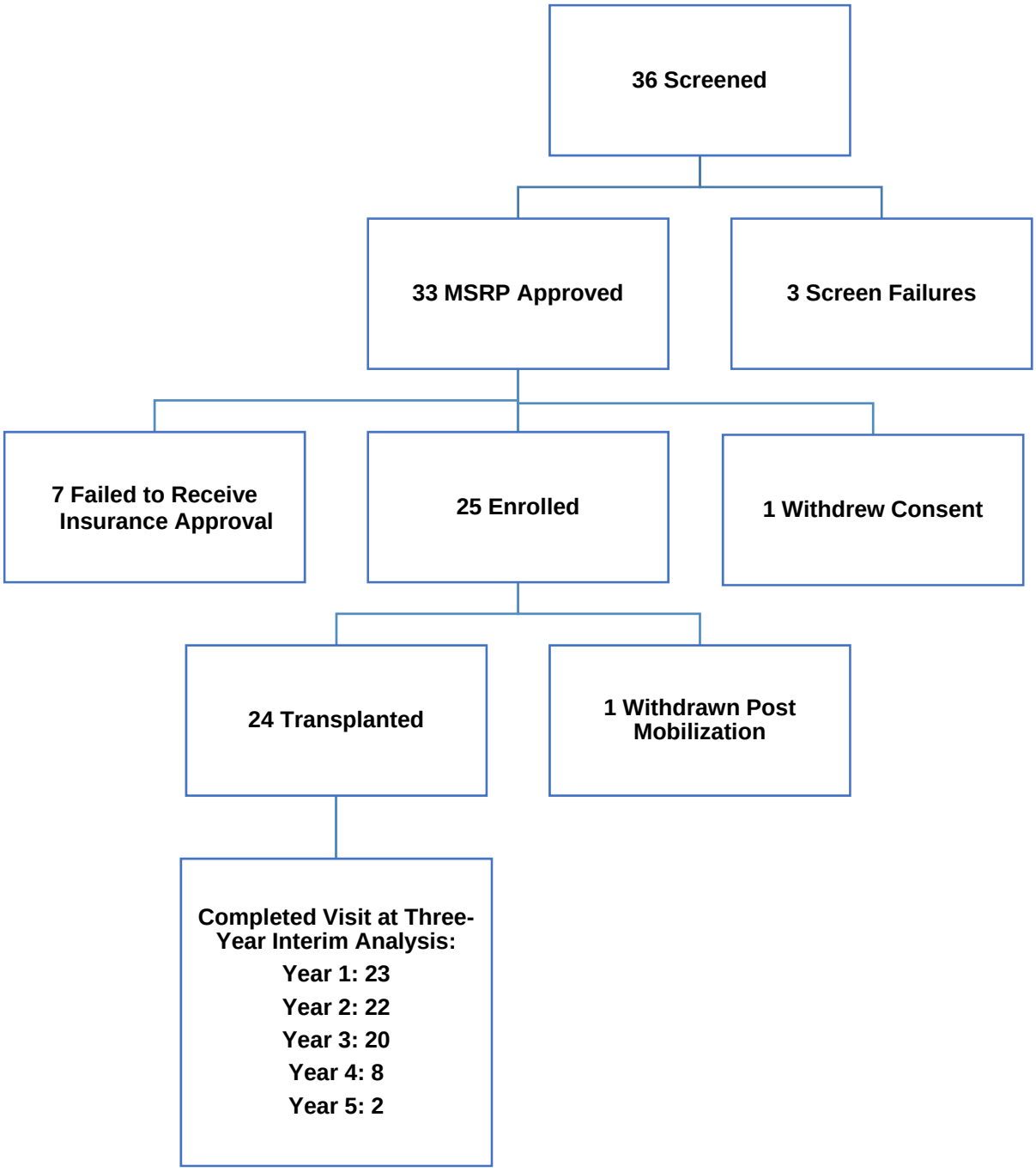
Supplementary Online Content

Nash RA, Hutton GJ, Racke MK, et al. High-Dose Immunosuppressive Therapy and Autologous Hematopoietic Cell Transplantation for Relapsing-Remitting Multiple Sclerosis (HALT-MS): a 3-year interim report. *JAMA Neurol*. Published online December 29, 2015. doi:10.1001/jamaneurol.2014.3780.

