Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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SCLERODERMA: CYCLOPHOSPHAMIDE OR TRANSPLANTATION (SCOT) TRIAL

SUPPLEMENTARY APPENDIX

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Methods S1A. Calculation of the Modified Rodnan Skin Score

Skin thickness of the patient is rated by palpation at each of 17 anatomic sites using a scale of 0-3 (0 = normal skin; 1= mild thickness; 2= moderate thickness; 3=severe thickness with an inability to pinch the skin into a fold). The scores at each site are summed with a minimum of 0 (normal) and maximum of 51 (severe scleroderma). Minimally important differences range from 3.2 to 5.3 points. Rodnan scores of 16.0 or greater are associated with poorer outcomes.

Sites	Score Range	Score Range
Face	0-3	
Anterior Chest	0-3	
Abdomen	0-3	
L/R Upper Arms	0-3	0-3
L/R Forearms	0-3	0-3
L/R Dorsum Hands	0-3	0-3
L/R Fingers	0-3	0-3
L/R Thighs	0-3	0-3
L/R Lower Legs	0-3	0-3
L/R Dorsum Feet	0-3	0-3

Maximum Score (17 sites):51

Clements PS, Lachenbruch PA, Siebold JR, et al. Skin thickness scores in systemic sclerosis an assessment of interobserver variability in 3 independent studies. J Rheumatol. 1993; 20:1892-6. (2).

Khanna D, Furst, Hays RD, Park GS, Wong WK, Seibold JR, et al. Minimally important difference in diffuse systemic sclerosis: results from the D-penicillamine study. Ann Rheum Dis. 2006; 65: 1325-9. (3).

Methods S1B. Calculation of the Health Assessment Questionnaire-Disability Index (HAQ-DI)

Eight domain scores are computed as the maximum value over all variables in the domain. Domains include dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities with 2-3 questions per domain. Possible scores for each domain are 0 (without any difficulty), 1 (with some difficulty), 2 with much difficulty, and 3 (unable to do). The total score, HAQ-DI, is computed as the mean over all the non-missing domain scores. If less than 6 domain scores are available, HAQ-DI is missing.

The mean scores vary between 0.8 and 1-2 in arthritis populations. The minimal clinically important difference varies between 0.14 and 0.22 points in scleroderma populations.

Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980; 23: 137-45. (4).

Khanna D, Furst DE, Weng KW, Tsevat J, Clements PJ, Park GS, et al. Reliability, validity and minimally important differences of the SF-S6 in systemic sclerosis. Qual Life Res 2007; 16: 1083-92. (5).

Methods S2. Primary and Key Secondary Endpoints and GRCS Hierarchy

Definition of Event-Free Survival

Event-free survival (EFS) is defined as survival without significant organ damage, where an event indicative of failure includes any one of the following:

a. Death.
b. Respiratory failure as defined by one of the following 3 criteria without explanations indicative of causation other than disease progression: (i) a demonstrated decrease of > 30% in DLCO[1] or a decrease of > 20% in FVC[2] measured in percent predicted units; (ii) resting arterial pO_2 < 60 mmHg or pCO_2 > 50 mmHg without supplemental oxygen; (iii) resting O_2 saturation of < 88% as determined by forehead pulse oximeter**.**
c. Renal failure, as defined by (i) chronic dialysis > 6 months or (ii) transplantation.
d. The occurrence of cardiomyopathy defined by (i) clinical CHF (New York Class III or IV), or (ii) LVEF < 30% by echocardiogram.

To account for reversible post-transplant declines in organ function, EFS evaluations began at month 14 for respiratory and month 8 for renal components. For more details on rules for confirming and documenting events constituting failure of EFS, see Protocol Section 3.1.1.1 *Definition of Event-free Survival*.

Global Rank Composite Score (GRCS)

The primary endpoint for this study is the GRCS at 54 months; a key secondary endpoint is the GRCS at 48 months. First proposed as a joint rank test by Finklestein and Schoenfeld (Stat Med 1999;18:1341-54), the GRCS combines mortality and longitudinal outcomes in hierarchical ordering. The GRCS reflects each subject's "order" relative to every other subject based on the following hierarchy of component outcome variables: death, failure of EFS, Forced Vital Capacity (FVC), Health Assessment Questionnaire –Disability Index (HAQ-DI), and modified Rodnan Skin Score (mRSS). The order and definitions (discussed below) of these component outcomes where conceived of and agreed upon by the SCOT Steering Committee.

It is important to note that the GRCS is constructed such that all deaths and EFS failures by Month 54 are "equal". That is, earlier deaths or EFS failures do not fair worse in the hierarchy than later deaths or failures. This was intentional. The expectation when planning the study design was that transplanted subjects may have worse outcomes early on, but in the long run could fair better. As such, the GRCS endpoint was designed to evaluate status at a selected long term time points.

To derive the GRCS, each subject is first compared to every other subject and assigned a pair-wise comparison score of 1 (better off), 0 (no different), or -1 (worse off). As a result of these pair-wise comparisons, each subject will have a set of n-1 subscores (where n equals the number of subjects), which

[1] DLCO change = {DLCO at assessment ((% predicted) – DLCO at baseline (% predicted))}/ DLCO at baseline (% predicted). Adjusted DLCO will be used based upon a subject's hemoglobin <13 or >17 gm/dL and altitude adjustments. Hemoglobin will be adjusted per the Cotes (1972) formula, and percent predicted per the Crapo Morris equation.
[2] FVC change = {FVC at assessment ((% predicted) – FVC at baseline (% predicted))}/ FVC at baseline (% predicted).

are then summed to yield the GRCS. To determine subscores for pairs of subjects, subject pairs are compared with respect to each component outcome in the hierarchy, in sequence, until either ties are broken or all components are evaluated. The following steps describe how subscores for the primary endpoint would be defined for two hypothetical subjects, A and B:

- **STEP 1, Deaths by 54 months:** Death is the first component of the hierarchy. Subjects who have died by month 54 are worse off than subjects who are alive. For example, if Subject A is still alive at month 54 and Subject B has died, then Subject A gets a subscore of 1 and Subject B gets a subscore of -1. If subject A and B have both died, they will each receive a subscore of zero; all deaths will be considered equivalent. If subjects A and B are both alive, then proceed to STEP 2.

- **STEP 2, Comparison of EFS Events:** For subjects who have not died by month 54, each pair will be compared with respect to EFS events at month 54. For example, if Subject A is event-free at month 54 and Subject B is not, then Subject A gets a subscore of 1 and Subject B gets a subscore of -1 for this comparison. If subjects A and B both experience events by month 54 or if both are event-free at month 54, then proceed to STEP 3 to break these ties. Please, see below for the definition of EFS.

- **STEP 3, FVC at 54 Months:** At this step, subjects are compared using the FVC measured closest to (but not after) month 54. An ordinal FVC variable is derived as: 1: Improvement (an increase from baseline ≥10%), 0: No change (neither an increase nor a decrease of ≥10%), -1: Worsening (a decrease from baseline of ≥10%). For example, if Subject A has a higher FVC ordinal value than Subject B, then Subject A gets a subscore of 1 and Subject B gets a subscore of -1 for this comparison. If both Subject A and Subject B have the same FVC ordinal value, then proceed to STEP 4.

- **STEP 4, HAQ-DI at 54 Months**: At this step, subjects are compared using the HAQ-DI measured closest to (but not after) month 54. An ordinal HAQ-DI variable is derived as: 1: Improvement (a **decrease** from baseline >0.4, 0: No change (neither an increase nor a decrease of>0.4), -1: Worsening (an **increase** from baseline of >0.4). For example, if Subject A has a higher ordinal SHAQ value than Subject B, then Subject A gets a subscore of 1 and Subject B gets a subscore of -1 for this comparison. If both Subject A and Subject B have the same ordinal HAQ-DI value, then proceed to STEP 5.

- **STEP 5, mRSS at 54 Months**: At this step, subjects are compared using the mRSS measured closest to (but not after) month 54. An ordinal mRSS variable is derived as: 1: Improvement (a decrease from baseline ≥25%, 0: No change (neither an increase nor a decrease of ≥ 25%), -1: Worsening (an increase from baseline of ≥25%). For example, if Subject A has a higher ordinal mRSS value than Subject B, then Subject A gets a subscore of 1 and Subject B gets a subscore of -1 for this comparison. If both Subject A and Subject B have the same ordinal mRSS value, then both will get subscores of 0.

Once a subject has been compared to all other subjects, the set of n-1 subscores are added to yield the GRCS. A positive GRCS means the participant generally fared better than other subjects with respect to the outcomes in the composite endpoint conditional on the pre-specified order of the components.

For the primary analysis of the GRCS endpoint, we require that assessments for evaluation of the EFS and the Month 54 visit follow standard procedures. For the primary analysis, non-conforming data will not be used to break ties for the pairwise comparison scores. Specifically:

1) Pulmonary function tests (PFTs) for assessing respiratory failure must be done at the same SCOT transplant center.

2) Typically, hemoglobin values used for adjustment of the % predicted DLCO should be assessed within 2 weeks of the PFTs. If an appropriate hemoglobin value is not available, the unadjusted % predicted DLCO will be used. In this population, adjustment is needed for hemoglobin values that are too low. Under this scenario, unadjusted % predicted DLCO will be lower than the adjusted value. Hence, with this approach, meeting failure criteria is easier, but failure of the EFS endpoint requires confirmation at a subsequent visit. In the event, that a hemoglobin value is not available at the baseline visit, then evaluation of endpoint failure during follow-up will be based on changes from baseline using the unadjusted % predicted DLCO values.

3) EFS evaluations for Month 54 must be completed no earlier than 53 months (230 weeks) after randomization. If a Month 54 assessment is not available, a post-Month 54 assessment showing that the endpoint has not been achieved is sufficient for evaluating the Month 54 endpoint. Subjects who were successes at assessment points after Month 54 would have to be successes at Month 54, as well. The reverse would not necessarily be true although this did not occur.

Methods S3. GRCS Computation and the SCOT Redesign

Example of GRCS Computation

	Hierarchy of component outcomes →					Pairwise Comparisons						
						Subject						
Subject	Mortality	EFS Failure	FVC	HAQ-DI	mRSS	1	2	3	4	5	6	GRCS
1	Dead (2 mo)					.	0	-1	-1	-1	-1	-4
2	Dead (50 mo)					0	.	-1	-1	-1	-1	-4
3	Alive	Yes (renal)	↓>10%	No Δ	↓>25%	1	1	.	-1	-1	-1	-1
4	Alive	Yes (lung)	↓>10%	↓>0.4	No Δ	1	1	1	.	-1	-1	1
5	Alive	No	No Δ	No Δ	↓>25%	1	1	1	1	.	-1	3
6	Alive	No	↑>10%	↓>0.4	No Δ	1	1	1	1	1	.	5

The GRCS is an analytic tool that accounts for multiple disease manifestations simultaneously but does not measure clinical disease activity or severity; it reflects how participants compare to one another based on a hierarchy of ordered outcomes. To compute the GRCS, each subject is first compared to every other subject and assigned a "pairwise comparison score" of 1 (better off), 0 (no different), or -1 (worse off). The table provides an example of how 6 hypothetical subjects would be scored.

1. Subjects 1 and 2 both died before Month 54. All deaths are assumed "equal". There is no attempt to order deaths using subsequent levels of the hierarchy. For pairwise comparisons,
   - Subjects 1 and 2 are tied with each other (score=0), but are worse off than all other subjects (scores=-1).
2. Subjects 3 and 4 are both alive at Month 54, but have failed a disease component of the EFS endpoint. At the 3rd level of hierarchy (FVC), they both got worse. The tie is resolved at the 4th level of hierarchy (HAQ-DI) where there was no change for Subject 3, but Subject 4 improved. Hence, for pairwise comparisons,
   - Subject 3 is better off than Subjects 1 and 2 (scores =1) and worse off than Subject 4 and Subjects 5 and 6, who survived event-free to Month 54 (scores=-1).
   - Subject 4 is better off than Subjects 1 through 3 (scores=1) and worse off than Subjects 5 and 6 (scores=-1).
3. Subjects 5 and 6 both survive event-free to Month 54, the tie is resolved at the 3rd level of hierarchy (FVC).
   - Subject 5 is better off than Subjects 1 through 4 (scores=1) but worse off than Subject 6 (score=-1).
   - Subject 6 is better off than all of than subjects (scores=1).
4. The GRCS equals the sum of the pairwise comparison scores. Lower scores indicate worse outcomes.

