Grade 3	1 (1.6%)	1 (1.7%)	2 (1.6%)

	Treatment Arm		
	Prednisone (N=64) N (%)	**Sirolimus (N=58) N (%)**	**Total (N=122) N (%)**
Grade 5	1 (1.6%)	1 (1.7%)	2 (1.6%)
Left Ventricular Systolic Dysfunction			
Grade 0 - 2	62 (96.9%)	58 (100.0%)	120 (98.4%)
Grade 4	1 (1.6%)	0 (0.0%)	1 (0.8%)
Grade 5	1 (1.6%)	0 (0.0%)	1 (0.8%)
Somnolence			
Grade 0 - 2	62 (96.9%)	52 (89.7%)	114 (93.4%)
Grade 3	2 (3.1%)	5 (8.6%)	7 (5.7%)
Grade 4	0 (0.0%)	1 (1.7%)	1 (0.8%)
Seizure			
Grade 0 - 2	63 (98.4%)	58 (100.0%)	121 (99.2%)
Grade 4	1 (1.6%)	0 (0.0%)	1 (0.8%)
Thrombotic Thrombocytopenic Purpura			
Grade 0 - 2	63 (98.4%)	55 (94.8%)	118 (96.7%)
Grade 3	1 (1.6%)	2 (3.4%)	3 (2.5%)
Grade 4	0 (0.0%)	1 (1.7%)	1 (0.8%)
Capillary Leak Syndrome			
Grade 0 - 2	64 (100.0%)	58 (100.0%)	122 (100.0%)
Hypoxia			
Grade 0 - 2	53 (82.8%)	46 (79.3%)	99 (81.1%)
Grade 3	4 (6.3%)	6 (10.3%)	10 (8.2%)
Grade 4	5 (7.8%)	5 (8.6%)	10 (8.2%)
Grade 5	2 (3.1%)	1 (1.7%)	3 (2.5%)
Dyspnea			
Grade 0 - 2	54 (84.4%)	48 (82.8%)	102 (83.6%)
Grade 3	3 (4.7%)	5 (8.6%)	8 (6.6%)
Grade 4	5 (7.8%)	4 (6.9%)	9 (7.4%)
Grade 5	2 (3.1%)	1 (1.7%)	3 (2.5%)
ALT			
Grade 0 - 2	53 (82.8%)	52 (89.7%)	105 (86.1%)
Grade 3	10 (15.6%)	6 (10.3%)	16 (13.1%)
Grade 4	1 (1.6%)	0 (0.0%)	1 (0.8%)
AST			
Grade 0 - 2	58 (90.6%)	52 (89.7%)	110 (90.2%)
Grade 3	6 (9.4%)	5 (8.6%)	11 (9.0%)
Grade 4	0 (0.0%)	1 (1.7%)	1 (0.8%)
Bilirubin			
Grade 0 - 2	58 (90.6%)	55 (94.8%)	113 (92.6%)
Grade 3	5 (7.8%)	2 (3.4%)	7 (5.7%)
Grade 4	1 (1.6%)	1 (1.7%)	2 (1.6%)
Alkaline Phosphate			
Grade 0 - 2	62 (96.9%)	56 (96.6%)	118 (96.7%)
Grade 3	1 (1.6%)	2 (3.4%)	3 (2.5%)
Grade 4	1 (1.6%)	0 (0.0%)	1 (0.8%)

	Treatment Arm		
	Prednisone (N=64) N (%)	**Sirolimus (N=58) N (%)**	**Total (N=122) N (%)**
Abnormal Liver Symptoms			
Yes	7 (10.9%)	3 (5.2%)	10 (8.2%)
No	57 (89.1%)	55 (94.8%)	112 (91.8%)
Veno-occlusive Disease			
Yes	0 (0.0%)	1 (1.7%)	1 (0.8%)
No	64 (100.0%)	57 (98.3%)	121 (99.2%)
Thrombotic Microangiopathy			
Yes	1 (1.6%)	6 (10.3%)	7 (5.7%)
No	63 (98.4%)	52 (89.7%)	115 (94.3%)

(b)

Serious Adverse Event		**Prednisone**			**Sirolimus**		
		Events	**Participants**	**% of participants**	**Events**	**Participants**	**% of participants**
System Organ Class	**Preferred Term**						
Gastrointestinal disorders	Small intestinal obstruction	0	0	0.00%	1	1	1.72%
Hepatobiliary disorders	Hepatic cirrhosis	0	0	0.00%	1	1	1.72%
Infections and infestations	Appendicitis	0	0	0.00%	1	1	1.72%
	Diverticulitis	0	0	0.00%	1	1	1.72%
	Pneumonia	0	0	0.00%	1	1	1.72%
Metabolism and nutrition disorders	Failure to thrive	0	0	0.00%	1	1	1.72%
Psychiatric disorders	Delirium	1	1	1.56%	0	0	0.00%
	Mental status changes	0	0	0.00%	1	1	1.72%
Renal and urinary disorders	Cystitis non-infective	1	1	1.56%	0	0	0.00%
Respiratory, thoracic and mediastinal disorders	Hypoxia	1	1	1.56%	0	0	0.00%
	Pulmonary embolism	0	0	0.00%	1	1	1.72%
Total Serious Adverse Events		3	3	4.69%	8	8	13.79%

