Online Supplement 2

Hawkey CJ, Allez M, Clark M, et al. Autologous hematopoietic stem cell transplantation for refractory Crohn disease. *JAMA*. doi:10.1001/jama.2015.9162.

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

eAppendix 1. Inclusion/Exclusion Criteria

Inclusion criteria: mandatory

1) Age between 18 and 50 years
   a) Patients aged 50-65 can participate if specially approved by the Trial Steering Committee
2) Confirmed diagnosis of active Crohn's Disease:
   a) Diagnosis of Crohn's disease based on typical radiological appearances and / or typical histology
   b) Active disease at the time of registration to the trial, defined as
      i) Crohn's disease activity index (CDAI) ≥ 250 at any time within 3 months prior to trial entry **and** ≥ 2 of the following:
      ii) raised CRP,
      iii) endoscopic evidence of active disease confirmed on histology
      iv) clear evidence of active small bowel Crohn's disease on small bowel barium study.
3) Unsatisfactory course despite 3 immunosuppressive agents (usually azathioprine, methotrexate and infliximab) in addition to corticosteroids. Patients should have relapsing disease (i.e. ≥ 1 exacerbation/year) despite thiopurines, methotrexate and/or infliximab maintenance therapy or clear demonstration of intolerance / toxicity to these drugs.
4) Impaired function and quality of life, compared to population means, on at least one of the following:
   a) IBDQ (Appendix 5)
   b) European Questionnaire of Lifequality (EuroQol–5D, Appendix 4)
   c) Impaired function on Karnofsky index (Appendix 6)
5) Current problems unsuitable for surgery and patient at risk for developing short bowel syndrome.
6) Informed consent
   (Sample Information Sheet and Consent Form given in Appendices 1 and 2 respectively)
   a) Prepared to enter controlled study.
   b) Prepared to undergo additional study procedures as per trial schedule
   c) Patient has undergone intensive counselling about risks
   d) Consent to future genotyping assessments is optional, but is not required for the patient to enter the trial

Inclusion criteria: discretionary

1. Wherever possible, diseased tissue should be accessible endoscopically for objective histological study
   a. Small bowel disease that is extensive but does not extend to duodenum or terminal ileum

is an exception, which will allow participation without endoscopy of diseased areas. All patients will however undergo flexible sigmoidoscopy

2. Smokers may enter the study provided they have received intensive counselling about smoking.
3. Patients with an ileostomy or colostomy may enter the study. Clinical activity should be assessed using modified CDAI and Harvey Bradshaw scoring method (See Appendix 3 and 8).

Exclusion criteria

1) Pregnancy or unwillingness to use adequate contraception during the study, if a woman of childbearing age

2) Concomitant severe disease

a) renal: creatinine clearance < 40 ml/min (measured or estimated)

b) cardiac: clinical evidence of refractory congestive heart failure; left ventricular ejection fraction < 45% by multigated radionuclide angiography (MUGA) or cardiac echo; chronic atrial fibrillation necessitating oral anticoagulation; uncontrolled ventricular arrhythmia; pericardial effusion with hemodynamic consequences as evaluated by an experienced echo cardiographer

c) psychiatric disorders including active drug or alcohol abuse

d) concurrent neoplasms or myelodysplasia

e) bone marrow insufficiency defined as leucocytopenia <3.0 x 10^9/l, thrombocytopenia <50 x 10^9/l, anaemia < 8 g/dl, $CD4^+$ T lymphopenia < 200 x 10^6/l

f) uncontrolled hypertension, defined as resting systolic blood pressure ≥ 140ml and/or resting diastolic pressure ≥ 90ml mercury despite at least 2 anti-hypertensive agents.

g) Uncontrolled acute or chronic infection with HIV, HTLV – 1 or 2, hepatitis viruses or any other infection the investigator or Steering Committee consider a contraindication to participation.

h) Other chronic disease causing significant organ failure, including established cirrhosis with evidence of impaired synthetic function on biochemical testing and known respiratory disease causing resting arterial oxygen tension <8 kpa or carbon dioxide tension >6.7 kpa. Patients not known to have respiratory disease need not have blood gas measurements.