Abbreviations: EFS, event free survival; FVC, forced vital capacity; GRCS, global rank composite score; Health Assessment Questionnaire –Disability Index (HAQ-DI), and modified Rodnan Skin Score (mRSS).

The SCOT Redesign

The SCOT trial was originally designed as a Phase III study with event-free survival (EFS) at 44 months as the primary endpoint and a sample size of 113 per arm. Slow enrollment motivated early amendments that modified entry criteria to expand the pool of eligible patients. These attempts, however, proved insufficient, so with support of the Steering Committee and the DSMB, the protocol was redesigned as a Phase 2 study with the Global Rank Composite Score (GRCS) at 54 months as the primary endpoint.

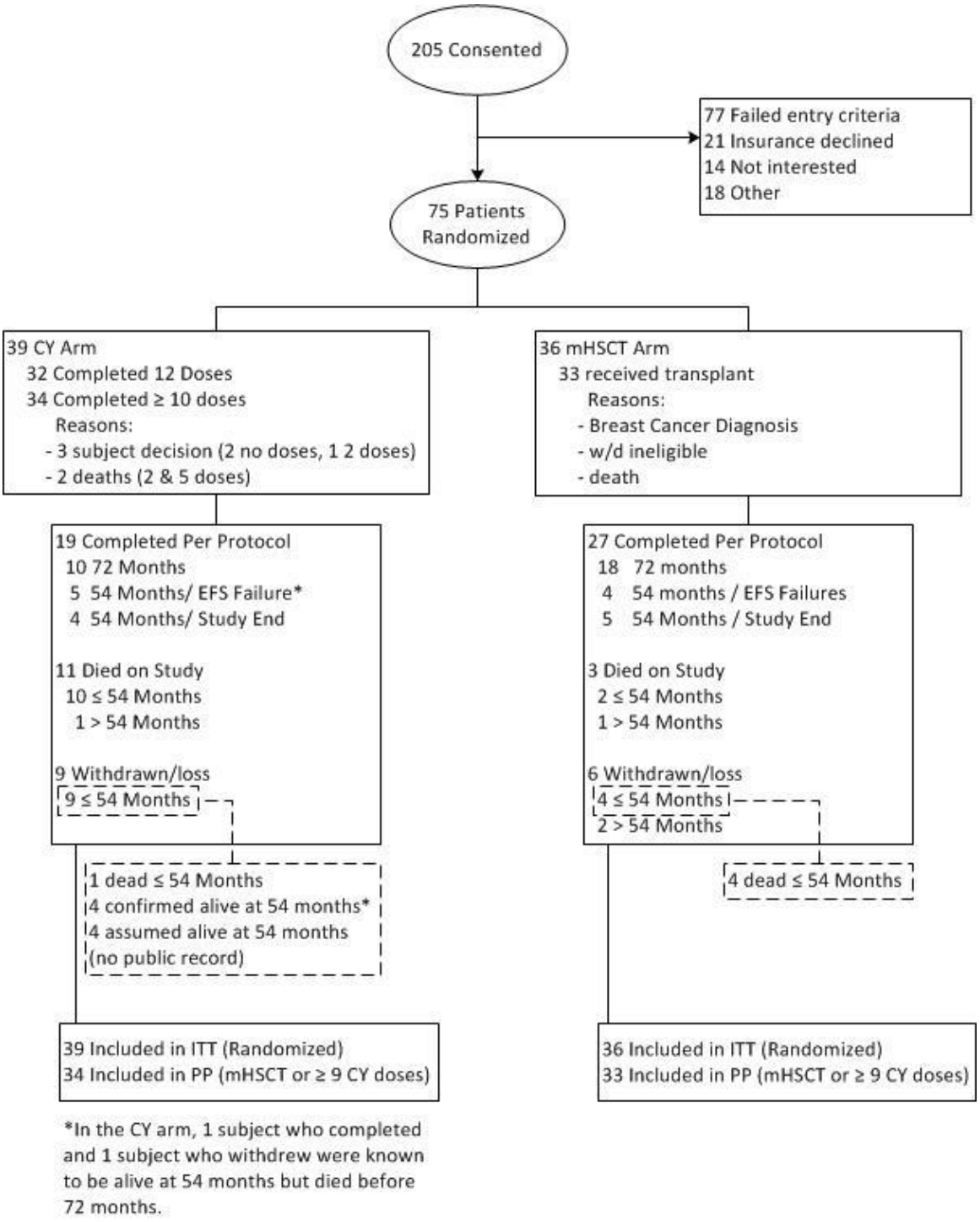
The redesign was undertaken with minimal knowledge of data from the SCOT study, but as an unblinded study, site investigators had knowledge of the clinical status of their own subjects. In addition, site personnel received reports of all deaths that occurred on-study, but never saw any data compiled across all sites for all subjects. The DSMB saw compiled safety data (deaths, SAEs, AEs) by arm prior to the redesign. No one involved in the trial, including at the coordinating center, had seen results of the EFS or GRCS analyses at the time of the redesign.

Preliminary discussions regarding the GCRS approach were originally initiated with the DSMB in 2007 after the accrual issue became apparent. In 2008, after it became clear that loosening entry criteria would not solve the problem, the final decision was made to move forward with the GRCS. Formal discussions with the DSMB and FDA regarding the re-design commenced in Spring 2009. On January 1, 2009, 48 subjects had been randomized with a maximum follow-up time of 36 months, and 5 randomized subjects had died. At this point, data were too sparse to provide a basis for predicting future results for EFS or the GRCS at 48 or 54 months.

Furthermore, the redesign process proceeded without any use of data from SCOT. The redesign was informed using data from two published studies (references 4 and 9 of the manuscript). Details on how these data were used for the redesign are presented in Appendix Q of the protocol. The redesign was completed in October 2009 (Protocol version 7.0). In October 2010, the DSMB noted the continued slow accrual and recommended enrollment be halted in March 2011. They had not reviewed any efficacy data at the time this decision was made.

Two years after completion of the redesign, in September 2011, the DSMB received the first of 4 annual interim analysis reports that included data on mortality, EFS, and the GRCS at 54 and 48 months. The analyses on mortality and EFS were designed to evaluate the validity of our design assumptions. The analyses for the GRCS were designed as futility analyses with no intent of stopping the trial for efficacy. Neither the SCOT Steering Committee nor the study investigators had access to these interim reports or knowledge of their content. These groups saw outcome results for the first time in September 2016 after data lock.

Figure S1. CONSORT Diagram for the SCOT trial.

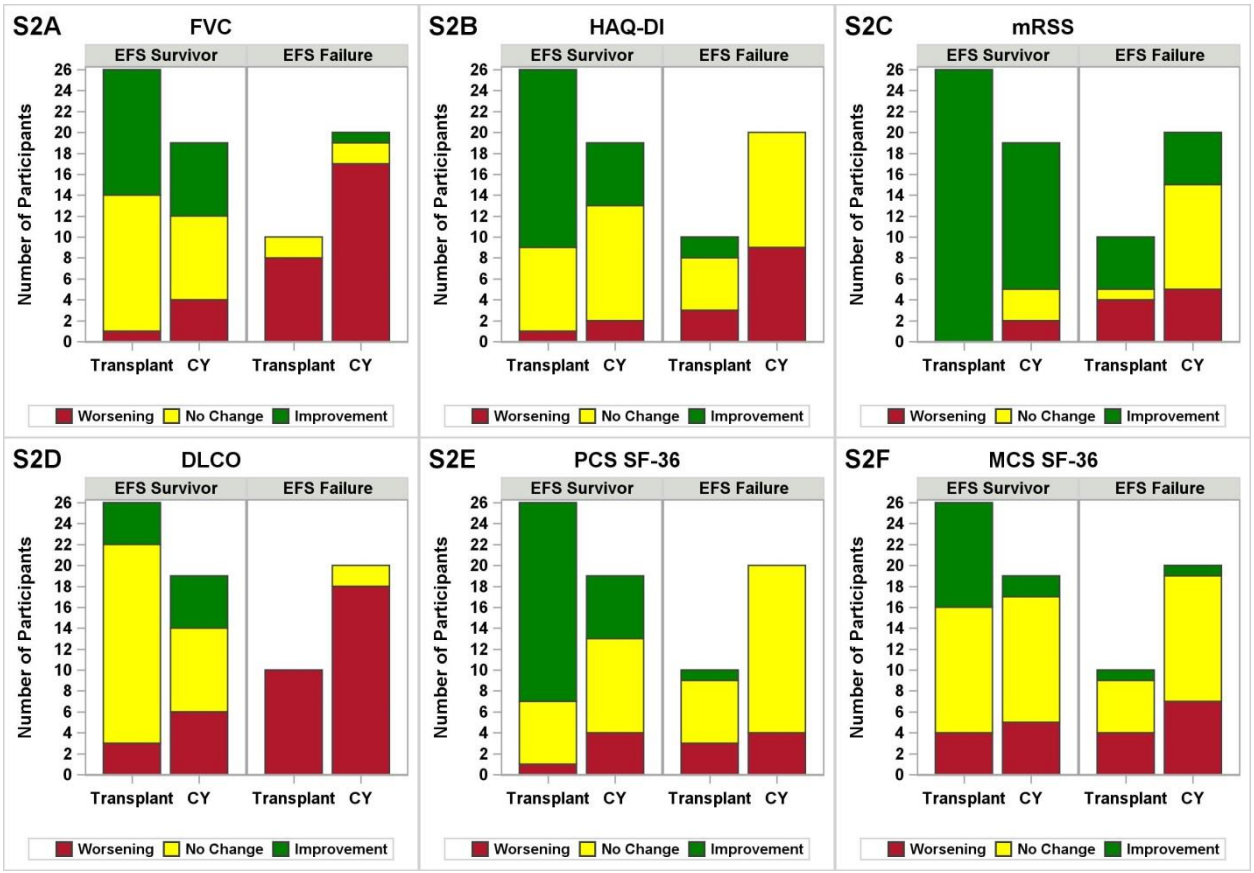


Abbreviations: CY, cyclophosphamide; mHSCT, myeloablative hematopoietic stem cell transplantation; ITT, intention-to-treat; PP, per protocol

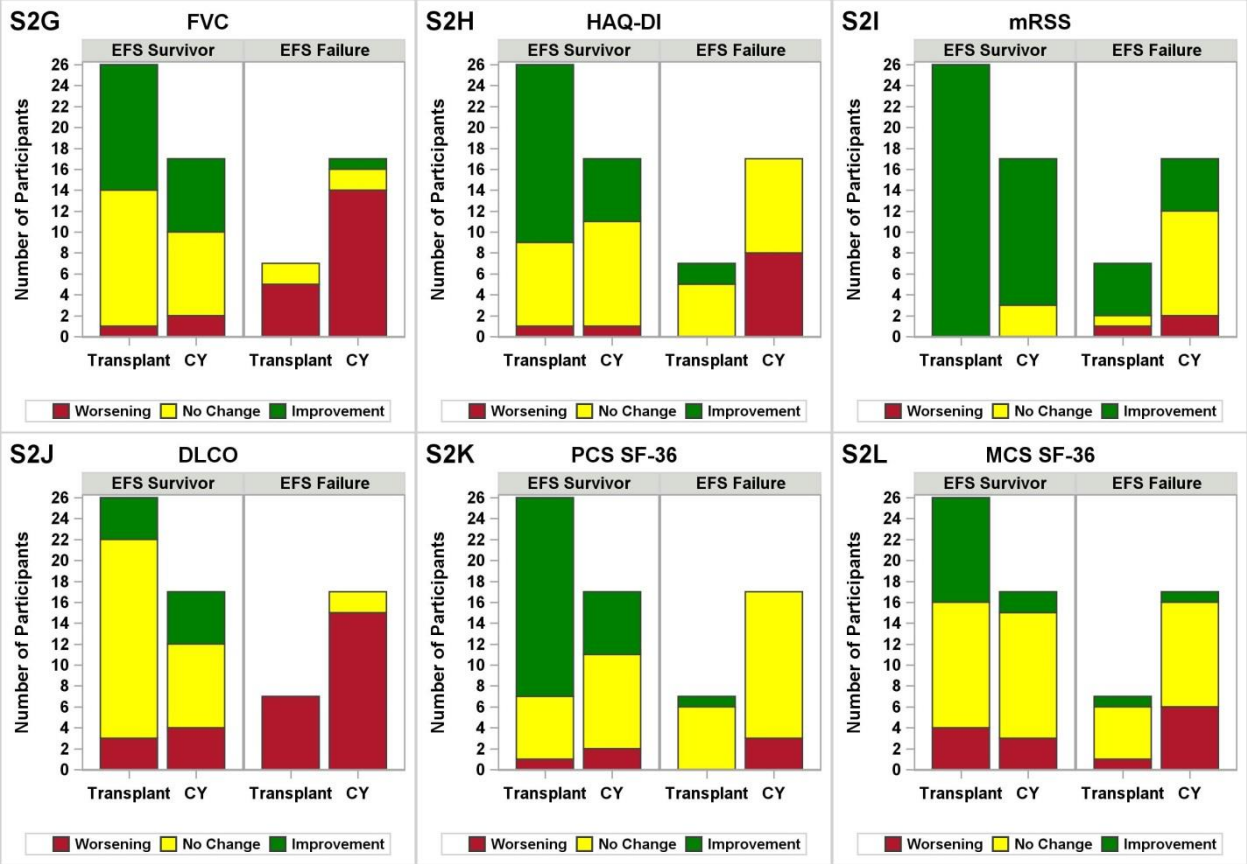
Randomization was 1:1 and stratified by site. For randomization, sites used a secure interactive web response system developed and maintained at the Statistical and Clinical Coordinating Center.