(c)

Primary Cause of Death	Prednisone		Sirolimus		All	
	N	%	N	%	N	%
Recurrence/Persistence	6	35.3	2	16.7	8	27.6
Graft Rejection/Failure	1	5.9	0	0	1	3.4
Acute GVHD	1	5.9	0	0	1	3.4
Infection[1]	1	5.9	4	33.3	5	17.2
Multiple Organ Failure	3	17.6	2	16.7	5	17.2
Interstitial Pneumonia	1	5.9	0	0	1	3.4
Other[2]	4	23.5	3	25.0	7	24.1
Unknown	0	0	1	8.3	1	3.4
Total	17	100.0	12	100.0	29	100.0
Total Deaths	17	26.6	12	20.7	29	23.8
Total Enrolled/Analyzable	64	100.0	58	100.0	122	100.0

[1] Prednisone arm: n=1 total death, bacterial blood infection. Sirolimus arm: n=4 total deaths; type was bacterial (n=2), viral (n=1), and fungal (n=1); sites of infection were lung (n=2), stool (n=1), and other (n=1).

[2] Prednisone arm: respiratory failure (n=1), undifferentiated pneumonitis (n=1), brainstem CVA (n=1), sepsis (n=1)
Sirolimus arm: respiratory failure (n=1), occipital lobe CVA (n=1), aspiration or embolic phenomenon (n=1)

Supplemental table 3: Systemic infections reported on trial according to study arm

		Prednisone (N=64) N (%)	Sirolimus (N=58) N (%)
Total Number of Infections		66 (100.0%)	61 (100.0%)
Infection Site	Blood/Buffy Coat	19 (28.8%)	13 (21.3%)
	Disseminated - Generalized, Isolated at 2 or More Distinct Sites	2 (3.0%)	1 (1.6%)
	Brain	2 (3.0%)	0 (0.0%)
	Small Intestine	0 (0.0%)	1 (1.6%)
	Large Intestine	1 (1.5%)	1 (1.6%)
	Feces/Stool	4 (6.1%)	5 (8.2%)
	Gastrointestinal Tract Unspecified	2 (3.0%)	1 (1.6%)
	Upper Airway and Nasopharynx	6 (9.1%)	6 (9.8%)
	Lower Respiratory Tract (Lung)	7 (10.6%)	10 (16.4%)
	Sinuses	2 (3.0%)	1 (1.6%)
	Respiratory Tract Unspecified	5 (7.6%)	5 (8.2%)
	Kidneys, Renal Pelvis, Ureters and Bladder	2 (3.0%)	2 (3.3%)
	Genito-Urinary Tract Unspecified	3 (4.5%)	3 (4.9%)
	Genital Area	0 (0.0%)	1 (1.6%)
	Rash, Pustules, or Abscesses Not Typical of Any of the Above	0 (0.0%)	2 (3.3%)
	Skin Unspecified	4 (6.1%)	0 (0.0%)
	Wound site	0 (0.0%)	7 (11.5%)
	Joints	2 (3.0%)	0 (0.0%)
	Bone Marrow	0 (0.0%)	1 (1.6%)
	Other Unspecified	5 (7.6%)	1 (1.6%)
Time of Onset Post-randomization	Median days (Range)	78 (2-334)	105 (0-358)
	0 - 90 days	33 (50.0%)	28 (45.9%)
	91 - 180 days	11 (16.7%)	17 (27.9%)
	181 - 270 days	9 (13.6%)	7 (11.5%)
	271 - 365 days	13 (19.7%)	9 (14.8%)
Infection Severity	Grade 2 (Moderate)	44 (66.7%)	48 (78.7%)
	Grade 3 (Severe / Life Threatening)	22 (33.3%)	13 (21.3%)

Supplemental table 4: Change from baseline to subsequent measures and comparison of change across study groups for functional myopathy assessment tools. (a) Hip flexor strength. (b) quadriceps strength. (c) two minute walk test. (d) 5 time sit-to-stand test time. (e) Adult myopathy assessment tool score.

(a)

	Prednisone			Sirolimus			
Assessment Time	**N**	**Median (Range)**	**p-value[1]**	**N**	**Median (Range)**	**p-value[1]**	**Treatment Comparison p-value[2]**
Baseline	51	14.8 (3.3, 91.0)	-	45	14.8 (3.3, 72.5)	-	-
Day 56	43	14.0 (2.8, 93.5)	0.408	31	14.0 (3.0, 86.0)	0.307	0.986
Day 180	35	16.3 (3.5, 77.8)	0.563	20	18.5 (7.3, 89.5)	0.265	0.579

(b)

	Prednisone			Sirolimus			
Assessment Time	**N**	**Median (Range)**	**p-value[1]**	**N**	**Median (Range)**	**p-value[1]**	**Treatment Comparison p-value[2]**
Baseline	51	15.0 (3.3, 90.8)	-	44	14.5 (3.0, 50.5)	-	-
Day 56	43	16.5 (4.0, 98.3)	0.539	31	15.5 (2.8, 68.5)	0.302	0.749
Day 180	35	17.3 (4.8, 58.0)	0.807	20	20.5 (4.3, 94.3)	0.462	0.522