i) Crohn's Disease symptoms predominantly due to fibrotic stricturing and unlikely to respond to immune manipulation, in the opinion of any of the investigators or the steering committee

3) Infection or risk thereof

a) Current abscess or significant active infection.

b) Perianal sepsis is not an exclusion provided there is natural free drainage or a Seton suture(s) have been placed.

c) History of tuberculosis or at current increased risk of tuberculosis

d) Mantoux test result or other investigations that the investigator or Steering Committee regard as evidence of active tuberculosis.

e) Abnormal chest x ray (CXR) consistent with active infection or neoplasm.

4) Significant malnutrition: Body Mass Index (BMI) ≤ 18, serum albumin $\underline{<}$ 20 g/l

5) Previous poor compliance

6) Concurrent enrolment in any other protocol using an investigational drug or hematopoietic growth factor up to four weeks before study entry.

7) Lack of funding

eAppendix 2. Criteria for Requests for Earlier Transplantation

PRINCIPLES TO BE APPLIED TO PATIENTS RANDOMISED TO LATE TRANSPLANTATION IN ASTIC TO ESTABLISH WHETHER THERE IS A VALID CASE FOR EARLY TRANSPLANTATION

Members of the Steering Committee have considered the development of objective transparent criteria against which any requests for early transplantation are judged. These are as follows –

1. The patient has a CDAI of 350 or more despite being on corticosteroids (prednisolone equivalent ≥30mg/day) and at least one or preferably two immunosuppressive agents (such as adalimumab and azathioprine), and there is objective evidence of greater disease activity (either endoscopic, radiological or exceptionally by CRP blood result) than at the time of trial entry (when the Investigator and patient were aware that a wait of one year was a possibility).

2. If the worsening of Crohn's disease is amenable to surgery, this approach should be employed, because in a situation more urgent than at trial entry it is important to use a relatively safe proven treatment rather than a risky unproven treatment. Patients who undergo surgery during the year before transplantation remain eligible for transplantation appropriate at or after the due date.

3. There may be cases where the indication for early stem cell transplantation is to avoid a threat to the patient's life, although the risks associated with the procedure make it difficult to envisage such a situation. The criteria, therefore, will be considered by the Steering Committee on a case by case basis.

Patients in whom an early transplant is considered should undergo a further period of counselling given by a third party, which could be a member of the Steering Committee.

In all patients approved for an earlier transplant, a full baseline evaluation prior to transplant must be carried out by completing the Week 52 Visit at the end of CRF5 including colonoscopy, endoscopy and small bowel imaging.

Requests for early transplantation should be made on the attached form.

FORM: PRINCIPLES TO BE APPLIED TO PATIENTS RANDOMISED TO LATE TRANSPLANTATION IN ASTIC TO ESTABLISH WHETHER THERE IS A VALID CASE FOR EARLY TRANSPLANTATION

Please complete and return to astic@nottingham.ac.uk

CENTRE NUMBER:	TRIAL NUMBER:	INITIALS:

Narrative reason why the patient should undergo early transplantation:

DATE:	BASELINE	CURRENT
CDAI		
CDEIS Colonic		
CDEIS Upper GI		
Small Bowel Radiology		

CRP		
Albumin		
Haemoglobin		
Platelet Count		
Treatment		

eAppendix 3. Adjudication Committee Procedure

GI Tract involvement: Final definitions and operating procedure

In the original protocol, an absence of active disease at ileo-colonoscopy and on barium studies was part of the requirement for sustained disease remission. At the end of the trial and prior to analysis, it was realised that the replacement in many centres of barium studies by MRI enteroclysis and the recruitment into the trial of patients with upper gastrointestinal disease reduced the appropriateness of this requirement. At a meeting of the Writing and Analytical Group on Feb 1st 2013, a more appropriate and stringent criterion was introduced that required patients to be free of active disease throughout the gastrointestinal tract. This was operationalised by establishing a blinded adjudication committee (Allez, Lindsay, Rogler) who reviewed data from all sources (which could be both endoscopic and radiological) to adjudicate whether each of 10 segments (mouth, oesophagus, stomach, duodenum, upper small bowel, terminal ileum, ascending colon, transverse colon, left colon, rectum) showed evidence of active disease (as indicated by mucosal erosion or ulceration).