The box with dashed lines includes findings from searches of public records for subjects lost to follow-up prior to Month 54.

Figure S2. Secondary Outcomes (ITT Population).



Secondary Outcomes (PP Population)



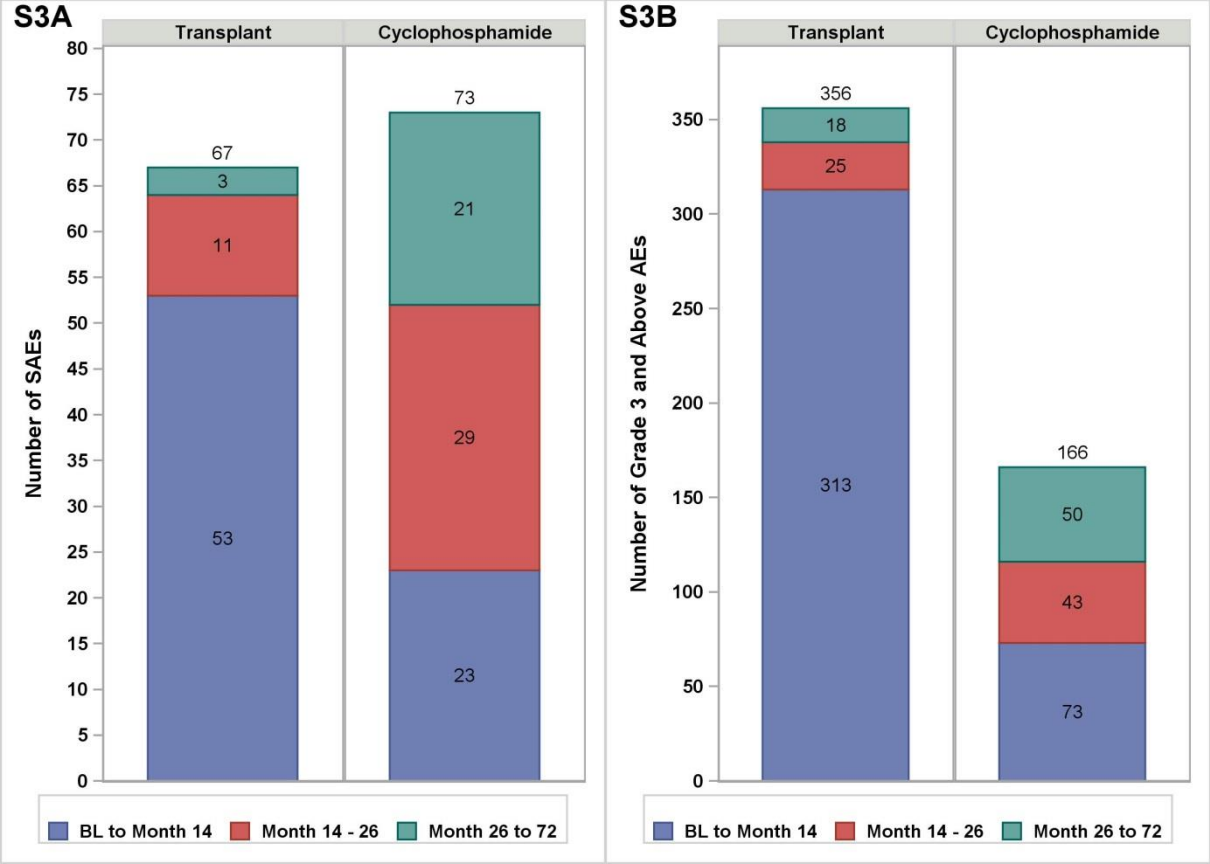
Frequency histograms for the ordinal outcomes, Forced Vital Capacity (FVC), Health Assessment Questionnaire Disability Index (HAQ-DI), modified Rodnan Skin Score (mRSS), diffusion capacity for carbon monoxide (DLCO) , Short Form 36 (SF-36) Physical component score (PCS), SF-36 Mental component (MCS) score by event-free survival (EFS) status in the Intention-to-Treat (ITT) population (panels **S2A-S2F**) and the per Protocol (PP) population (panels **S2G-S2L)** for the transplant and cyclophosphamide (CY) arms. For EFS survivors, assessments are at 54 months (or closest available assessment). For EFS failures, assessments are from the last available prior to failure. For each outcome, worsening (red) and improvement (green) are defined by changes from baseline as follows: ± ≥10% change in FVC % predicted; ± ≥0.4 change in HAQ-DI; ± ≥25% change in mRSS (or ± ≥5 if baseline mRSS ≤ 20); ± ≥15% change in DLCO % predicted; ± ≥10 point change in SF-36 PCS or SF-36 MCS. P-values for comparisons of treatment groups within EFS stratum (survivor or failure) are based on Wilcoxon signed-rank test or Pearson's chi-square for cases with only 2 categories. Comparisons of treatment groups after accounting differences in EFS status are based on the Van Elteren extension of the Wilcoxon signed-rank test.

For **S2A** (FVC, ITT), p-values = 0.3, 0.8, and 0.3, for EFS survivors, EFS failures, and pooled, respectively. For **S2B** (HAQ-DI, ITT), p-values = 0.03, 0.2, and 0.01, for EFS survivors, EFS failures, and pooled, respectively. For **S2C** (mRSS, ITT), p-values = 0.01, 0.7, and 0.05, for EFS survivors, EFS failures, and pooled, respectively. For **S2D** (DLCO, ITT), p-values = 0.6, 0.3, and 0.9, for EFS survivors, EFS failures, and pooled, respectively. For **S2E**

(PCS, ITT), p-values = 0.004, 0.9, and 0.02, for EFS survivors, EFS failures, and pooled, respectively. For **S2F** (MCS, ITT), p-values = 0.06, 0.9, and 0.1, for EFS survivors, EFS failures, and pooled, respectively.

For **S2G** (FVC,PP), p-values = 0.6, 0.6, and 0.5, for EFS survivors, EFS failures, and pooled, respectively. For **S2H** (HAQ-DI, PP), p-values = 0.06, 0.01, and 0.002, for EFS survivors, EFS failures, and pooled, respectively. For **S2I** (mRSS, PP), p-values = 0.03, 0.1, and 0.01, for EFS survivors, EFS failures, and pooled, respectively.For **S2J** (DLCO, PP), p-values = 0.9, 0.3, and 0.6, for EFS survivors, EFS failures, and pooled, respectively. For **S2K** (PCS, PP), p-values = 0.02, 0.1, and 0.003, for EFS survivors, EFS failures, and pooled, respectively. For **S2L** (MCS, PP), p-values = 0.1, 0.3, and 0.1, for EFS survivors, EFS failures, and pooled, respectively.

Figure S3. Serious Adverse Events and Grade 3 and Above Adverse Events (Safety Population)



Frequency histograms for serious adverse events (SAEs, panel **S3A**) and adverse events (AE, panel **S3B**) partitioned by start day of event: baseline (BL) to Month 14 (blue); Month 14-Month 26 (coral); Month 26-Month 72 (aqua).

Table S1A. SCOT Committees, Sites, Study Personnel, and Allied Investigators

Steering Committee: Keith Sullivan, M.D, (Principal Investigator and NIH Contract Holder), Daniel Furst, M.D. and Peter McSweeney, M.D. (Protocol Co-chairs), Ellen Goldmuntz, M.D., Ph.D. (Medical Monitor), Lynette Keyes- Elstein, Dr. P.H. (Senior Statistical Scientist), Leslie Crofford ,M.D., Richard Nash M.D., Maureen Mayes M.D.

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Chemistry Manufacturing Control-Monitoring Committee: Julia Goldstein, M.D. (chair), Linda Griffith, M.D., M.H.S.,Ph.D., Carolyn Keever-Taylor, Ph.D., Shelly Heimfeld, Ph.D.

Endpoint Review Committee: Jerry Molitor, M.D., Ph.D.(chair), Laura Hummers, M.D., Scott Rowley, M.D.

Scientific Advisory Committee: John Varga, M.D. (chair), Sergio Jimenez, M.D.

Pharmaceutical partners: David Amrani, Ph.D., and Deborah Livingston (Baxter International, Los Angeles, CA)

SCOT Sites and Study Personnel:

Secondary and Tertiary Rheumatology Centers (RCs) and Transplant Centers (TCs): Number of Participants Enrolled/Randomized in parenthesis.

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Lexington, KY (RC, 6/2): Leslie Crofford, M.D., Kristine Lohr, M.D.,M.S., Mary Johnson, Laura Ashe, Kathy Holbrook, RN, Linda Rice, RN, University of Kentucky

Los Angeles, CA (RC, 19/5): Daniel E Furst, M.D., Suzanne Kafaja M.D., Jonathan Goldin, M.D., Emma Hassan, Lynne Yoder, RN,, Sara Spencer, RN, MPH, Irene DaCosta, Jeraldine Guzman, Maricela Rodriquez, Gabriel Valdiva, University of California, Los Angeles

New York, NY (RC, 4/0): Robert Spiera, M.D., Stacey Kloiber, Hospital for Special Surgery

Madison, WI (RC, 3/0): Kevin McKown M.D., Constance Trantow, M.S., University of Wisconsin

Milwaukee, WI (combined TC/RC, 26/2): Mary Ellen Csuka, M.D., Christopher Bredeson, M.D., Marcelo Pasquini, M.D., Parameswaran Hari, M.D., Carolyn Keever-Taylor, Ph.D., Kathleen Brown, RN, BSN,

Sharon Vine, Marit Johnson, Deb Metcalf, Debra Pastorek, Rachel Theumling, Medical College of Wisconsin

Pittsburgh, PA (RC, 2/1): Thomas Medsger, M.D., Robyn Domsic, M.D., MPH, Carol Blair*, Jennifer Jablon, Dana Ivanco, EMT-I, CCMA, CCRC, University of Pittsburgh

Saskatoon, Saskatchewan (RC, 4/1): Janet Markland, M.D.*, Edith Block, Royal University Hospital

Scottsdale, AZ (RC, 6/2): Leroy Griffing, M.D., Joyce Wisbey, RN, Stacey Jones, Kelly Ryan, RN, Mayo Clinic Scottsdale

Seattle, WA (TC and RC, 21/8): Richard Nash, M.D., Peter McSweeney, M.B., Ch.B.., Mark H. Wener, M.D., Jerry Molitor, M.D., Ph.D., Shelly Heimfeld, Ph.D., George E. Georges, M.D., Gretchen Henstorf , CCRC Bernadette McLaughlin, RN, Anna Nelson, Christine Kane, Jessica Geoghegan, Fred Hutchinson Cancer Research Center, University of Washington and Virginia Mason Medical Center.

St Louis, MO (RC, 8/2): Richard Brasington, M.D., Teresa Arb, RN, BSN, Tamera Roussey,RN, BSN, Washington University, St Louis

Toledo, OH (RC, 4/1): Bashar Kahaleh, M.D., Nicole Amadio, RN, Carol Albright, Wendy Boone, RN, MPH, CCRC, Stephanie Smiddy,RN, University of Toledo Medical Center.

Washington, DC (RC, 1/0): Virginia Steen, M.D., Adrienne Marshall, Aida Manu, Georgetown University Medical Center

Immune Function Studies: Paul Wallace, Ph.D., Gregory Sempowski, Ph.D.

Mechanistic Studies: Andrew Nixon,Ph.D., Chumming Dong, M.D., PJ Utz, M.D., William Robinson, M.D., Purvesh Kharti, Ph.D., David Adams, Ph.D., Shervin Assassi, M.D., Michael Whitfield, Ph.D.