1 Wilcoxon signed rank tests on changes in scores from baseline within each arm
2 Wilcoxon rank sum tests comparing changes in scores from baseline between arms

(c)

	Prednisone			Sirolimus			
Assessment Time	**N**	**Median (Range)**	**p-value[1]**	**N**	**Median (Range)**	**p-value[1]**	**Treatment Comparison p-value[2]**
Baseline	53	124.0 (0.0, 628.0)	-	42	97.5 (0.0, 600.0)	-	-
Day 56	42	138.0 (0.0, 634.0)	0.006	33	132.0 (0.0, 600.0)	0.001	0.781
Day 180	36	124.5 (0.0, 426.0)	0.939	21	130.0 (0.0, 600.0)	0.132	0.091

Note: For participants that could not complete the Two Minute Walk Test, a distance of zero meters was recorded.

1 Wilcoxon signed rank tests on changes in scores from baseline within each arm
2 Wilcoxon rank sum tests comparing changes in scores from baseline between arms

(d)

	Prednisone			Sirolimus			
Assessment Time	**N**	**Median (Range)**	**p-value[1]**	**N**	**Median (Range)**	**p-value[1]**	**Treatment Comparison p-value[2]**
Baseline	55	15.0 (7.0, 300.0)	-	46	16.0 (7.0, 300.0)	-	-

	Prednisone			Sirolimus			
Assessment Time	**N**	**Median (Range)**	**p-value[1]**	**N**	**Median (Range)**	**p-value[1]**	**Treatment Comparison p-value[2]**
Day 56	44	14.5 (6.0, 300.0)	0.324	33	15.0 (0.0, 300.0)	0.701	0.365
Day 180	36	13.5 (5.0, 300.0)	0.622	20	13.0 (6.0, 300.0)	0.907	0.966

Note: For participants that could not complete the 5 Time Sit-to-Stand Test, a time of 300 seconds was recorded. Medians should be interpreted as restricted medians.

1 Wilcoxon signed rank tests on changes in scores from baseline within each arm
2 Wilcoxon rank sum tests comparing changes in scores from baseline between arms

(e)

	Prednisone			Sirolimus			
Assessment Time	**N**	**Median (Range)**	**p-value[1]**	**N**	**Median (Range)**	**p-value[1]**	**Treatment Comparison p-value[2]**
Baseline	55	17.0 (8.0, 18.0)	-	45	17.0 (9.0, 18.0)	-	-
Day 56	44	18.0 (0.0, 18.0)	0.975	33	18.0 (0.0, 18.0)	0.079	0.182
Day 180	36	18.0 (6.0, 18.0)	0.645	21	18.0 (14.0, 18.0)	0.086	0.105

1 Wilcoxon signed rank tests on changes in scores from baseline within each arm
2 Wilcoxon rank sum tests comparing changes in scores from baseline between arms

Supplemental table 5: Change from baseline to subsequent measures and comparison of change across study groups for functional myopathy assessment tools. Comparisons are made across the prednisone arm of the trial, sirolimus-treated subjects that did not receive steroids by day 56 post-randomization, and sirolimus-treated subjects that did receive steroids by day 56 post-randomization: (a) Hip flexor strength. (b) quadriceps strength. (c) two minute walk test. (d) 5 time sit-to-stand test time. (e) adult myopathy assessment tool (AMAT) score.

(A)

	Prednisone			Sirolimus, No Steroids[1]			Sirolimus, Got Steroids[2]		
Assessment Time	**N**	**Median (Range)**	**p-value[3]**	**N**	**Median (Range)**	**p-value[3]**	**N**	**Median (Range)**	**p-value[3]**
Baseline	51	14.8 (3.3, 91.0)	-	26	12.5 (3.3, 53.8)	-	19	15.5 (7.8, 72.5)	-
Day 56	43	14.0 (2.8, 93.5)	0.408	22	14.4 (3.0, 86.0)	0.393	9	14.0 (4.3, 22.8)	0.465
Day 180	35	16.3 (3.5, 77.8)	0.563	16	22.0 (8.3, 89.5)	0.051	4	7.6 (7.3, 11.8)	0.125

[1] Sirolimus arm patients that did not receive steroids before Day 56 post-randomization

[2] Sirolimus arm patients that did receive steroids before Day 56 post-randomization

[3] Wilcoxon signed rank tests on changes in scores from baseline within each group

P-values[4] for Comparisons of Change Scores in Hip Flexor Strength		
	Assessment Time	
	Day 56	**Day 180**
Prednisone vs. Sirolimus, No Steroids	1.000	0.570
Prednisone vs. Sirolimus, Got Steroids	1.000	0.402
Sirolimus, No Steroids vs. Sirolimus, Got Steroids	1.000	0.078

[4] Wilcoxon rank sum tests were used to compare changes in scores from baseline between each pair of treatment groups. Across each time point, p-values are Bonferroni-corrected for the three pairwise comparisons.