After an initial meeting to formalise the approach all relevant reports were coded and sent to the three adjudicators who returned scores separately and then discussed by email and teleconference, those where there was initial disagreement. This was followed by a one day meeting at which all the ileo-colonoscopy data were reviewed under still blinded conditions and the SES-CD score confirmed and all data reviewed to achieve final consensus on involvement and activity in the entire GI tract. After this any outstanding disagreements were resolved by email. Once all scores were confirmed the data were unblinded and no further adjustments were made.

eTable 1. Additional Secondary Outcome Measures

	HSCT	Control	Difference Median (95% CI)[a]	p (adjusted for centre)
CDAI variables	**Median (IQR)**	**Median (IQR)**		
CDAI at 1 year	166.7 (77.4 to 291.0), n=21	298.3 (230.5 to 370.0), n=21	-131.6 (-243 to -6)	0.019
Number of weeks CDAI < 150	7 (0 to 34) , n=21	0 (0 to 9), n=19	7 (0 to 33)	0.054
Mean CDAI months 3-12	163.3 (95.4 to 287.5) , n=21	263.0 (224.2 to 287.1) n=19	-99.7 (-153.8 to 15.1)	0.082
Percent weeks CDAI ≤ 150 months 3-12	13% (0 to 65.0%), n=21	0% (0 to 18.5%) n=19	13% (0 to +52%)	0.072
	N (%)	**N (%)**		
CDAI decrease ≥100	15/21 (71.4%)	8/21 (38.1%)	33.3% (+2.0 to +66.4%)	0.035