CT Imaging Studies: Jonathan Goldin, M.D., Irene Da Costa

SCOT Consultants: Oana Craciunescu, Ph.D., (Radiation Therapy), Rodney J. Folz, M.D., Ph.D., (Pulmonary)

* Deceased

Table S1B. Summary of Enrollment and Randomization by Site

			Randomized			
Site Name	**Total Screened**	**Screen Failures**	**Cyclophosphamide Arm**	**Transplant Arm**	**Total**	**Transplant Site [1]**
102: Washington University St. Louis	8	6	1	1	2	202 (1)
103: University of Alabama at Birmingham	1	1	0	0	0	
104: North Shore-Long Island Jewish Health System	2	2	0	0	0	
105: Mayo Clinic Scottsdale	6	4	1	1	2	
107: Medical University of Ohio at Toledo	4	3	1	.	1	
109: Boston University School of Medicine/ 204: Massachusetts General Hospital	17	7	5	5	10	202 (1), 204 (2)
110: University of Wisconsin	3	3	0	0	0	
112: Mercy Arthritis Center	2	2	0	0	0	
113: University of Kentucky	6	4	1	1	2	202 (1)
115: St. Peters Hospital - Albany Medical College	3	3	0	0	0	
116: Medical University of South Carolina	6	3	2	1	3	202 (1)
118: Hospital for Special Surgery, New York	4	4	0	0	0	
119: Georgetown University Medical Center	1	1	0	0	0	
120: UCLA Medical School/ 201: City of Hope National Medical Center	19	14	3	2	5	
123: Univ. of Texas-Houston Medical School/ 206: MD Anderson Cancer Center	20	13	4	3	7	206 (2)
128: University of Pittsburgh	2	1	0	1	1	202 (1)
202: Duke University Medical Center	29	11	9	9	18	206 (1)
203: Fred Hutchinson Cancer Research Center 203: University of Washington	21	13	4	4	8	
205: Medical College of Wisconsin	26	24	1	1	2	
207: University of Michigan	16	5	5	6	11	
302: Dr. Markland Medical Professional Corporation	4	3	0	1	1	401 (1)
401: University of Calgary	5	3	2	0	2	
Overall	**205**	**130**	**39**	**36**	**75**	

[1[If transplant was done at site other than randomizing site: transplant site number (number of subjects who received transplant at that site).

Table S2A. Transplant Procedures: Mobilization, Conditioning, and Supportive Care

	Day	Day												
	M1-M5	-5	-4	-3	-2	-1	0	+1	+3	+5	+6-+37	+38-+60	+39-+75	+76-+365
Mobilization														
G-CSF (16 µg/kg/day)[0]	**X** (Days 1-4)													
Apheresis	**X** (Days 4-5)													
Conditioning														
TBI (800 cGy/4 fractions over 2 days/200 cGy to lungs and kidneys with shielding		**X**	**X**											
Methylprednisolone (1 mg/kg, prior to ATGAM)		**X**		**X**		**X**		**X**	**X**	**X**				
ATGAM (15 mg/kg/day)		**X**		**X**		**X**		**X**	**X**	**X**				
CY (60 mg/kg/day)				**X**	**X**									
Mesna 50 mg/kg/day				**X**	**X**									
Hydration (50-200 cc/hr)				**X**	**X**									
Auto-CD34+HPC Infusion							**X**							
Other Supportive Care														
Corticosteroids: 0.5 mg/kg/day Days +6-+21, then tapered through Day 37											**X**			
Growth Factors: G-CSF (5 µg/kg/day) until sustained neutrophil engraftment[*]										**X**	**X**			
ACE Inhibitors: Lisinopril 10-20 mg/day or equivalent		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Infection Prophylaxis														
TMP-SMX, Bactrim or equivalent second line agent for allergy		**X***	**X**	**X**	**X**						**X***	**X**	**X**	**X**

*Days -9- -2 regular strength, then DS strength from engraftment through day 365														
Fluconazole 400 mg daily							**X**	**X**	**X**	**X**	**X**	**X**	**X**	
HSV seropositive: Acyclovir 250 mg/m^2 BID IV, convert to oral ACV (800 mg BID) or valacyclovir (500 mg BID) through Day 30. VZV seropositive: continue until day 365		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
All blood products with exception of the autologous PBSC graft to be irradiated to 2500 cGy until 2 years post-transplant. CMV seronegative patients to receive CMV negative products or alternatively leukocyte-poor (PALL) filtered blood products.														

Abbreviations: ACE, Angiotensin Converting Enzyme; ACV, Acyclovir; ATGAM, Antithymocyte Globulin (equine); CY, Cyclophosphamide; DS, Double Strength; G-CSF, Granulocyte Colony-Stimulating Factor; HRCT, High Resolution Computed Tomography; HSV, Herpes Simplex Virus; PBSC, Peripheral Blood Stem Cells; TBI, Total Body Irradiation; TMP-SMX, Trimethoprim Sulfamethoxazole; VZV, Varicella Zoster Virus.

[0]One patient who mobilized poorly with G-CSF received additional cyclophosphamide (2gm/m^2/day x 2) and G-CSF (10 µg/kg/day x 3) for successful mobilization.

CD-34+ stem cells were isolated by immunomagnetic bead separation. The manufacture, cell recovery and quality assessments of the hematopoietic progenitor products used in the SCOT trial have been recently accepted for publication: Keever-Taylor, CA, Heimfeld, S, Steinmiller, KC, Nash, RA, Sullivan, KM, Czarniecki, CW, et al. Manufacture of autologous CD34+ selected grafts in the NIAID-sponsored HALT-MS and SCOT multicenter clinical trials for autoimmune diseases. Biol Blood Marrow Transplant.2017; S 1083-8791. DOI 10.1016/J.bbmt.2017.05.018. (1)

ATGAM was specified in the protocol; otherwise sites were allowed to use drug brands from their local formularies.

Antimicrobial monitoring, prophylaxis and treatment was per institutional practice.

Baseline bronchoalveolar lavage (BAL) was performed to confirm the diagnosis of alveolitis in individuals without ground glass on HRCT and to assess for occult infection. Active alveolitis was diagnosed by centralized cell counts from BAL fluid.

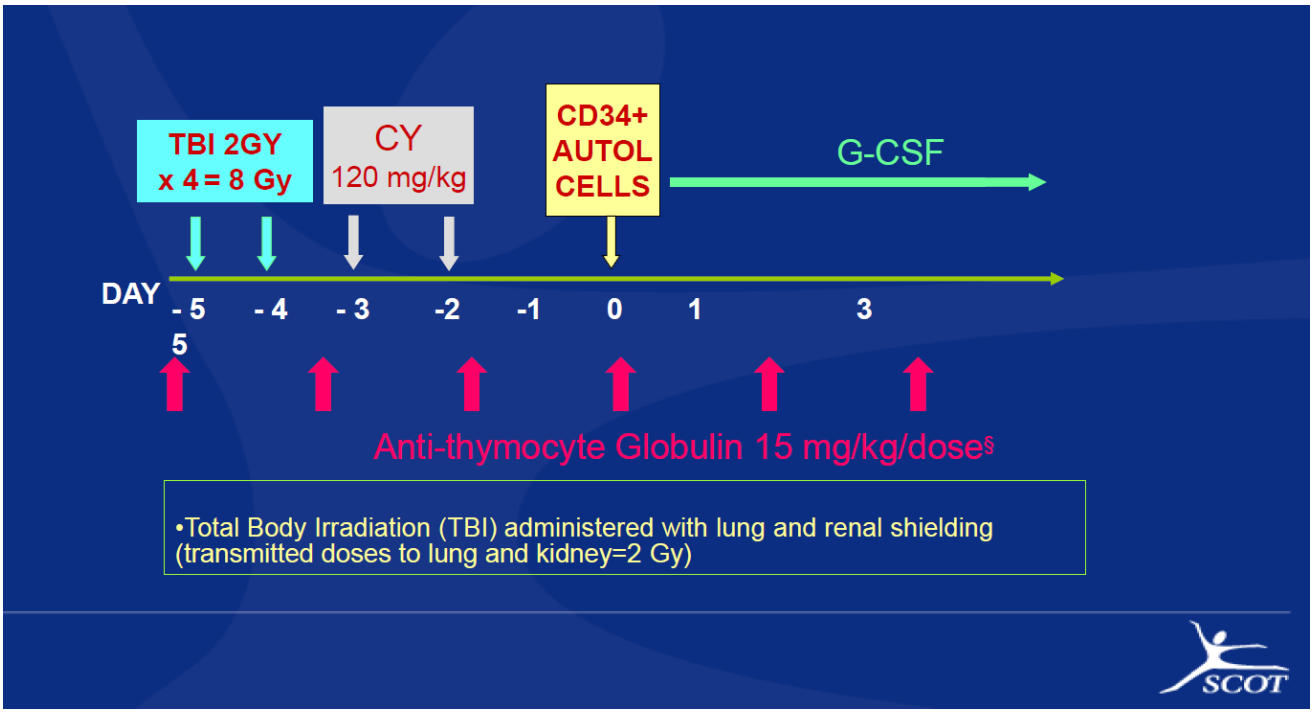
TBI 2GY
x 4 = 8 Gy
CY
120 mg/kg
CD34+
AUTOL
CELLS
G-CSF
DAY
- 5
- 4
- 3
-2
-1
0
1
3
5
Anti-thymocyte Globulin 15 mg/kg/dose§
•Total Body Irradiation (TBI) administered with lung and renal shielding
(transmitted doses to lung and kidney=2 Gy)
SCOT

Table S2B. Viral Surveillance and Preemptive Therapy for Transplant Recipients

Pretransplant CMV Serostatus	Post-Transplant Monitoring	Preemptive Therapy
CMV seronegative	Weekly monitoring for CMV antigenemia or CMV DNA until Day 60	None
CMV seropositive (with no evidence of reactivation)	Weekly monitoring for CMV antigenemia or CMV DNA until Day 100, then every 2 weeks for 6 months.	None
CMV seropositive with reactivation	Weekly monitoring until at least Day 100, and longer if remain antigen and/or DNA positive or are on steroids. Weekly monitoring should continue until antigen and/or PCR negative for at least 1 month, and they are clinically stable and off GCV and steroids. Monitoring to then continue every 2 weeks through Day 365.	See Protocol Section 5.4.1.5 for GCV dosing guidelines and guidelines for using foscarnet.
EBV serology for antibodies, including antibody titers, to EBV viral capsid antigen and/or nuclear antigen at baseline; EBV PCR amplification performed to evaluate viral load independent of baseline serology	EBV PCR weekly monitoring from Day +14 through Day 100; twice weekly for rising copy number. EBV PCR every other week from Day +101 through 6 months; if rising copy number increase to once/twice weekly per institutional standard.	Viral load > 1000 copies per mL plasma will receive individualized monitoring/ID consult per local institutional standards. See Protocol Section 5.4.1.5. for guidance on preemptive rituximab treatment and additional work-up including flow cytometry, CT/MRI imaging, and tissue biopsy to evaluate for PTLD.

Table S2C. Immunization Schedule for Transplant Recipients

Vaccine/Toxoid	Week 12	Month 8	Month 14	Month 16	Month 26	Month 28
Heptavalent pneumococcal conjugate vaccine (PCV7)	X	X	X			
Diphtheria, tetanus			X	X	X	
Haemophilus influenza type b (Hib) conjugate			X	X	X	
Hepatitis (HepB)			X	X	X	
Influenza		Lifelong, seasonal administration, beginning before HSCT and resuming ≥ 6 months after HSCT.				
Inactivated polio (IPV)			X	X	X	
Measles-mumps-rubella (MMR)[a]					X	

Abbreviations: EBV, Epstein-Barr Virus; CMV, Cytomegalovirus

[a]MMR was given only at 26-month endpoint visit and only in immunocompetent persons off all immunosuppressive agents.