(B)

	Prednisone			Sirolimus, No Steroids[1]			Sirolimus, Got Steroids[2]		
Assessment Time	**N**	**Median (Range)**	**p-value[3]**	**N**	**Median (Range)**	**p-value[3]**	**N**	**Median (Range)**	**p-value[3]**
Baseline	51	15.0 (3.3, 90.8)	-	25	13.8 (3.0, 47.0)	-	19	15.8 (7.3, 50.5)	-
Day 56	43	16.5 (4.0, 98.3)	0.539	22	15.8 (3.0, 68.5)	0.447	9	15.3 (2.8, 29.5)	0.742
Day 180	35	17.3 (4.8, 58.0)	0.807	16	21.1 (8.8, 94.3)	0.318	4	7.8 (4.3, 23.8)	0.875

[1] Sirolimus arm patients that did not receive steroids before Day 56 post-randomization
[2] Sirolimus arm patients that did receive steroids before Day 56 post-randomization
[3] Wilcoxon signed rank tests on changes in scores from baseline within each group

P-values[4] for Comparisons of Change Scores in Quadriceps Strength		
	Assessment Time	
	Day 56	**Day 180**
Prednisone vs. Sirolimus, No Steroids	1.000	1.000
Prednisone vs. Sirolimus, Got Steroids	1.000	1.000
Sirolimus, No Steroids vs. Sirolimus, Got Steroids	1.000	1.000

[4] Wilcoxon rank sum tests were used to compare changes in scores from baseline between each pair of treatment groups. Across each time point, p-values are Bonferroni-corrected for the three pairwise comparisons.

(C)

	Prednisone			Sirolimus, No Steroids[1]			Sirolimus, Got Steroids[2]		
Assessment Time	**N**	**Median (Range)**	**p-value[3]**	**N**	**Median (Range)**	**p-value[3]**	**N**	**Median (Range)**	**p-value[3]**
Baseline	53	124.0 (0.0, 628.0)	-	23	129.0 (0.0, 600.0)	-	19	86.0 (0.0, 587.0)	-
Day 56	42	138.0 (0.0, 634.0)	0.006	23	132.0 (0.0, 600.0)	0.056	10	133.5 (0.0, 499.0)	0.004
Day 180	36	124.5 (0.0, 426.0)	0.939	17	130.0 (0.0, 600.0)	0.542	4	128.0 (69.0, 512.0)	0.125

Note: For participants that could not complete the Two Minute Walk Test, a distance of zero meters was recorded.
[1] Sirolimus arm patients that did not receive steroids before Day 56 post-randomization
[2] Sirolimus arm patients that did receive steroids before Day 56 post-randomization
[3] Wilcoxon signed rank tests on changes in scores from baseline within each group

P-values[4] for Comparisons of Change Scores in Two Minute Walk Test		
	Assessment Time	
	Day 56	**Day 180**
Prednisone vs. Sirolimus, No Steroids	1.000	1.000
Prednisone vs. Sirolimus, Got Steroids	0.660	0.060
Sirolimus, No Steroids vs. Sirolimus, Got Steroids	0.756	0.297

[4] Wilcoxon rank sum tests were used to compare changes in scores from baseline between each pair of treatment groups. Across each time point, p-values are Bonferroni-corrected for the three pairwise comparisons.

(D)

	Prednisone			Sirolimus, No Steroids[1]			Sirolimus, Got Steroids[2]		
Assessment Time	**N**	**Median (Range)**	**p-value[3]**	**N**	**Median (Range)**	**p-value[3]**	**N**	**Median (Range)**	**p-value[3]**
Baseline	55	15.0 (7.0, 300.0)	-	26	16.5 (7.0, 300.0)	-	20	16.0 (7.0, 300.0)	-
Day 56	44	14.5 (6.0, 300.0)	0.324	23	15.0 (0.0, 300.0)	0.823	10	15.0 (7.0, 300.0)	0.836
Day 180	36	13.5 (5.0, 300.0)	0.622	17	13.0 (6.0, 300.0)	0.820	3	13.0 (8.0, 27.0)	1.000

Note: For participants that could not complete the 5 Time Sit-to-Stand Test, a time of 300 seconds was recorded. Medians should be interpreted as restricted medians.

[1] Sirolimus arm patients that did not receive steroids before Day 56 post-randomization

[2] Sirolimus arm patients that did receive steroids before Day 56 post-randomization

[3] Wilcoxon signed rank tests on changes in scores from baseline within each group

P-values[4] for Comparisons of Change Scores in Sit-to-Stand Test		
	Assessment Time	
	Day 56	**Day 180**
Prednisone vs. Sirolimus, No Steroids	1.000	1.000
Prednisone vs. Sirolimus, Got Steroids	1.000	1.000
Sirolimus, No Steroids vs. Sirolimus, Got Steroids	1.000	1.000

[4] Wilcoxon rank sum tests were used to compare changes in scores from baseline between each pair of treatment groups. Across each time point, p-values are Bonferroni-corrected for the three pairwise comparisons.