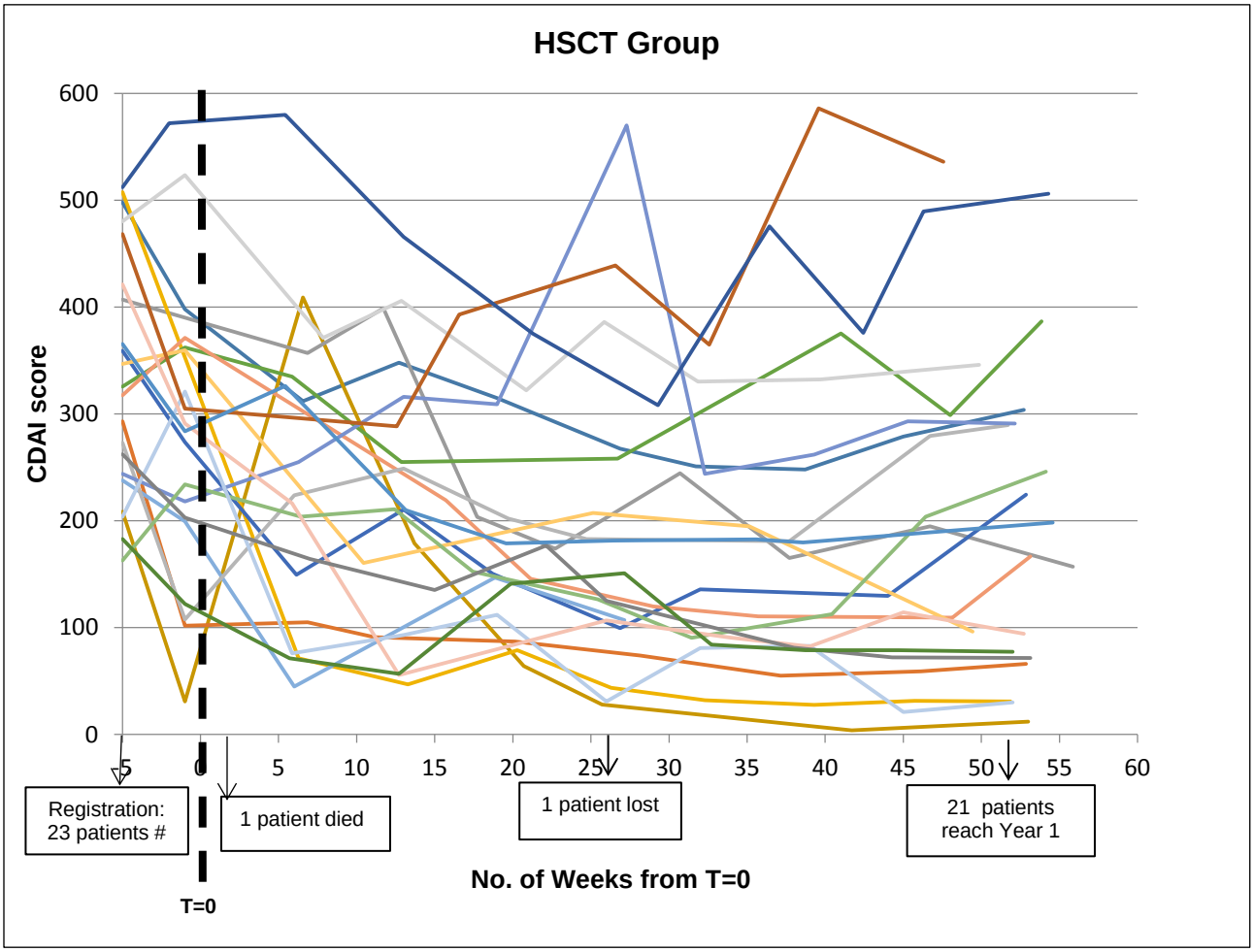
	HSCT	Control	Difference Median (95% CI)[a]	p (adjusted for centre)
Harvey Bradshaw	**Median (IQR)**	**Median (IQR)**	**Difference (95% CI)**	
Harvey Bradshaw score at 1 year	5 (2 to 10) n=21	12 (8 to 14) n=21	-7 (-10 to 1)	0.009
Endoscopic score (SES-CD)				
Number of segments examined	4 (3 to 5), n=21	3 (2 to 5) , n=19	1 (-1 to 3)	0.115
SES-CD at 12 months	3 (1 to 8), n=21	7 (3.5 to 13.5) n=19	-4 (-10 to 1)	0.110
	N (%)	**N (%)**		
Active perianal disease	6 (28.6%), n=21	6 (28.6%) n=21	0% (-26.0 to +26.0%)	0.978
Quality of Life	**Median (IQR)**	**Median (IQR)**		
EQ-VAS at 1 year	61.5 (80.0 to 85.0) n=19	36.3 (55.0 to 70.0) n=14	25.0 (3.0 to 45.0)	0.022
EQ5D at 1 year	0.735 (0.796 to 1.000) n=18	0.728 (0.736 to 0.799) n=13	0.06 (-0.06 to 0.23)	0.727

	HSCT	Control	Difference Median (95% CI)[a]	p (adjusted for centre)
IBDQ at 1 year	138.0 (120.3 to 199.8) n=18	116.0 (89.0 to 137.0) n=16	22.0 (9.0 to 84.0)	0.213
Karnofsky score at 1 year	70 (80 to 90) n=16	70 (70 to 80) n=14	10 (-5 to 20)	1.000
Laboratory variables				
Haemoglobin at 1 year g/dL	12.9 (11.9 to 13.4) n=21	12.7 (12.3 to 13.5) ; n=21	0.2 (-0.6 to 0.7)	0.476
Haemoglobin g/dL change from baseline	0.2 (-1.1 to 1.2) n=21	0.6 (-0.4 to +1.3), n=21	-0.4 (-1.8 to 0.6)	0.127
Platelets $x10^9$ /L at 1 year	219 (174.5 to 285) n=21	280 (222 to 332), n=21	-61 (-125 to 21)	0.034
Platelets $x10^9$ /L change from baseline	-95 (-162 to -27) n=21	-19 (-69 to 43), n=21	-76 (-147 to 5)	0.027
Albumin g / dL at 1 year	41 (34.7 to 43.3) n=20	39 (33 to 41.7), n=19	2 (-2.48 to 8)	0.302