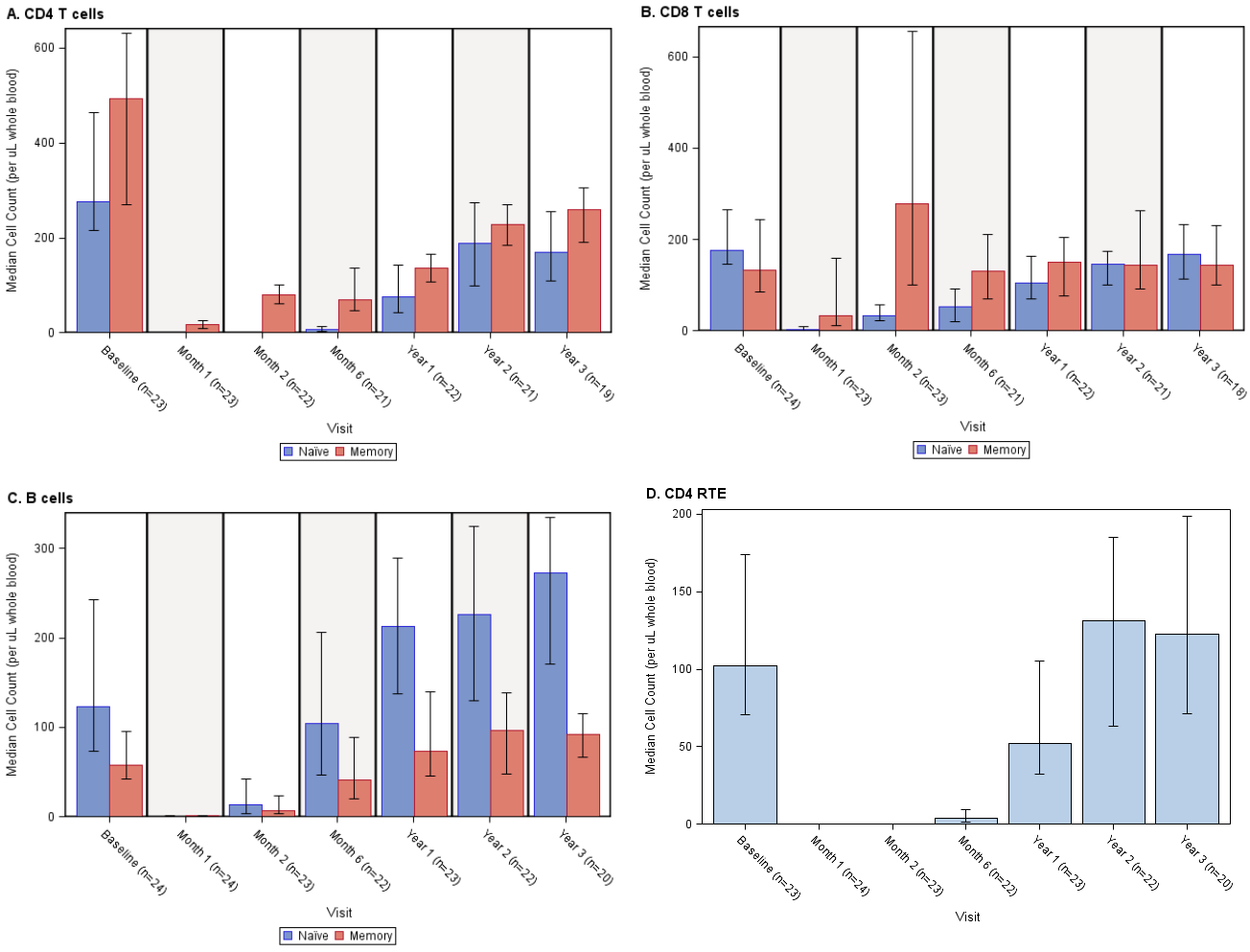
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Screening, Enrollment and Follow-up



Following enrollment, one subject with known stable arteriovenous malformation developed heparin induced thrombocytopenia following mobilization, and did not subsequently receive transplant on this study. At the date of data lock for the 3-year interim analysis, 23 subjects had completed the Year 1 visit and 1 missed the visit. For Year 2, 22 subjects had completed the visit, 1 terminated the trial early, and 1 missed the visit. For Year 3, 20 subjects had completed the visit, 1 subject died, 1 subject terminated the trial early, and 2 subjects missed the visit. For Year 4, 8 subjects had completed the visit, 1 subject died, 1 subject terminated the trial early, 1 subject missed the visit, and 13 are expected to return in the future for the visit. For Year 5, 2 subjects had completed the visit, 2 subjects died, 1 terminated the study early, and 19 are expected to return in the future for the visit. Last subject last visit is expected in May 2015.