(E) Adult Myopathy Assessment Tool (AMAT) Score

	Prednisone			Sirolimus, No Steroids[1]			Sirolimus, Got Steroids[2]		
Assessment Time	**N**	**Median (Range)**	**p-value[3]**	**N**	**Median (Range)**	**p-value[3]**	**N**	**Median (Range)**	**p-value[3]**
Baseline	55	17.0 (8.0, 18.0)	-	26	16.5 (10.0, 18.0)	-	19	17.0 (9.0, 18.0)	-
Day 56	44	18.0 (0.0, 18.0)	0.975	23	18.0 (0.0, 18.0)	0.219	10	18.0 (11.0, 18.0)	0.375
Day 180	36	18.0 (6.0, 18.0)	0.645	17	18.0 (14.0, 18.0)	0.135	4	17.0 (16.0, 18.0)	1.000

[1] Sirolimus arm patients that did not receive steroids before Day 56 post-randomization

[2] Sirolimus arm patients that did receive steroids before Day 56 post-randomization

[3] Wilcoxon signed rank tests on changes in scores from baseline within each group

P-values[4] for Comparisons of Change Scores in AMAT		
	Assessment Time	
	Day 56	**Day 180**

Prednisone vs. Sirolimus, No Steroids	0.693	0.321
Prednisone vs. Sirolimus, Got Steroids	1.000	1.000
Sirolimus, No Steroids vs. Sirolimus, Got Steroids	1.000	1.000

[4] Wilcoxon rank sum tests were used to compare changes in scores from baseline between each pair of treatment groups. Across each time point, p-values are Bonferroni-corrected for the three pairwise comparisons.

Supplemental table 6: Change from baseline to subsequent measures and comparison of change across study groups for patient-reported outcomes: (a) SF-36 physical component summary (PCS) score. (b) SF-36 mental component summary (MCS) score. (c) FACT-BMT total score. (d) FACT-BMT Trial Outcome Index (TOI) Score. (e) MDASI Mean Core Symptom Severity Score. (f) MDASI Mean Interference Score.

(a)

	Prednisone Arm (N=64)						Sirolimus Arm (N=58)						
Assessment Time	**N**	**Mean**	**SE**	**Median**	**Range**	**p-value[1]**	**N**	**Mean**	**SE**	**Median**	**Range**	**p-value[1]**	**Treatment Comparison p-value[2]**
Baseline	56	35.2	1.4	32.9	(14.9, 55.7)	-	48	33.3	1.3	33.5	(6.2, 55.1)	-	-
Day 56	49	36.8	1.3	35.9	(18.9, 53.9)	0.139	30	38.9	1.7	38.4	(22.6, 57.5)	0.002	0.329
Day 180	35	38.9	1.6	37.3	(23.4, 54.9)	0.037	26	43.8	1.9	44.8	(20.4, 58.1)	0.000	0.012
Day 365	32	41.3	1.8	40.9	(17.8, 57.5)	0.021	26	42.2	2.0	43.4	(23.9, 56.4)	0.002	0.480

* SF36 Standard, US Version 2.0

[1] One sample t-test of changes in scores from baseline within each arm

[2] Independent samples t-tests comparing changes in scores from baseline between arms

(b)

	Prednisone Arm (N=64)						Sirolimus Arm (N=58)						
Assessment Time	**N**	**Mean**	**SE**	**Median**	**Range**	**p-value[1]**	**N**	**Mean**	**SE**	**Median**	**Range**	**p-value[1]**	**Treatment Comparison p-value[2]**
Baseline	56	43.3	1.6	44.2	(18.5, 63.3)	-	48	46.9	1.4	48.3	(19.5, 63.0)	-	-
Day 56	49	44.0	1.7	45.9	(16.9, 65.1)	0.783	30	51.7	1.9	53.2	(27.3, 66.4)	0.078	0.175
Day 180	35	48.2	1.6	48.8	(25.7, 63.0)	0.008	26	53.2	1.5	54.0	(39.3, 65.0)	0.005	0.671
Day 365	32	47.9	2.1	48.6	(19.5, 66.8)	0.110	26	53.7	1.6	56.3	(31.5, 62.6)	0.004	0.657

* SF36 Standard, US Version 2.0

[1] One sample t-test of changes in scores from baseline within each arm

[2] Independent samples t-tests comparing changes in scores from baseline between arms

(c)

	Prednisone Arm (N=64)						Sirolimus Arm (N=58)						
Assessment Time	**N**	**Mean**	**SE**	**Median**	**Range**	**p-value[1]**	**N**	**Mean**	**SE**	**Median**	**Range**	**p-value[1]**	**Treatment Comparison p-value[2]**
Baseline	55	94.4	2.9	93.0	(53.0, 136.0)	-	46	96.3	2.8	96.5	(49.5, 139.0)	-	-
Day 56	49	100.6	2.7	101.0	(66.0, 138.0)	0.034	31	106.9	3.3	108.0	(68.8, 139.0)	0.017	0.406
Day 180	37	104.4	3.3	101.0	(65.3, 139.0)	0.000	26	115.0	4.2	120.9	(71.8, 144.0)	0.000	0.135
Day 365	33	103.7	4.5	107.0	(45.0, 144.0)	0.036	28	112.5	4.4	116.0	(61.9, 146.0)	0.001	0.269

* FACT-BMT version 4.0

[1] One sample t-test of changes in scores from baseline within each arm

[2] Independent samples t-tests comparing changes in scores from baseline between arms

(d)