	HSCT	Control	Difference Median (95% CI)[a]	p (adjusted for centre)
Albumin g /dL change from baseline	+5 (0.75 to 7.50) n=20	3 (-3 to +5.9), n=19	2 (-2 to 7)	0.165
CRP mg/L at 1 year	6 (2.5 to 26.9) n=21	9 (2.98 to 24.30) n=20	-3 (-17.9 to 7.5)	0.903
CRP mg/L change from baseline	0 (-10 to +17) n=21	-5.5 (-27.1 to +3.4) n=20	5.5 (-5.1 to 26.5)	0.278

a Asymptotic CI for the difference of proportions or Nonparametric CI for difference of medians (percentile bootstrap, stratified by the grouping variable). Any discrepancies between p value and 95% CI are due to inclusion of a centre effect in calculating p values but not 95% CIs.

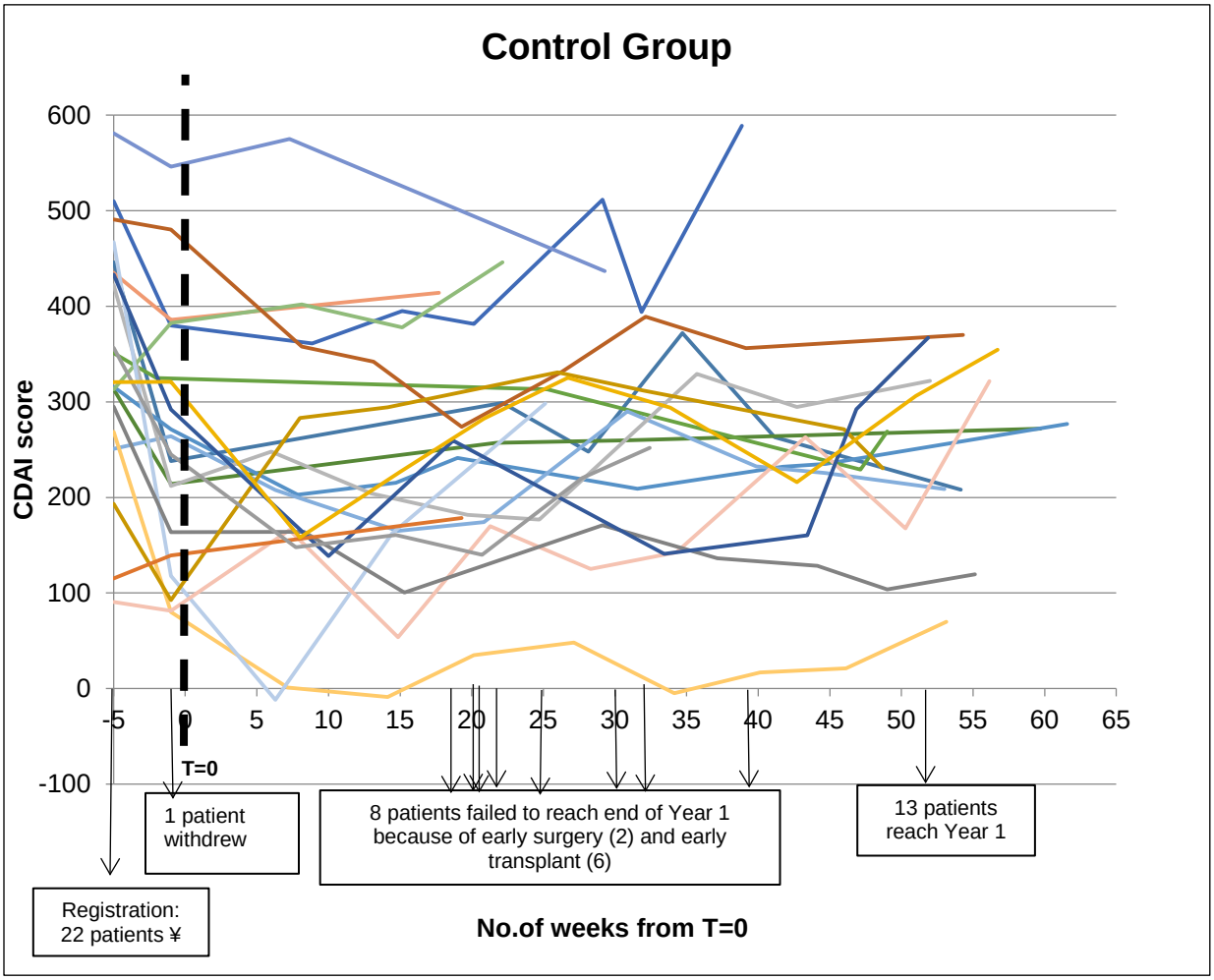
eFigureA. Change in Crohn Disease Activity Index (CDAI) scores for HSCT Patients