Table S3: Summary of Baseline and Demographic Characteristics (ITT population)

	mHSCT (N=36)	CY (N=39)	Total (N=75)
Age (Years), mean (SD)	44.9 (10.9)	46.9 (10.4)	45.9 (10.6)
Female, n (%)	19 (52.8)	29 (74.4)	48 (64.0)
Race, n (%)			
White	29 (80.6)	31 (79.5)	60 (80.0)
Black or African American	2 (5.6)	4 (10.3)	6 (8.0)
Asian	2 (5.6)	1 (2.6)	3 (4.0)
Other	3 (8.3)	3 (7.7)	6 (8.0)
Smoking History, n (%)			
Current	1 (2.8)	2 (5.1)	3 (4.0)
Ever	13 (36.1)	8 (20.5)	21 (28.0)
Never	22 (61.1)	29 (74.4)	51 (68.0)
Scleroderma Duration (Months) from Randomization, mean (SD)	25.1 (12.9)	29.0 (16.0)	27.1 (14.6)
DMARD Use in Prior 6 Months, n (%)	26 (72.2)	25 (64.1)	51 (68.0)
Prior Cyclophosphamide Use, n(%)	8 (22.2)	17 (43.6)	25 (33.3)
Lung Involvement, n (%)	36(100.0)	37 (94.9)	73 (97.3)
Modified Rodnan Skin Score, mean (SD)	28.5 (8.7)	30.8 (10.5)	29.7 (9.7)
BMI, mean (SD)	24.9 (4.1)	25.9 (5.9)	25.4 (5.1)
FVC (% Predicted), mean (SD)	74.5 (14.8)	73.8 (17.0)	74.1 (15.9)
DLCO (% Predicted), mean (SD)	53.9 (7.6)	52.7 (8.2)	53.3 (7.9)
[1]Left Ventricular Ejection Fraction (%), mean (SD)	61.0 (6.1)	59.9 (4.3)	60.4 (5.2)
Creatinine Clearance (mL/min), mean (SD)	122.8 (41.7)	124.9 (54.3)	123.9 (48.3)
[1]ESR (mm/hr), mean (SD)	29.8 (26.5)	32.2 (24.9)	31.1 (25.4)
[2]Anti-nuclear Antibody (ANA) Positive, n (%)	32 (88.9)	34 (87.2)	66 (88.0)

	mHSCT (N=36)	CY (N=39)	Total (N=75)
[2]Anti-SCL 70 Positive, n (%)	13 (36.1)	16 (41.0)	29 (38.7)
Anti-RNA Pol III, n (%)			
Positive	2 (5.6)	6 (15.4)	8 (10.7)
Negative	13 (36.1)	11 (28.2)	24 (32.0)
Not Done	21 (58.3)	22 (56.4)	43 (57.3)
[2]Anti-Centromere Positive, n (%)	2 (5.6)	2 (5.1)	4 (5.3)
[1]SF36 Physical, mean (SD)	29.5 (9.2)	28.9 (9.5)	29.2 (9.3)
[1]SF36 Mental, mean (SD)	44.7 (10.7)	44.6 (9.9)	44.6 (10.2)
[1]HAQ-DI, mean (SD)	1.2 (0.6)	1.4 (0.9)	1.3 (0.8)

Abbreviations: BMI, Body Mass Index; CY, Cyclophosphamide; DLCO, Diffusion Capacity Lung for Carbon Monoxide;
DMARD, Disease Modifying Anti-rheumatic Drug; ESR, Erythrocyte Sedimentation Rate; FVC, Forced Vital Capacity;
HAQ-DI, Health Assessment Questionnaire-Disability Index; ITT, Intention to Treat; mHSCT, Myeloablative
Hematopoietic Stem Cell Transplant; SD, Standard Deviation; SF 36, short form 36;

Table 1 Footnotes:
Although the treatment group differences for sex, prior CY use, and smoking history appear potentially clinically
relevant, no p-values for treatment group comparisons were <0.05, based on t-tests for numeric variables and
Fisher's exact test for categorical variables. For sex, the p-value=0.06; for smoking history, the p-value=0.4, for CY
use=0.06.
[1]Mean(SD) are for ITT participants with available data (mHSCT, CY): Left Ventricular Ejection Fraction (36,37
participants; ESR (29,34); SF36 Physical and Mental (35,35); and HAQ-DI (35,38).
[2]The number of participants without autoantibody assessments are as follows (mHSCT,CY): Anti-ANA (1,1);
Anti-SCL70 (1, 0); And Anti-centromere (3,5). Participants with missing assessments are included in the denominator for calculating percents.

Table S4. 54 Month Endpoints Adjusted for Baseline Imbalances (ITT Population)

		Transplant	Cyclophos-phamide	Transplant	Cyclophos-phamide	p-value (1)
Sex		Male		Female		
	n	17	10	19	29	
GRCS	Median (min, max)	17.0 (-58, 52)	5.5 (-58, 52)	17.0 (-58,52)	-10.0 (-58, 52)	0.02
	% favorable	58.8	41.2	69.5	30.5	
	p-value(2)	0.5		0.02		
EFS	n (%) failure	4 (23.5)	5 (50.0)	13 (31.6)	15 (51.7)	0.06
	p-value(2)	0.2		0.2		
Mortality	n (%) failure	3 (17.7)	1 (10.0)	3 (15.8)	10 (34.5)	0.4
	p-value(2)	0.2		0.4		
Smoking Status		Former/Current		Never		
	N	14	10	22	29	
GRCS	Median (min, max)	9.0 (-58, 52)	13.0 (-58, 52)	22.0 (-58,52)	-19.0 (-58, 52)	0.01
	% favorable	48.6	51.4	77.0	23.0	
	p-value(2)	0.9		0.001		
EFS	n (%) failure	6 (42.9)	4 (40.0)	4 (18.2)	16 (55.2)	0.04
	p-value(2)	>0.9		0.01		
Mortality	n (%) failure	5 (35.7)	2 (20.0)	1 (4.6)	9 (31.0)	0.2
	p-value(2)	0.7		0.03		
Prior Cyclophosphamide Use		Yes		No		
	N	8	17	28	22	
GRCS	Median (min, max)	0.5 (-58, 52)	-6.0 (-58, 52)	19.5 (-58,52)	-0.5 (-58, 52)	0.04
	% favorable	55.5	44.5	68.2	31.8	
	p-value(2)	0.7		0.03		
EFS	n (%) failure	4 (50.0)	9(52.9)	6(21.4)	11(50.0)	0.07
	p-value(2)	>0.9		0.04		
Mortality	n (%) failure	2 (25.0)	4 (23.5)	4(14.3)	7(31.8)	0.2
	p-value(2)	>0.9		0.2		

Abbreviations: EFS, Event Free Survival; GRCS, Global Rank Composite Score; ITT, Intention-to-Treat; Min, Minimum; Max, Maximum.

[1] Comparison of treatment arms after controlling for covariates (sex, smoking status, or prior cyclophosphamide use) based on the van Elteren extension of the Wilcoxon statistic for GRCS and Mantel-Haenszel for EFS and Mortality.
[2] Comparison of treatment arms within stratum (male, female; former/current smoker, never smoked; prior cyclophosphamide use (Y/N))) based on Wilcoxon statistic for GRCS and Fisher's Exact for EFS and Mortality.

After controlling for baseline imbalances, treatment groups differences in GRCS at 54 months for the ITT population are still significant. Likewise, adjusted comparisons for EFS at 54 months still support superiority of transplant over cyclophosphamide in the ITT population. The advantage of transplant is most apparent among the subset of subjects who never smoked, where the differences in GRCS, EFS, and overall survival at 54 months are all significant. In contrast, among former and current smokers, transplant has no advantage over cyclophosphamide.

Table S5. Sensitivity Analyses for GRCS at Month 54 in ITT population.

There are 7 cyclophosphamide and 3 transplant participants in the ITT population that were alive at Month 54, but for whom EFS status could not be evaluated due to early withdrawal or missed assessments (Figure 1). This includes 4 cyclophosphamide participants who are assumed alive, because deaths could not be found in public records. For these 11 individuals, we don't know if they were better or worse off than any other subject alive at 54 months, so we assume they are tied for computing GRCS for the primary analysis. In Figure 2B, these subjects are represented with a "blank" in the EFS column, and cells for FVC, HAQ-DI and mRSS are colored coded with faded tones to indicate status at the last available assessment, but these data are not used to break the ties. These subjects all have a score of 17 (Figure 2A). Subjects who scored higher than 17 have fared better than at least some other subjects for whom the EFS scores are available (and vice versa.

Results of sensitivity analyses to evaluate the robustness or our primary analysis findings are displayed in the table below. Row 1 gives the p-value for the primary analyses of GRCS at 54 months in the ITT population. In Row 2, we break ties for subjects who are missing EFS data by assuming they failed EFS at Month 54, and then use data for FVC, HAQ-DI, and mRSS from the last available assessment to move down the hierarchy. In Row 3, we also use hierarchical data for FVC, HAQ-DI, and mRSS from the last available assessment after first assuming the subjects are event free survivors. Rows 4 and 5 represent the 2 extreme possibilities. In Row 4, we assume those with missing EFS data have worsened on all elements of the hierarchy and, hence, have the lowest GRCS score among all those who are alive at 54 months. At the other extreme, Row 5 gives results when we assume EFS survival and improvement on FVC, HAQ-DI, and mRSS. This last option still favors transplant, but it is the only sensitivity analysis that is not significant. We argue, however, that it is also the most unreasonable assumption, because at least some subjects who were too ill to travel for SCOT visits missed required assessments and were less likely to show improvements.

Row	Assumption for unknown EFS at 54 months	p-value
1	Primary: Ties not broken	0.01
2	Assume EFS failure, move down the hierarchy using last available data	0.005
3	Assume EFS survivor, move down the hierarchy using last available data	0.01
4	Assume EFS failure and FVC, HAQ-DI, mRSS all worsened (lowest GRCS score for alive)	0.005
5	Assume EFS survivor and FVC, HAQ-DI, mRSS all improved (highest GRCS score)	0.09

Abbreviations: EFS, Event Free Survival; FVC, Forced Composite Score; HAQ-DI, Health Assessment Questionnaire-Disability Index; ITT, Intention-to-Treat; mRSS, Modified Rodnan Skin Score

Table S6: Serious Adverse Events and Grade 3 and Above Adverse Events (Safety Population)

	Transplant (N=34) n(%) [Events]	Cyclophosphamide (N=37) n(%) [Events]	Transplant P-T rate*	Cyclophosphamide P-T rate*	Rate Ratio	Rate p-Val [1]
Any SAE	25 (73.5) [67]	19 (51.4) [73]	0.38	0.52	0.74	0.08
Treatment Related SAE [2]	14 (41.2) [20]	3 (8.1) [5]	0.11	0.04	3.24	0.01
Any Grade 4 or higher AE	29 (85.3) [100]	19 (51.4) [33]	0.57	0.23	2.45	<0.001
Treatment Related Grade 4 or higher AE [2]	27 (79.4) [81]	4 (10.8) [6]	0.46	0.04	10.94	<0.001
Any Grade 3 or higher AE	34(100.0) [356]	31 (83.8) [166]	2.04	1.18	1.74	<0.001
Treatment Related Grade 3 or higher AE [2]	34(100.0) [188]	12 (32.4) [18]	1.08	0.13	8.46	<0.001
Any Grade 3 or higher AE by MedDRA SOC						
Respiratory, thoracic and mediastinal disorders [3]	27 (79.4) [51]	24 (64.9) [42]	0.29	0.30	0.98	0.9
Blood and lymphatic system disorders	31 (91.2) [169]	18 (48.6) [36]	0.97	0.25	3.80	<0.001
Infections and infestations [4]	21 (61.8) [36]	11 (29.7) [18]	0.21	0.13	1.62	0.09
Gastrointestinal disorders	9 (26.5) [18]	10 (27.0) [18]	0.10	0.13	0.81	0.5
Metabolism and nutrition disorders	12 (35.3) [15]	4 (10.8) [12]	0.09	0.08	1.01	>0.9
Investigations	9 (26.5) [13]	4 (10.8) [5]	0.07	0.04	2.11	0.1
General disorders and administration site conditions	9 (26.5) [12]	3 (8.1) [3]	0.07	0.02	3.24	0.04
Musculoskeletal and connective tissue disorders	6 (17.6) [7]	6 (16.2) [6]	0.04	0.04	0.95	>0.9
Cardiac disorders	3 (8.8) [4]	6 (16.2) [8]	0.02	0.06	0.41	0.1
Renal and urinary disorders	4 (11.8) [5]	3 (8.1) [4]	0.03	0.03	1.01	>0.9
Skin and subcutaneous tissue disorders	6 (17.6) [7]	1 (2.7) [1]	0.04	0.01	5.67	0.05
Psychiatric disorders	3 (8.8) [3]	2 (5.4) [3]	0.02	0.02	0.81	0.8
Vascular disorders	4 (11.8) [5]	1 (2.7) [1]	0.03	0.01	4.05	0.1
Neoplasms benign, malignant and unspecified (inc cysts/ polyps)	3 (8.8) [4]	1 (2.7) [1]	0.02	0.01	3.24	0.2
Myelodysplastic syndrome	2 (5.9) [2]	0	0.01	0.00		NA
Acute myeloid leukemia	1 (2.9) [1]	0	0.01	0.00		NA
Breast cancer recurrent	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Papillary thyroid cancer	1 (2.9) [1]	0	0.01	0.00		NA
Nervous system disorders	1 (2.9) [2]	3 (8.1) [3]	0.01	0.02	0.54	0.5