	Prednisone Arm (N=64)						Sirolimus Arm (N=58)						
Assessment Time	**N**	**Mean**	**SE**	**Median**	**Range**	**p-value[1]**	**N**	**Mean**	**SE**	**Median**	**Range**	**p-value[1]**	**Treatment Comparison p-value[2]**
Baseline	55	53.8	2.3	54.0	(20.0, 86.0)	-	46	52.6	2.2	53.0	(22.5, 88.0)	-	-
Day 56	49	59.5	2.0	60.0	(33.0, 87.0)	0.013	31	63.1	2.6	64.0	(37.0, 90.0)	0.001	0.204
Day 180	37	62.8	2.5	60.0	(36.0, 89.0)	0.000	26	71.2	3.1	73.1	(42.0, 92.0)	0.000	0.034
Day 365	33	64.1	3.3	66.4	(24.0, 93.0)	0.017	28	69.8	3.1	72.0	(35.9, 94.0)	0.000	0.155

* FACT-BMT version 4.0

[1] One sample t-test of changes in scores from baseline within each arm

[2] Independent samples t-tests comparing changes in scores from baseline between arms

(e)

	Prednisone Arm (N=64)						Sirolimus Arm (N=58)						
Assessment Time	**N**	**Mean**	**SE**	**Median**	**Range**	**p-value[1]**	**N**	**Mean**	**SE**	**Median**	**Range**	**p-value[1]**	**Treatment Comparison p-value[2]**
Baseline	57	2.93	0.27	2.54	(0.15, 7.38)	-	48	3.08	0.20	3.04	(0.85, 6.46)	-	-
Day 56	52	2.13	0.24	1.85	(0.00, 7.69)	0.013	32	2.02	0.26	1.62	(0.15, 5.77)	0.002	0.301
Day 180	37	1.85	0.27	1.23	(0.15, 6.69)	0.007	26	1.68	0.32	1.31	(0.00, 7.46)	0.000	0.219
Day 365	31	1.93	0.32	1.15	(0.00, 7.77)	0.333	27	1.77	0.30	1.08	(0.23, 7.15)	0.001	0.151

* MDASI version 1.0

[1] One sample t-test of changes in scores from baseline within each arm

[2] Independent samples t-tests comparing changes in scores from baseline between arms

(f)

	Prednisone Arm (N=64)						Sirolimus Arm (N=58)						
Assessment Time	**N**	**Mean**	**SE**	**Median**	**Range**	**p-value[1]**	**N**	**Mean**	**SE**	**Median**	**Range**	**p-value[1]**	**Treatment Comparison p-value[2]**
Baseline	56	3.50	0.36	2.92	(0.00, 10.00)	-	47	3.66	0.33	3.33	(0.00, 8.17)	-	-
Day 56	52	3.21	0.37	2.67	(0.00, 9.83)	0.770	32	2.71	0.35	2.50	(0.00, 7.17)	0.043	0.283
Day 180	37	2.59	0.41	2.00	(0.00, 8.33)	0.017	26	2.06	0.51	1.00	(0.00, 9.50)	0.001	0.289
Day 365	31	2.68	0.50	2.00	(0.00, 10.00)	0.204	27	1.76	0.38	1.33	(0.00, 6.83)	0.016	0.502

* MDASI version 1.0

[1] One sample t-test of changes in scores from baseline within each arm

[2] Independent samples t-tests comparing changes in scores from baseline between arms

Supplemental table 7: Acute GVHD biopsy information for AA1/2 patients

	Treatment Arm		
	Prednisone	**Sirolimus**	**Total**
Skin Biopsy Results (N=83)			
Positive	19 (42.2%)	18 (47.4%)	37 (44.6%)
Negative	4 (8.9%)	4 (10.5%)	8 (9.6%)
Equivocal	2 (4.4%)	1 (2.6%)	3 (3.6%)
Not Done	20 (44.5%)	15 (39.5%)	35 (42.2%)
Upper GI Biopsy Results (N=54)			
Positive	8 (28.6%)	8 (30.8%)	16 (29.6%)
Negative	2 (7.1%)	0 (0.0%)	2 (3.7%)
Equivocal	1 (3.6%)	0 (0.0%)	1 (1.9%)
Not Done	17 (60.7%)	18 (69.2%)	35 (64.8%)
Upper GI Biopsy Results, Isolated UGI GVHD Patients only (N=31)			
Positive	5 (38.5%)	7 (38.9%)	12 (38.7%)
Negative	0 (0.0%)	0 (0.0%)	0 (0.0%)
Equivocal	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Done	8 (61.5%)	11 (61.1%)	19 (61.3%)
Lower GI Biopsy Results (N=23)			
Positive	2 (11.1%)	2 (40.0%)	4 (17.4%)
Negative	1 (5.6%)	0 (0.0%)	1 (4.3%)
Equivocal	2 (11.1%)	0 (0.0%)	2 (8.7%)
Not Done	13 (72.2%)	3 (60.0%)	16 (69.6%)
Liver Biopsy Results (N=1)			
Not Done	1 (100.0%)	0 (0.0%)	1 (100.0%)