T=0 for HSCT patients is the Date of Transplant

#2 patients not shown as insufficient data: 1 patient died 14 days post-transplant (T=0); 1 patient only had data at Registration and Week 52.

eFigure B. Change in Crohn Disease Activity Index (CDAI) scores for Control Patients



T=0 for Control patients is Start date of Mobilisation plus 5 weeks (equivalent time point to Transplant date for HSCT patients)

¥ 2 patients not shown as insufficient data: 1 withdrew at T-1; 1 had accelerated transplant at T+20

Negative CDAI scores are possible, in that there is an adjustment for weight so that an obese patient with CD in remission might get a negative score.

eTable 2. Secondary End Points: Worst Case/Best Case Scenario

	Complete cases		**Best scenario (all missing are best score)** HSCT n=23; Control n=22		**Worse scenario (all missing are worst score)** HSCT n=23; Control n=22	
	Difference Median (95% CI)	**p value**	**Difference Median (95% CI)**	**p value**	**Difference Median (95% CI)**	**p value**
CDAI at 1 year HSCT n=21; Control n=21	-131.6 (-243 to -6)	0.019	-130.6 (-244 to -22.8)	0.018	-111.6 (-227.3 to 15.15)	0.098
CDAI change from baseline HSCT n=21; Control n=21	-87.7 (-13.5 to -155.0)	0.038	-102.7 (-23.2 to -171.5)	0.050	-81.75 (-168.3 to 58.35)	0.218
HB at 1 year HSCT n=21; Control n=21	-7 (-10 to 1)	0.009	-6.5 (-11.0 to -1.5)	0.008	-6 (-10 to 0)	0.091
HB change from baseline HSCT n=21; Control n=21	-4 (-9 to -1)	0.002	-5.5 (-9 to -2)	0.003	-5 (-9.5 to -1)	0.063
SESCD at 1 year HSCT n=21; Control n=19	-4 (-10 to 1)	0.110	-3 (-9 to 1.5)	0.160	-5 (-14 to 1.5)	0.148
SESCD change from baseline HSCT n=21; Control n=19	-7 (-13 to -1)	0.033	-4.5 (-13 to 5)	0.1743	-7.5 (-14 to -2)	0.0350