	Transplant (N=34) n(%) [Events]	Cyclophosphamide (N=37) n(%) [Events]	Transplant P-T rate*	Cyclophosphamide P-T rate*	Rate Ratio	Rate p-Val [1]
Injury, poisoning and procedural complications	2 (5.9) [2]	2 (5.4) [2]	0.01	0.01	0.81	0.8
Immune system disorders	2 (5.9) [2]	0	0.01	0.00		NA
Surgical and medical procedures	0	1 (2.7) [2]	0.00	0.01	0.00	NA
Eye disorders	1 (2.9) [1]	0	0.01	0.00		NA
Hepatobiliary disorders	0	1 (2.7) [1]	0.00	0.01	0.00	NA

Abbreviations: AE, Adverse Event; SAE, Serious Adverse Event; MedDRA, Medical Dictionary for Regulatory Activities; P-T; Person-Time (in years); SOC, System Organ Class

Footnotes:

* Total person-time for the duration of the study is 174.4 years for the transplant arm and 141.3 years for the cyclophosphamide arm.
[1] P-value comes from a Poisson regression comparing the person-year adjusted event rates between the two treatment arms.
[2] “Related” includes events deemed probably or definitely related to the treatment regimen or CD34+HPC as reported by the site investigator
[3] Respiratory events include the SOC='Respiratory, thoracic and mediastinal disorders', plus the preferred terms of 'Pulmonary function test decreased', 'Vital capacity decreased', 'Forced expiratory volume', and 'Forced expiratory volume decreased'.
[4] Infections include the SOC='Infections and infestations' plus any event identified by investigators as an infection.

Table S7. Serious Adverse Events and Grade 3 and Above Adverse Events over the First 26 Months (Safety Population)

	Transplant (N=34) n(%) [Events]	Cyclophosphamide (N=37) n(%) [Events]	Transplant P-T* rate	Cyclophosphamide P-T* rate	Rate Ratio	Rate p-value [1]
Any SAE	25 (73.5) [64]	15 (40.5) [52]	0.92	0.73	1.26	0.2
Treatment Related SAE [2]	14 (41.2) [20]	3 (8.1) [5]	0.29	0.07	4.14	0.002
Any Grade 4 or higher AE	28 (82.4) [98]	14 (37.8) [22]	1.41	0.31	4.55	<0.001
Treatment Related Grade 4 or higher AE [2]	27 (79.4) [81]	4 (10.8) [6]	1.16	0.08	14.50	<0.001
Any Grade 3 or higher AE	34(100.0) [338]	27 (73.0) [116]	4.86	1.62	3.00	<0.001
Treatment Related Grade 3 or higher AE [2]	34(100.0) [187]	12 (32.4) [18]	2.69	0.25	10.76	<0.001
Any Grade 3 or higher AE by SOC						
Respiratory, thoracic, mediastinal disorders [3]	26 (76.5) [46]	19 (51.4) [28]	0.66	0.39	1.69	0.03
Blood and lymphatic system disorders	31 (91.2) [169]	17 (45.9) [32]	2.43	0.45	5.40	<0.001
Infections and infestations [4]	20 (58.8) [33]	6 (16.2) [12]	0.47	0.17	2.76	0.001
Gastrointestinal disorders	9 (26.5) [18]	9 (24.3) [13]	0.26	0.18	1.44	0.3
Metabolism and nutrition disorders	12 (35.3) [15]	3 (8.1) [8]	0.22	0.11	2.00	0.1
Investigations	9 (26.5) [12]	2 (5.4) [2]	0.17	0.03	5.67	0.004
General disorders/administration site conditions	9 (26.5) [12]	2 (5.4) [2]	0.17	0.03	5.67	0.004
Musculoskeletal and connective tissue disorders	5 (14.7) [6]	3 (8.1) [3]	0.09	0.04	2.25	0.3
Cardiac disorders	3 (8.8) [4]	5 (13.5) [5]	0.06	0.07	0.86	0.8
Renal and urinary disorders	3 (8.8) [4]	3 (8.1) [4]	0.06	0.06	1.00	>0.9
Skin and subcutaneous tissue disorders	5 (14.7) [6]	1 (2.7) [1]	0.09	0.01	9.00	0.04
Psychiatric disorders	2 (5.9) [2]	2 (5.4) [2]	0.03	0.03	1.00	>0.9
Vascular disorders	4 (11.8) [5]	1 (2.7) [1]	0.07	0.01	7.00	0.08
Neoplasms benign, malignant, unspecified	2 (5.9) [2]	0	0.03	0.00		
Myelodysplastic syndrome	1 (2.9) [1]	0	0.01	0.00		
Acute myeloid leukemia	0	0	0.00	0.00		
Breast cancer recurrent	0	0	0.00	0.00		
Papillary thyroid cancer	1 (2.9) [1]	0	0.01	0.00		

	Transplant (N=34) n(%) [Events]	Cyclophosphamide (N=37) n(%) [Events]	Transplant P-T* rate	Cyclophosphamide P-T* rate	Rate Ratio	Rate p-value [1]
Nervous system disorders	1 (2.9) [1]	2 (5.4) [2]	0.01	0.03	0.33	0.6
Injury, poisoning and procedural complications	1 (2.9) [1]	0	0.01	0.00		
Immune system disorders	2 (5.9) [2]	0	0.03	0.00		
Surgical and medical procedures	0	0	0.00	0.00		
Eye disorders	0	0	0.00	0.00		
Hepatobiliary disorders	0	1 (2.7) [1]	0.00	0.01	0.00	

Abbreviations: AE, Adverse Event; SAE, Serious Adverse Event; SOC, System Organ Class

*Total person-time at 26 months is 69.6 years for the transplant arm and 71.6 years for the cyclophosphamide arm.

[1] P-value comes from a Poisson regression comparing the person-year adjusted event rates between the two treatment groups.
[2] Related includes definitely or probably related to treatment regimen or CD34+ cells.
[3] Respiratory events include the SOC='Respiratory, thoracic and mediastinal disorders', plus the preferred terms of 'Pulmonary function test decreased', 'Vital capacity decreased', 'Forced expiratory volume', and 'Forced expiratory volume decreased'.
[4] Infections include the SOC='Infections and infestations' plus any event identified by investigators as an infection.

In the transplant arm, 25 subjects (73.5%) experienced at least 1 SAE during the first 26 months compared to 15 subjects (40.5%) in the cyclophosphamide arm; the rate of events is ~30% higher in the transplant arm. In contrast, over the full duration of the study, the rate of SAEs is ~30% higher in the cyclophosphamide arm even though fewer cyclophosphamide subjects have reported SAEs (25 transplant, 19 cyclophosphamide). Grade 3 and above AEs occurred in 34 (100%) transplant and 27 (73.0%) cyclophosphamide subjects during the first 26 month. The vast majority of events, 95.0% in the transplant arm accrue over the first 26 months compared to 69.9% in the cyclophosphamide arm.

Table S8. Infections over the 72 Month Duration of the Study (Safety Population)

A. Summary of Infections (Safety Population)

	Transplant (N=34) n(%) [Events]	Cyclophosphamide (N=37) n(%) [Events]	Transplant P-T* rate	Cyclophosphamide P-T* rate	Rate Ratio	Rate p-value [1]
Any SAE	12 (35.3) [17]	9 (24.3) [16]	0.10	0.11	0.91	0.7
SAEs by Severity						
Grade 2 (moderate)	2 (5.9) [3]	3 (8.1) [3]	0.02	0.02	1.00	0.8
Grade 3 (severe)	6 (17.6) [8]	7 (18.9) [11]	0.05	0.08	0.63	0.3
Grade 4 (life-threatening)	4 (11.8) [5]	1 (2.7) [1]	0.03	0.01	3.00	0.1
Grade 5 (fatal)	1 (2.9) [1]	1 (2.7) [1]	0.01	0.01	1.00	0.9
Any AE	33 (97.1) [131]	31 (83.8) [112]	0.75	0.79	0.95	0.7
AEs by Severity						
Grade 2 (moderate)	30 (88.2) [92]	28 (75.7) [93]	0.53	0.66	0.80	0.1
Grade 3 (severe)	21 (61.8) [33]	11 (29.7) [17]	0.19	0.12	1.58	0.1
Grade 4 (life-threatening)	4 (11.8) [5]	1 (2.7) [1]	0.03	0.01	3.00	0.1
Grade 5 (fatal)	1 (2.9) [1]	1 (2.7) [1]	0.01	0.01	1.00	0.9

B. Summary of Infections by System Organ Class, Preferred Term, and Severity (Safety Population)

	NCI-CTCAE Severity Grade	Transplant (N=34) n(%) [Events]	Cyclophosphamide (N=37) n(%) [Events]	Transplant P-T* rate	Cyclophosphamide P-T* rate	Rate Ratio	Rate p-value [1]
Infections and infestations							
Upper respiratory tract infection	2	9 (26.5) [14]	8 (21.6) [19]	0.08	0.13	0.62	0.1
Urinary tract infection	2	1 (2.9) [1]	11 (29.7) [19]	0.01	0.13	0.08	<0.001
	3	1 (2.9) [1]	2 (5.4) [4]	0.01	0.03	0.33	0.1
	4	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Herpes zoster	2	10 (29.4) [10]	1 (2.7) [1]	0.06	0.01	6.00	0.01
	3	3 (8.8) [3]	0	0.02	0.00		NA
Pneumonia	2	5 (14.7) [6]	1 (2.7) [1]	0.03	0.01	3.00	0.08
	3	2 (5.9) [2]	1 (2.7) [1]	0.01	0.01	1.00	0.7
	4	2 (5.9) [2]	0	0.01	0.00		NA
Cellulitis	2	3 (8.8) [3]	2 (5.4) [2]	0.02	0.01	2.00	0.8
	3	2 (5.9) [2]	1 (2.7) [2]	0.01	0.01	1.00	0.8

	NCI-CTCAE Severity Grade	Transplant (N=34) n(%) [Events]	Cyclophosphamide (N=37) n(%) [Events]	Transplant P-T* rate	Cyclophosphamide P-T* rate	Rate Ratio	Rate p-value [1]
Nasopharyngitis	2	5 (14.7) [12]	2 (5.4) [5]	0.07	0.04	1.75	0.2
Infected skin ulcer	2	2 (5.9) [4]	4 (10.8) [9]	0.02	0.06	0.33	0.07
	3	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Bronchitis	2	2 (5.9) [2]	2 (5.4) [2]	0.01	0.01	1.00	0.8
	3	1 (2.9) [1]	0	0.01	0.00		NA
Bacteremia	3	4 (11.8) [4]	0	0.02	0.00		NA
Cytomegalovirus infection	2	1 (2.9) [1]	0	0.01	0.00		NA
	3	3 (8.8) [3]	0	0.02	0.00		NA
Paronychia	2	2 (5.9) [2]	1 (2.7) [2]	0.01	0.01	1.00	0.8
Sinusitis	2	3 (8.8) [4]	0	0.02	0.00		NA
Body tinea	2	2 (5.9) [2]	1 (2.7) [1]	0.01	0.01	1.00	0.7
Bronchitis acute	2	1 (2.9) [1]	2 (5.4) [2]	0.01	0.01	1.00	0.4
Respiratory tract infection	2	0	2 (5.4) [2]	0.00	0.01	0.00	NA
	3	1 (2.9) [1]	0	0.01	0.00		NA
Cystitis	2	2 (5.9) [2]	0	0.01	0.00		NA
Fungal rash	2	1 (2.9) [1]	1 (2.7) [1]	0.01	0.01	1.00	0.9
Gastroenteritis	2	1 (2.9) [1]	1 (2.7) [1]	0.01	0.01	1.00	0.9
Influenza	2	1 (2.9) [1]	0	0.01	0.00		NA
	3	1 (2.9) [1]	0	0.01	0.00		NA
Localized infection	2	0	2 (5.4) [2]	0.00	0.01	0.00	NA
Osteomyelitis	3	1 (2.9) [1]	1 (2.7) [1]	0.01	0.01	1.00	0.9
Overgrowth bacterial	2	1 (2.9) [1]	1 (2.7) [1]	0.01	0.01	1.00	0.9
Pharyngitis streptococcal	2	1 (2.9) [1]	1 (2.7) [1]	0.01	0.01	1.00	0.9
Postoperative infection	2	1 (2.9) [1]	0	0.01	0.00		NA
	3	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Sepsis	3	2 (5.9) [2]	0	0.01	0.00		NA
Septic shock	4	1 (2.9) [1]	0	0.01	0.00		NA
	5	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Skin infection	2	1 (2.9) [1]	1 (2.7) [1]	0.01	0.01	1.00	0.9
Staphylococcal infection	3	1 (2.9) [1]	1 (2.7) [1]	0.01	0.01	1.00	0.9
Tinea cruris	2	1 (2.9) [1]	1 (2.7) [1]	0.01	0.01	1.00	0.9
Tooth abscess	2	0	2 (5.4) [2]	0.00	0.01	0.00	NA
Bacterial infection	3	1 (2.9) [1]	0	0.01	0.00		NA
Bronchitis viral	3	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Bronchopulmonary aspergillosis	3	1 (2.9) [1]	0	0.01	0.00		NA
Candidiasis	2	1 (2.9) [1]	0	0.01	0.00		NA
Cellulitis staphylococcal	3	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Cytomegalovirus viremia	3	1 (2.9) [1]	0	0.01	0.00		NA
Dental caries	2	1 (2.9) [1]	0	0.01	0.00		NA
Ear infection	2	1 (2.9) [1]	0	0.01	0.00		NA