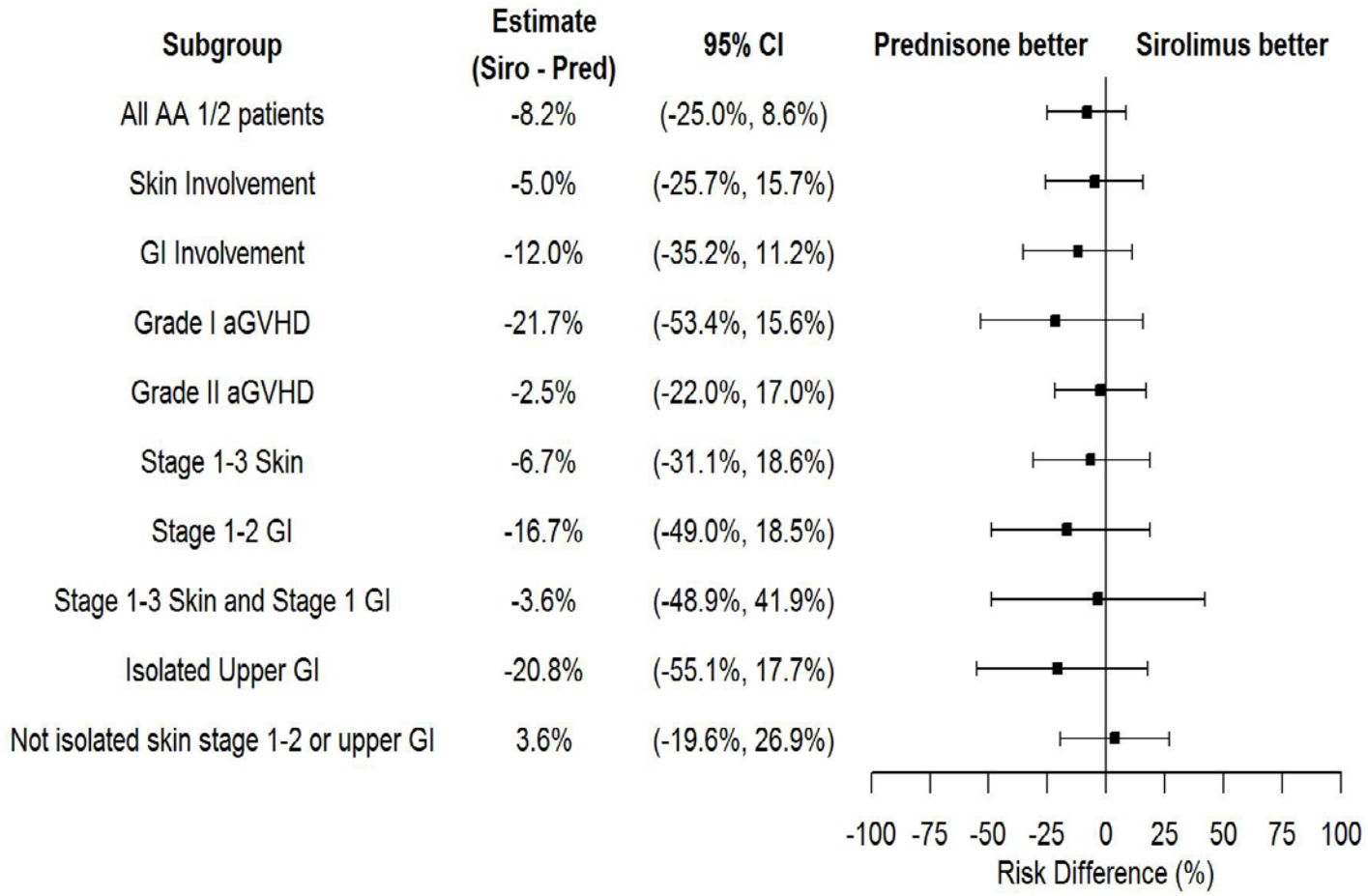
Supplemental table 8: Sirolimus Trough Levels (ng/mL) in Sirolimus Arm Patients

	Skin Involvement Only at Baseline (N=31)				
Assessment Time	**N**	**Mean**	**Median**	**Interquartile Range**	**Range**
Day 7	30	8.18	7.50	(4.40, 10.80)	(0.00, 26.40)
Day 14	30	8.00	9.60	(3.20, 11.90)	(0.00, 21.70)
Day 21	30	6.21	6.30	(0.00, 10.70)	(0.00, 15.90)
Day 28	28	5.73	6.40	(0.00, 11.30)	(0.00, 15.60)
Day 35	26	5.84	7.25	(0.00, 9.20)	(0.00, 14.90)
Day 42	27	3.91	3.80	(0.00, 6.90)	(0.00, 14.20)
Day 49	27	3.78	3.00	(0.00, 7.80)	(0.00, 12.10)
Day 56	24	2.93	0.90	(0.00, 5.25)	(0.00, 11.30)
	Any GI Involvement at Baseline (N=27)				
Assessment Time	**N**	**Mean**	**Median**	**Interquartile Range**	**Range**
Day 7	25	7.86	7.00	(4.20, 10.90)	(0.00, 27.50)
Day 14	25	7.73	7.60	(5.74, 10.70)	(0.00, 15.20)
Day 21	24	7.56	7.85	(4.25, 9.25)	(0.00, 23.00)
Day 28	25	6.93	8.00	(3.80, 9.10)	(0.00, 21.40)
Day 35	25	6.11	6.20	(5.00, 8.20)	(0.00, 21.50)
Day 42	23	5.81	6.90	(0.00, 9.70)	(0.00, 14.00)
Day 49	23	5.68	6.40	(0.00, 9.70)	(0.00, 16.20)
Day 56	23	5.20	5.60	(0.00, 9.90)	(0.00, 13.90)