eTable 3. Sensitivity Analysis for Quality of Life: Imputation Data

QOL	Complete cases analysis		Multiple imputation	
	Difference Median (95% CI)[a]	p value	Difference Median (95% CI)[a]	p value
EQVAS at 1y HSCT n=19; Control n=14	25.0 (3.0 to 45.0)	0.022	37.5 (10 to 45)	0.003
EQVAS change from baseline HSCT n=19; Control n=14	14.5 (-7.5 to 33)	0.503	17.5 (0 to 30)	0.271
EQ5D at 1 year HSCT n=18; Control n=13	0.06 (-0.06 to 0.23)	0.727	0.002 (-0.094 to 0.103)	0.501
EQ5D change from baseline HSCT n=17; Control n=13	0.025 (-0.072 to 0.163)	0.406	0.0075 (-0.105 to-0.133)	0.507
IBDQ at 1 year HSCT n=18; Control n=16	22.0 (-9.0 to 84.0)	0.213	66.5 (5 to 105)	0.023 [a]
IBDQ change from baseline HSCT n=18; Control n=16	34.5 (-8 to 54.5)	0.539	42 (10.5 to 60.5)	0.120
Karnofsky Index at 1 year HSCT n=16; Control n=14	10 (-5 to 20)	1.000	10 (-5 to 20)	0.882
Karnofsky Index change from baseline HSCT n=15; Control n=14	10 (-7.5 to 20)	0.850	10 (-5 to 20)	0.682

a With multiple imputation the change in IBDQ at one year becomes statistically significant. Significance of all other values is not changed by multiple imputation.

eTable 4. Adverse Events[a] (AEs)

		Mobilisation[b]				Conditioning[b]				Follow up[b]				Total			
Treatment group		**HSCT**		**Control**		**HSCT**		**Control**		**HSCT**		**Control**		**HSCT**		**Control**	
Duration (range), days		45 (33 - 78)		41 (39 - 43)		100		100		276 (96 - 298)		256 (17 - 325)		418 (252-455)		397 (158 - 465)	
		AEs	**Patients**	**AEs**	**Patients**	**AEs**	**Patients**	**AEs**	**Patients**	**AEs**	**Patients**	**AEs**	**Patients**	**AEs**	**Patients**	**AEs**	**Patients**
Total AEs		**81**	**15**	**64**	**19**	**117**	**19**	**27**	**11**	**67**	**15**	**43**	**14**	**265**	**22**	**134**	**20**
Median (95%CI) difference between HSCT & controls[c]	*No. AEs*	1 (-2 to 3) p=0.687				3.5 (0.5 to 8) p=0.0004				1 (-1.5 to 2.5) p=0.286				4 (-1 to 10) p=0.039			
	% Patients	-21.1% (-43.33% to 4.21%) p=0.097				36.9% (9.83% to 58.03%) p=0.010				1.58% (-24.68% to 27.7%) p=0.911				0.2% (-16.86% to 17.82%) p=0.975			
Infectious AEs		**7**	**5**	**7**	**6**	**25**	**13**	**3**	**3**	**19**	**9**	**6**	**5**	**51**	**17**	**16**	**9**
Median (95%CI) difference between HSCT & controls[c]	*No. AEs*	0 (0 to 0) p=0.959				1 (0 to 2) p=0.004				0 (0 to 1) p=0.064				2 (0 to 3) p=0.004			
	% Patients	-5.53% (-29.65% to 19.08%) p=0.699				42.8% (15.02% to 62.82%) p=0.005				16.4% (-10.38% to 40.11%) p=0.251				33% (4.2% to 55.25%) p=0.028			
Break down for infectious AEs	*Viral*	*1*	*1*	*0*	*0*	*7*	*6*	*0*	*0*	*2*	*2*	*0*	*0*	*10*	*9*	*0*	*0*
	Sepsis	*1*	*1*	*1*	*1*	*4*	*4*	*1*	*1*	*0*	*0*	*0*	*0*	*5*	*5*	*2*	*2*
	Localised	*5*	*3*	*6*	*5*	*14*	*9*	*2*	*2*	*17*	*9*	*6*	*5*	*36*	*15*	*14*	*7*
GI AEs		**19**	**10**	**13**	**5**	**20**	**10**	**14**	**6**	**20**	**11**	**13**	**7**	**59**	**20**	**40**	**12**
Median (95%CI) difference between HSCT & controls[c]	*No. AEs*	0 (0 to 1) p=0.614				0 (0 to 1) p=0.432				0 (-0.5 to 1) p=0.416				0.5 (-1 to 3) p=0.239			
	% Patients	20.7% (-6.59% to 44.15%) p=0.154				16.2% (-11.26 to 40.45%) p=0.178				16.01% (-11.94% to 40.67%) p=0.257				32.4% (-5.81% to 54.04%) p=0.021			
Break down for GI AEs	*Disease flare*	*1*	*1*	*2*	*2*	*0*	*0*	*2*	*2*	*4*	*3*	*5*	*3*	*5*	*4*	*9*	*6*
	Non-flare Symptoms	*18*	*9*	*11*	*5*	*20*	*10*	*12*	*4*	*16*	*8*	*8*	*6*	*54*	*19*	*31*	*12*
Hematologic AEs		**5**	**3**	**4**	**4**	**1**	**1**	**1**	**1**	**4**	**2**	**5**	**1**	**10**	**5**	**10**	**6**
Median (95%CI)	*No. AEs*	0 (0 to 0) p=0.785				0 (0 to 0) p=0.956				0 (0 to 0) p=0.814				0 (0 to 0) p=0.944			
	%	-5.14% (-27.18% to 16.83%)				-0.2% (-17.82 to 16.86%)				4.15% (-14.1% to 22.63%)				-5.53% (-29.65% to 19.08%)			