	NCI-CTCAE Severity Grade	Transplant (N=34) n(%) [Events]	Cyclophosphamide (N=37) n(%) [Events]	Transplant P-T* rate	Cyclophosphamide P-T* rate	Rate Ratio	Rate p-value [1]
Enterococcal infection	3	1 (2.9) [1]	0	0.01	0.00		NA
Fungemia	3	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Fungal infection	2	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Gastrointestinal infection	2	1 (2.9) [1]	0	0.01	0.00		NA
Herpes simplex	2	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Hordeolum	2	1 (2.9) [1]	0	0.01	0.00		NA
Laryngitis	2	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Lung infection	2	1 (2.9) [1]	0	0.01	0.00		NA
Meningitis enterococcal	5	1 (2.9) [1]	0	0.01	0.00		NA
Meningitis viral	3	1 (2.9) [1]	0	0.01	0.00		NA
Nail infection	2	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Oral candidiasis	2	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Pharyngitis	2	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Pneumonia primary atypical	2	1 (2.9) [1]	0	0.01	0.00		NA
Pyelonephritis	3	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Rash pustular	2	1 (2.9) [1]	0	0.01	0.00		NA
Respiratory moniliasis	3	1 (2.9) [1]	0	0.01	0.00		NA
Respiratory syncytial virus infection	2	1 (2.9) [1]	0	0.01	0.00		NA
Rhinovirus infection	2	1 (2.9) [1]	0	0.01	0.00		NA
Staphylococcal bacteremia	3	1 (2.9) [1]	0	0.01	0.00		NA
Streptococcal bacteremia	3	1 (2.9) [1]	0	0.01	0.00		NA
Tinea capitis	2	1 (2.9) [1]	0	0.01	0.00		NA
Tinea versicolour	2	1 (2.9) [1]	0	0.01	0.00		NA
Tooth infection	2	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Viral infection	2	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Respiratory, thoracic and mediastinal disorders							
Pneumonia aspiration	2	1 (2.9) [1]	1 (2.7) [1]	0.01	0.01	1.00	0.9
	3	1 (2.9) [1]	1 (2.7) [1]	0.01	0.01	1.00	0.9
Aspiration	3	1 (2.9) [1]	0	0.01	0.00		NA
Pharyngolaryngeal pain	2	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Pneumonitis	4	1 (2.9) [1]	0	0.01	0.00		NA
Respiratory tract congestion	2	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Upper respiratory tract congestion	2	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Eye disorders							
Conjunctivitis	2	3 (8.8) [3]	1 (2.7) [1]	0.02	0.01	2.00	0.4

	NCI-CTCAE Severity Grade	Transplant (N=34) n(%) [Events]	Cyclophosphamide (N=37) n(%) [Events]	Transplant P-T* rate	Cyclophosphamide P-T* rate	Rate Ratio	Rate p-value [1]
Blood and lymphatic system disorders							
Febrile neutropenia	3	1 (2.9) [1]	1 (2.7) [1]	0.01	0.01	1.00	0.9
	4	1 (2.9) [1]	0	0.01	0.00		NA
Skin and subcutaneous tissue disorders							
Skin ulcer	2	0	3 (8.1) [3]	0.00	0.02	0.00	NA
Reproductive system and breast disorders							
Epididymitis	2	1 (2.9) [1]	0	0.01	0.00		NA
General disorders and administration site conditions							
Influenza like illness	2	1 (2.9) [1]	0	0.01	0.00		NA
Reproductive system and breast disorders							
Prostatitis	2	1 (2.9) [1]	0	0.01	0.00		NA
General disorders and administration site conditions							
Pyrexia	2	1 (2.9) [1]	0	0.01	0.00		NA
Renal and urinary disorders							
Leukocyturia	2	0	1 (2.7) [1]	0.00	0.01	0.00	NA
Gastrointestinal disorders							
Mouth ulceration	2	0	1 (2.7) [1]	0.00	0.01	0.00	NA

6A. * Total person-time for the duration of the study is 174.4 years for the Transplant arm and 141.3 years for the Cyclophosphamide arm.

6B. * Total person-time for the duration of the study is 174.4 years for the Transplant arm and 141.3 years for the Cyclophosphamide arm.

[1] P-values come from a Poisson regression comparing the person-year adjusted event rates between the two treatment groups.

Classifications for system organ class (SOC) and preferred term are according to the Medical Dictionary for Regulatory Activities [MedDRA] version 8.0. For this display, infections include events classified as SOC='Infections and infestations' plus any event identified by investigators as an infection. The severity grading is per the National Cancer Institute's (NCI's) Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. Only Grade 2 and above events were collected for this study. Grade2 = moderate; Grade3 = severe; Grade 4= life-threatening; Grade 5=fatal.

Table S9. Events and Subjects with Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Transplant Subject (%) (N=34)	 SAEs (%)	Cyclophosphamide Subject (%) (N=37)	 SAEs (%)	Total Subject (%) (N=71)	 SAEs (%)
Any SAE	25 (73.5)	67	19 (51.4)	73	44 (62.0)	140
Infections and infestations	10 (29.4)	12 (17.9)	7 (18.9)	13 (17.8)	17 (23.9)	25 (17.9)
Pneumonia	5 (14.7)	6 (9.0)	1 (2.7)	1 (1.4)	6 (8.5)	7 (5.0)
Urinary tract infection	0	0	2 (5.4)	4 (5.5)	2 (2.8)	4 (2.9)
Cellulitis	1 (2.9)	1 (1.5)	1 (2.7)	2 (2.7)	2 (2.8)	3 (2.1)
Septic shock	1 (2.9)	1 (1.5)	1 (2.7)	1 (1.4)	2 (2.8)	2 (1.4)
Bacteraemia	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Bronchitis viral	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Cellulitis staphylococcal	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Fungaemia	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Herpes zoster	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Meningitis enterococcal	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Sepsis	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Staphylococcal infection	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Viral infection	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Respiratory, thoracic and mediastinal disorders	7 (20.6)	11 (16.4)	8 (21.6)	11 (15.1)	15 (21.1)	22 (15.7)
Respiratory failure	0	0	4 (10.8)	4 (5.5)	4 (5.6)	4 (2.9)
Pneumonitis	3 (8.8)	3 (4.5)	0	0	3 (4.2)	3 (2.1)
Pneumonia aspiration	1 (2.9)	1 (1.5)	1 (2.7)	2 (2.7)	2 (2.8)	3 (2.1)
Interstitial lung disease	1 (2.9)	1 (1.5)	1 (2.7)	1 (1.4)	2 (2.8)	2 (1.4)
Acute respiratory failure	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Aspiration	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Capillary leak syndrome	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Dyspnoea	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Hypoxia	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Pulmonary alveolar haemorrhage	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Pulmonary embolism	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Pulmonary hypertension	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Pulmonary oedema	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Respiratory distress	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Blood and lymphatic system disorders	8 (23.5)	11 (16.4)	4 (10.8)	7 (9.6)	12 (16.9)	18 (12.9)
Lymphopenia	4 (11.8)	6 (9.0)	3 (8.1)	3 (4.1)	7 (9.9)	9 (6.4)
Neutropenia	2 (5.9)	2 (3.0)	2 (5.4)	2 (2.7)	4 (5.6)	4 (2.9)
Febrile neutropenia	2 (5.9)	2 (3.0)	1 (2.7)	1 (1.4)	3 (4.2)	3 (2.1)
Anaemia	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)

System Organ Class Preferred Term	Transplant Subject (%) (N=34)	 SAEs (%)	Cyclophosphamide Subject (%) (N=37)	 SAEs (%)	Total Subject (%) (N=71)	 SAEs (%)
Leukopenia	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Gastrointestinal disorders	4 (11.8)	8 (11.9)	7 (18.9)	13 (17.8)	11 (15.5)	21 (15.0)
Intestinal hypomotility	1 (2.9)	1 (1.5)	2 (5.4)	2 (2.7)	3 (4.2)	3 (2.1)
Small intestinal obstruction	1 (2.9)	4 (6.0)	1 (2.7)	1 (1.4)	2 (2.8)	5 (3.6)
Abdominal pain	1 (2.9)	1 (1.5)	1 (2.7)	1 (1.4)	2 (2.8)	2 (1.4)
Nausea	1 (2.9)	1 (1.5)	1 (2.7)	1 (1.4)	2 (2.8)	2 (1.4)
Colonic obstruction	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Diarrhoea	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Faecaloma	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Gastric antral vascular ectasia	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Gastrointestinal haemorrhage	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Ileus	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Pancreatitis	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Pneumatosis cystoides intestinalis	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Pneumoperitoneum	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Cardiac disorders	3 (8.8)	4 (6.0)	5 (13.5)	8 (11.0)	8 (11.3)	12 (8.6)
Cardiac failure congestive	0	0	3 (8.1)	4 (5.5)	3 (4.2)	4 (2.9)
Atrial fibrillation	0	0	2 (5.4)	2 (2.7)	2 (2.8)	2 (1.4)
Atrial flutter	1 (2.9)	2 (3.0)	0	0	1 (1.4)	2 (1.4)
Arrhythmia	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Left ventricular failure	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Myocardial infarction	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Pericardial effusion	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Renal and urinary disorders	2 (5.9)	2 (3.0)	3 (8.1)	5 (6.8)	5 (7.0)	7 (5.0)
Scleroderma renal crisis	1 (2.9)	1 (1.5)	3 (8.1)	5 (6.8)	4 (5.6)	6 (4.3)
Renal failure	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Investigations	1 (2.9)	1 (1.5)	4 (10.8)	5 (6.8)	5 (7.0)	6 (4.3)
Pulmonary function test decreased	1 (2.9)	1 (1.5)	4 (10.8)	5 (6.8)	5 (7.0)	6 (4.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (8.8)	4 (6.0)	1 (2.7)	1 (1.4)	4 (5.6)	5 (3.6)
Myelodysplastic syndrome	2 (5.9)	2 (3.0)	0	0	2 (2.8)	2 (1.4)
Acute myeloid leukaemia	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Breast cancer recurrent	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Papillary thyroid cancer	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
General disorders and administration site conditions	3 (8.8)	3 (4.5)	1 (2.7)	1 (1.4)	4 (5.6)	4 (2.9)

System Organ Class Preferred Term	Transplant Subject (%) (N=34)	 SAEs (%)	Cyclophosphamide Subject (%) (N=37)	 SAEs (%)	Total Subject (%) (N=71)	 SAEs (%)
Pyrexia	2 (5.9)	2 (3.0)	0	0	2 (2.8)	2 (1.4)
Chest pain	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Heparin-induced thrombocytopenia	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Musculoskeletal and connective tissue disorders	2 (5.9)	2 (3.0)	2 (5.4)	2 (2.7)	4 (5.6)	4 (2.9)
Scleroderma	0	0	2 (5.4)	2 (2.7)	2 (2.8)	2 (1.4)
Bone pain	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Myositis	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Metabolism and nutrition disorders	2 (5.9)	2 (3.0)	1 (2.7)	2 (2.7)	3 (4.2)	4 (2.9)
Hypokalaemia	0	0	1 (2.7)	2 (2.7)	1 (1.4)	2 (1.4)
Failure to thrive	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Fluid retention	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Nervous system disorders	2 (5.9)	2 (3.0)	1 (2.7)	1 (1.4)	3 (4.2)	3 (2.1)
Carotid artery stenosis	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Dizziness	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Dystonia	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Psychiatric disorders	1 (2.9)	1 (1.5)	2 (5.4)	2 (2.7)	3 (4.2)	3 (2.1)
Depression	1 (2.9)	1 (1.5)	1 (2.7)	1 (1.4)	2 (2.8)	2 (1.4)
Major depression	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Immune system disorders	2 (5.9)	2 (3.0)	0	0	2 (2.8)	2 (1.4)
Graft versus host disease	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Hypersensitivity	1 (2.9)	1 (1.5)	0	0	1 (1.4)	1 (0.7)
Vascular disorders	2 (5.9)	2 (3.0)	0	0	2 (2.8)	2 (1.4)
Hypotension	2 (5.9)	2 (3.0)	0	0	2 (2.8)	2 (1.4)
Hepatobiliary disorders	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Cholelithiasis	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Injury, poisoning and procedural complications	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)
Femoral neck fracture	0	0	1 (2.7)	1 (1.4)	1 (1.4)	1 (0.7)

Subject=Number of subjects reporting at least one adverse event with System Organ Class/Preferred Term; (%) =Percentage of subjects among Total (N); AEs=Count of individual adverse events occurring among the n subjects.