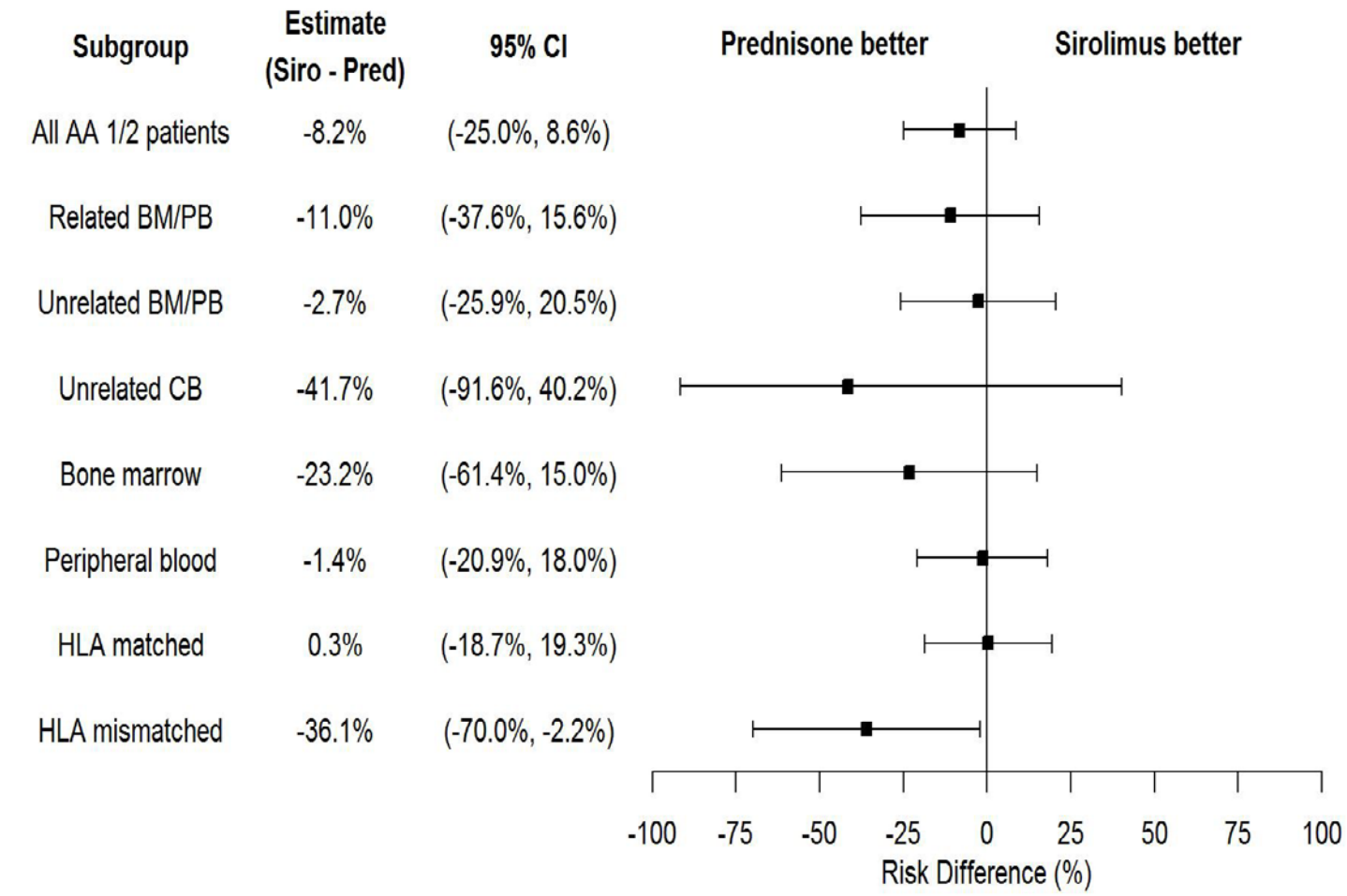
Supplemental figures:

Supplemental figure 1: Sub-group analyses examining difference in day 28 CR/PR rates between study arms. (a) Response according to presenting acute GVHD features. (b) Response according to transplant donor, graft source, and HLA match status.

(a)



(b)


Subgroup
Estimate (Siro - Pred)
95% CI
Prednisone better
Sirolimus better
All AA 1/2 patients
-8.2%
(-25.0%, 8.6%)
Related BM/PB
-11.0%
(-37.6%, 15.6%)
Unrelated BM/PB
-2.7%
(-25.9%, 20.5%)
Unrelated CB
-41.7%
(-91.6%, 40.2%)
Bone marrow
-23.2%
(-61.4%, 15.0%)
Peripheral blood
-1.4%
(-20.9%, 18.0%)
HLA matched
0.3%
(-18.7%, 19.3%)
HLA mismatched
-36.1%
(-70.0%, -2.2%)
-100
-75
-50
-25
0
25
50
75
100
Risk Difference (%)