		Mobilisation[b]				**Conditioning**[b]				**Follow up**[b]				**Total**			
Treatment group		**HSCT**		**Control**		**HSCT**		**Control**		**HSCT**		**Control**		**HSCT**		**Control**	
difference between HSCT & controls[c]	*Patients*	p=0.672				p=0.957				p=0.597				p=0.680			
Break down for haematologic AEs	*Anaemia*	*2*	*2*	*3*	*3*	*0*	*0*	*1*	*1*	*2*	*1*	*5*	*1*	*4*	*2*	*9*	*5*
	Neutropenia	*2*	*2*	*1*	*1*	*1*	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*3*	*3*	*1*	*1*
	Pancytopenia	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*1*	*0*	*0*	*1*	*1*	*0*	*0*
	Other	*1*	*1*	*0*	*0*	*0*	*0*	*0*	*0*	*1*	*1*	*0*	*0*	*2*	*2*	*0*	*0*
Fever AEs		**4**	**3**	**7**	**6**	**8**	**5**	**0**	**0**	**1**	**1**	**0**	**0**	**13**	**7**	**7**	**6**
Renal AEs		**1**	**1**	**0**	**0**	**3**	**2**	**0**	**0**	**0**	**0**	**1**	**1**	**4**	**3**	**1**	**1**
Respiratory AEs		**2**	**2**	**1**	**1**	**8**	**7**	**1**	**1**	**3**	**3**	**0**	**0**	**13**	**8**	**2**	**2**

a Adverse event (AE):

An adverse event is any untoward medical occurrence in a clinical trial subject to whom an intervention or medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product or intervention. This includes abnormal laboratory findings, symptoms, or disease temporally associated with the use of a medicinal product / intervention, whether or not considered related to the medicinal product / intervention. In order to distinguish those events classified as 'serious' as opposed to 'non-serious', please refer to the Definition of Serious Adverse Events as described at the bottom of Table 3 in the body of the main paper. This table shows the adverse events that have not been classified as serious adverse events.

Patients could have more than 1 adverse event, so numbers comprising breakdowns might sum to more than the reported totals.

b Conditioning phase covers 100 days from start of conditioning (or reference day for Control patients). Mobilisation phase covers period from start of mobilisation to start of conditioning. Follow up phase covers period from end of conditioning phase to one year assessment

c Median (95%CI) difference in the number of AEs experienced per patient and the median (95%CI) difference in the percentage of patients experiencing an

AE between patients undergoing HSCT & control treatment. Asymptotic CI for the difference of proportions or Nonparametric CI for difference of medians (percentile bootstrap, stratified by the grouping variable). Any discrepancies between p value and 95% CI are due to inclusion of a centre effect in calculating p values but not 95% CIs.