eFigure 2. Analysis of Lymphocytes and Subsets by Flow Cytometry



Depletion and reconstitution of immune cell populations were analyzed using real-time flow cytometry. Absolute cell numbers per uL of whole blood were calculated for **A)** $CD45RO^{+}CD45RA^{-}$ memory and $CD45RO^{-}CD45RA^{+}$ naïve CD4 T cells, **B)** $CD45RO^{+}CD45RA^{-}$ memory and $CD45RO^{-}CD45RA^{+}$ naïve CD8 T cells, **C)** $CD27^{+}CD19^{+}$ memory and $CD27^{-}CD19^{+}$ naïve B cells, and **D)** $CD31^{+}CD45RO^{-}CD45RA^{+}$ CD4 RTE (recent thymic emigrants). Data are plotted as median counts of memory (red) and naïve (blue) cells in panels A-C, and single columns in panel D. Error bars represent the 1^{st} and 3^{rd} quartiles. A Wilcoxon Signed-Rank test was used to compare the change from baseline in cell counts at each visit; $p > 0.05$ for CD8 memory T Cells at 6 months; for CD8 naive T cells at 3 years; for CD4 T cells either memory or naive at greater than 3 years; for B cells either memory or naive at 6 months; and for CD4 RTE at 2 years. In addition, at 3 years, naïve B cells are significantly different as compared to baseline ($p < 0.05$).

eTable 1. Multiple Sclerosis Functional Composite (MSFC): Summary of Component Raw Scores at Baseline

	Total(N=24)
Percent of PASAT-3 Correct	
n	24
Mean (SD)	69.24 (26.357)
Median	72.5
Min, Max	23.3, 100.0
Nine-hole Peg Test Time, Dominant Arm (s)	
n	24
Mean (SD)	27.42 (13.071)
Median	22.5
Min, Max	16.6, 73.5
25-Foot Walk Time (s)	
n	24
Mean (SD)	6.73 (3.052)
Median	6.1
Min, Max	3.2, 18.5

eTable1 Footnotes:

Note: The Multiple Sclerosis Functional Composite (MSFC) consists of results from the following tests: 1) paced auditory serial addition test; 2) nine-hole peg test; and 3) timed 25-foot walk. The summary statistics presented for the timed 25-foot walk and nine-hole peg tests are from an average of 3 trials for each individual.

eTable 2. Efficacy Analysis: Event-Free Survival[a]

	Primary Analysis [b]	Component Analysis [c]	Total Events [d]
Year 1			
Number (%) at Risk	23 (95.8%)		
Post-transplant event-free survival probability	95.8%		
90% Confidence Intervals [e]	(80.2%, 99.2%)		
Number of Treatment Failure Events:	1		2
EDSS increase > 0.5	0	100.0% (100.0%, 100.0%)	0
Clinical Relapse	1	95.8% (80.2%, 99.2%)	1
Two or more MS lesions on MRI	0	100.0% (100.0%, 100.0%)	1
Death	0		0
Year 2			
Number (%) at Risk	19 (79.2%)		
Post-transplant event-free survival probability	82.8%		
90% Confidence Intervals [e]	(65.0%, 92.0%)		
Number of Treatment Failure Events:	4		5
EDSS increase > 0.5	2	90.9% (73.7%, 97.1%)	2
Clinical Relapse	2	91.0% (73.9%, 97.1%)	2
Two or more MS lesions on MRI	0	100.0% (100.0%, 100.0%)	1
Death	0		0
Year 3			
Number (%) at Risk	18 (75.0%)		
Post-transplant event-free survival probability	78.4%		
90% Confidence Intervals [e]	(60.1%, 89.0%)		
Number of Treatment Failure Events:	5		7
EDSS increase > 0.5	2	90.9% (73.7%, 97.1%)	2
Clinical Relapse	3	86.3% (68.1%, 94.5%)	3
Two or more MS lesions on MRI	0	100.0% (100.0%, 100.0%)	1
Death	0		1
Year 4			
Number (%) at Risk	7 (29.2%)		
Post-transplant event-free survival probability	68.6%		
90% Confidence Intervals [e]	(44.9%, 83.7%)		
Number of Treatment Failure Events:	6		9
EDSS increase > 0.5	2	90.9% (73.7%, 97.1%)	2
Clinical Relapse	3	86.3% (68.1%, 94.5%)	3
Two or more MS lesions on MRI	1	87.5% (50.0%, 97.5%)	2
Death	0		2
Year 5			
Number (%) at Risk	3 (12.5%)		
Post-transplant event-free survival probability	58.8%		
90% Confidence Intervals [e]	(33.7%, 77.2%)		
Number of Treatment Failure Events:	7		10
EDSS increase > 0.5	2	90.9% (73.7%, 97.1%)	2
Clinical Relapse	3	86.3% (68.1%, 94.5%)	3
Two or more MS lesions on MRI	2	75.0% (39.7%, 91.4%)	3
Death	0		2

eTable 2 Footnotes:

[a] Events are defined as disease progression (defined as increase in EDSS > 0.5 from baseline), clinical relapse, presence of two or more independent lesions on MRI indicative of MS disease activity, or death.

[b] Subjects who withdraw early are censored at the date of last follow-up.

[c] Survival probabilities and 90% confidence intervals are estimated for primary endpoint events by component. Estimates are not provided for death as no subjects met primary endpoint with a death event.
[d] Includes events that occurred after a subject has met primary endpoint.
[e] Kaplan-Meier estimates of survival probability, with Wald-type CI based on Greenwood's formula for standard error.

eTable 3. Serious Adverse Events (SAEs): All SAEs and Subjects With SAEs by Organ Class and AE Term

Organ Class AE Term	All Enrolled Subjects (N=25)	
	Subjects (%)	SAEs
Any Adverse Events	16 (64.00)	63
Infections	6 (24.00)	10
Bacterial	5 (20.00)	7
Pneumonia	1 (4.00)	2
Viral reactivation (including CMV and EBV)	1 (4.00)	1
Cytopenias	5 (20.00)	6
Leukopenia	3 (12.00)	4
Lymphopenia	2 (8.00)	2
Respiratory, thoracic and mediastinal disorders	5 (20.00)	12
Respiratory arrest/failure	2 (8.00)	3
Pulmonary embolism	2 (8.00)	2
Asthma	1 (4.00)	3
Pneumonitis	1 (4.00)	2
Chest pain	1 (4.00)	1
Dyspnoea	1 (4.00)	1
Nervous system including visual disorders	4 (16.00)	7
Hemiparesis	2 (8.00)	2
Headache	1 (4.00)	1
Motor dysfunction	1 (4.00)	1
Multiple sclerosis exacerbation	1 (4.00)	1
Neurological symptom	1 (4.00)	1
Vision blurred	1 (4.00)	1
Cardiovascular disorders	3 (12.00)	3
Deep vein thrombosis	2 (8.00)	2
Atrioventricular block	1 (4.00)	1
General disorders	3 (12.00)	5
Pyrexia	2 (8.00)	4
Fatigue	1 (4.00)	1
Metabolism	3 (12.00)	4
Hypokalaemia	2 (8.00)	2
Alanine aminotransferase increased	1 (4.00)	1
Hyperuricaemia	1 (4.00)	1
Musculoskeletal disorders	3 (12.00)	3
Pain in extremity	2 (8.00)	2
Back pain	1 (4.00)	1
Immune system disorders	2 (8.00)	2
Engraftment syndrome, autologous	1 (4.00)	1
Meningitis aseptic	1 (4.00)	1
Psychiatric disorders	2 (8.00)	5
Suicide attempt	2 (8.00)	2
Depression	1 (4.00)	2
Mania	1 (4.00)	1

Organ Class AE Term	All Enrolled Subjects (N=25)	
	Subjects (%)	SAEs
Congenital, familial and genetic disorders	1 (4.00)	1
Arteriovenous malformation	1 (4.00)	1
Gastrointestinal disorders	1 (4.00)	2
Constipation	1 (4.00)	1
Dehydration	1 (4.00)	1
Hepatobiliary disorders	1 (4.00)	1
Gallbladder obstruction	1 (4.00)	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (4.00)	1
Breast cancer in situ	1 (4.00)	1
Pregnancy, puerperium and perinatal conditions	1 (4.00)	1
Pregnancy	1 (4.00)	1

eTable 3 Footnotes:

Note: Adverse events were grouped into AE Term and Organ Class based on judgment from the clinical study team.

Note: Subjects=Number of subjects reporting at least one serious adverse event with Organ Class/AE Term; (%)=Percentage of subjects among Safety Population (N); SAEs=Count of individual serious adverse events occurring among the N enrolled subjects.

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

Note: Subjects who experienced one or more adverse event are counted only once for that AE Term and Organ Class.