Note: If a subject experienced more than one episode of an adverse event, the subject is counted once for that Preferred Term. If a subject had more than one adverse event in a System Organ Class, the subject is counted only once in that System Organ Class.

Note: Incidences are displayed in descending order of frequency of the System Organ Class and by preferred term within System Organ Class, based on the overall frequency of subjects experiencing the event.

Note: Adverse events are coded according to MedDRA 8.1 by system organ class and preferred term.

Table S10. Events and Subjects with Adverse Events by System Organ Class and Preferred Term, Occurring in >10% of Subjects Either Treatment Arm (Safety Population)

System Organ Class Preferred Term	Transplant Subject (%) (N=34)	 AEs (%)	Cyclophosphamide Subject (%) (N=37)	 AEs (%)	Total Subject (%) (N=71)	 AEs (%)
Blood and lymphatic system disorders	32 (94.1)	246 (30.3)	31 (83.8)	105 (15.9)	63 (88.7)	351 (23.8)
Lymphopenia	31 (91.2)	79 (9.7)	25 (67.6)	56 (8.5)	56 (78.9)	135 (9.2)
Anaemia	19 (55.9)	41 (5.0)	16 (43.2)	24 (3.6)	35 (49.3)	65 (4.4)
Leukopenia	26 (76.5)	43 (5.3)	6 (16.2)	15 (2.3)	32 (45.1)	58 (3.9)
Neutropenia	27 (79.4)	36 (4.4)	5 (13.5)	8 (1.2)	32 (45.1)	44 (3.0)
Thrombocytopenia	29 (85.3)	39 (4.8)	0	0	29 (40.8)	39 (2.6)
Febrile neutropenia	4 (11.8)	4 (0.5)	1 (2.7)	1 (0.2)	5 (7.0)	5 (0.3)
Infections and infestations	32 (94.1)	118 (14.5)	29 (78.4)	100 (15.2)	61 (85.9)	218 (14.8)
Upper respiratory tract infection	9 (26.5)	14 (1.7)	8 (21.6)	19 (2.9)	17 (23.9)	33 (2.2)
Urinary tract infection	1 (2.9)	2 (0.2)	12 (32.4)	24 (3.6)	13 (18.3)	26 (1.8)
Herpes zoster	12 (35.3)	13 (1.6)	1 (2.7)	1 (0.2)	13 (18.3)	14 (1.0)
Pneumonia	9 (26.5)	10 (1.2)	2 (5.4)	2 (0.3)	11 (15.5)	12 (0.8)
Cellulitis	5 (14.7)	5 (0.6)	3 (8.1)	4 (0.6)	8 (11.3)	9 (0.6)
Nasopharyngitis	5 (14.7)	12 (1.5)	2 (5.4)	5 (0.8)	7 (9.9)	17 (1.2)
Infected skin ulcer	2 (5.9)	4 (0.5)	4 (10.8)	10 (1.5)	6 (8.5)	14 (1.0)
Bacteraemia	4 (11.8)	4 (0.5)	0	0	4 (5.6)	4 (0.3)
Cytomegalovirus infection	4 (11.8)	4 (0.5)	0	0	4 (5.6)	4 (0.3)
Investigations	33 (97.1)	81 (10.0)	25 (67.6)	51 (7.7)	58 (81.7)	132 (9.0)
Pulmonary function test decreased	23 (67.6)	31 (3.8)	16 (43.2)	21 (3.2)	39 (54.9)	52 (3.5)
Forced expiratory volume decreased	11 (32.4)	13 (1.6)	5 (13.5)	5 (0.8)	16 (22.5)	18 (1.2)
Vital capacity decreased	6 (17.6)	6 (0.7)	6 (16.2)	6 (0.9)	12 (16.9)	12 (0.8)
Alanine aminotransferase increased	9 (26.5)	10 (1.2)	1 (2.7)	1 (0.2)	10 (14.1)	11 (0.7)
Weight decreased	2 (5.9)	2 (0.2)	6 (16.2)	6 (0.9)	8 (11.3)	8 (0.5)
Weight increased	6 (17.6)	6 (0.7)	1 (2.7)	1 (0.2)	7 (9.9)	7 (0.5)
Gastrointestinal disorders	20 (58.8)	55 (6.8)	25 (67.6)	102 (15.5)	45 (63.4)	157 (10.7)
Nausea	4 (11.8)	5 (0.6)	7 (18.9)	24 (3.6)	11 (15.5)	29 (2.0)
Dysphagia	6 (17.6)	6 (0.7)	5 (13.5)	5 (0.8)	11 (15.5)	11 (0.7)
Gastrooesophageal reflux disease	5 (14.7)	6 (0.7)	5 (13.5)	5 (0.8)	10 (14.1)	11 (0.7)
Constipation	1 (2.9)	1 (0.1)	8 (21.6)	16 (2.4)	9 (12.7)	17 (1.2)
Diarrhoea	4 (11.8)	8 (1.0)	5 (13.5)	6 (0.9)	9 (12.7)	14 (1.0)
Musculoskeletal and connective tissue disorders	20 (58.8)	40 (4.9)	21 (56.8)	45 (6.8)	41 (57.7)	85 (5.8)
Arthralgia	9 (26.5)	9 (1.1)	4 (10.8)	5 (0.8)	13 (18.3)	14 (1.0)
Shoulder pain	4 (11.8)	5 (0.6)	0	0	4 (5.6)	5 (0.3)
Arthritis	0	0	4 (10.8)	4 (0.6)	4 (5.6)	4 (0.3)

System Organ Class Preferred Term	Transplant Subject (%) (N=34)	 AEs (%)	Cyclophosphamide Subject (%) (N=37)	 AEs (%)	Total Subject (%) (N=71)	 AEs (%)
Joint stiffness	0	0	4 (10.8)	4 (0.6)	4 (5.6)	4 (0.3)
Osteoporosis	4 (11.8)	4 (0.5)	0	0	4 (5.6)	4 (0.3)
Skin and subcutaneous tissue disorders	24 (70.6)	54 (6.6)	15 (40.5)	40 (6.1)	39 (54.9)	94 (6.4)
Skin ulcer	7 (20.6)	14 (1.7)	10 (27.0)	24 (3.6)	17 (23.9)	38 (2.6)
Rash	9 (26.5)	9 (1.1)	2 (5.4)	4 (0.6)	11 (15.5)	13 (0.9)
Pruritus	6 (17.6)	6 (0.7)	3 (8.1)	3 (0.5)	9 (12.7)	9 (0.6)
Respiratory, thoracic and mediastinal disorders	17 (50.0)	45 (5.5)	22 (59.5)	46 (7.0)	39 (54.9)	91 (6.2)
Cough	8 (23.5)	13 (1.6)	4 (10.8)	6 (0.9)	12 (16.9)	19 (1.3)
Dyspnoea	4 (11.8)	4 (0.5)	3 (8.1)	3 (0.5)	7 (9.9)	7 (0.5)
Pharyngolaryngeal pain	1 (2.9)	1 (0.1)	4 (10.8)	4 (0.6)	5 (7.0)	5 (0.3)
Pneumonitis	4 (11.8)	5 (0.6)	0	0	4 (5.6)	5 (0.3)
Respiratory failure	0	0	4 (10.8)	4 (0.6)	4 (5.6)	4 (0.3)
Metabolism and nutrition disorders	21 (61.8)	31 (3.8)	18 (48.6)	41 (6.2)	39 (54.9)	72 (4.9)
Hypoalbuminaemia	3 (8.8)	3 (0.4)	5 (13.5)	9 (1.4)	8 (11.3)	12 (0.8)
Hyponatraemia	4 (11.8)	4 (0.5)	0	0	4 (5.6)	4 (0.3)
Hypophosphataemia	4 (11.8)	4 (0.5)	0	0	4 (5.6)	4 (0.3)
General disorders and administration site conditions	18 (52.9)	27 (3.3)	11 (29.7)	19 (2.9)	29 (40.8)	46 (3.1)
Fatigue	6 (17.6)	8 (1.0)	5 (13.5)	8 (1.2)	11 (15.5)	16 (1.1)
Pyrexia	7 (20.6)	7 (0.9)	1 (2.7)	1 (0.2)	8 (11.3)	8 (0.5)
Psychiatric disorders	13 (38.2)	23 (2.8)	13 (35.1)	24 (3.6)	26 (36.6)	47 (3.2)
Depression	10 (29.4)	12 (1.5)	8 (21.6)	12 (1.8)	18 (25.4)	24 (1.6)
Insomnia	5 (14.7)	6 (0.7)	5 (13.5)	6 (0.9)	10 (14.1)	12 (0.8)
Nervous system disorders	12 (35.3)	23 (2.8)	10 (27.0)	23 (3.5)	22 (31.0)	46 (3.1)
Headache	4 (11.8)	6 (0.7)	5 (13.5)	7 (1.1)	9 (12.7)	13 (0.9)
Cardiac disorders	8 (23.5)	12 (1.5)	8 (21.6)	13 (2.0)	16 (22.5)	25 (1.7)
Vascular disorders	9 (26.5)	17 (2.1)	7 (18.9)	7 (1.1)	16 (22.5)	24 (1.6)
Hypotension	4 (11.8)	8 (1.0)	2 (5.4)	2 (0.3)	6 (8.5)	10 (0.7)
Raynaud's phenomenon	4 (11.8)	4 (0.5)	0	0	4 (5.6)	4 (0.3)
Injury, poisoning and procedural complications	7 (20.6)	7 (0.9)	9 (24.3)	9 (1.4)	16 (22.5)	16 (1.1)
Renal and urinary disorders	4 (11.8)	5 (0.6)	10 (27.0)	17 (2.6)	14 (19.7)	22 (1.5)

System Organ Class Preferred Term	Transplant Subject (%) (N=34)	 AEs (%)	Cyclophosphamide Subject (%) (N=37)	 AEs (%)	Total Subject (%) (N=71)	 AEs (%)
Eye disorders	5 (14.7)	6 (0.7)	4 (10.8)	4 (0.6)	9 (12.7)	10 (0.7)
Endocrine disorders	6 (17.6)	7 (0.9)	2 (5.4)	2 (0.3)	8 (11.3)	9 (0.6)
Hypothyroidism	5 (14.7)	6 (0.7)	2 (5.4)	2 (0.3)	7 (9.9)	8 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (11.8)	5 (0.6)	3 (8.1)	3 (0.5)	7 (9.9)	8 (0.5)
Immune system disorders	5 (14.7)	5 (0.6)	2 (5.4)	2 (0.3)	7 (9.9)	7 (0.5)
Reproductive system and breast disorders	4 (11.8)	4 (0.5)	1 (2.7)	1 (0.2)	5 (7.0)	5 (0.3)

Subject=Number of subjects reporting at least one adverse event with System Organ Class/Preferred Term; (%) =Percentage of subjects among Total (N); AEs=Count of individual adverse events occurring among the n subjects.

Note: If a subject experienced more than one episode of an adverse event, the subject is counted once for that Preferred Term. If a subject had more than one adverse event in a System Organ Class, the subject is counted only once in that System Organ Class.

Note: Incidences are displayed in descending order of frequency of the System Organ Class and by preferred term within System Organ Class, based on the overall frequency of subjects experiencing the event.

Note: Adverse events are coded according to MedDRA 8.1 by system organ class and preferred term.

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