Clinical trial results:
Autologous Stem cell Transplantation In refractory Crohn's disease - Low Intensity Therapy Evaluation

Summary

EudraCT number	2017-002545-30
Trial protocol	GB
Global end of trial date	29 November 2020

Results information

Result version number	v1 (current)
This version publication date	02 December 2021
First version publication date	02 December 2021

Trial information

Trial identification

Sponsor protocol code	IRAS220495

Additional study identifiers

ISRCTN number	ISRCTN17160440
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Barts Health NHS Trust
Sponsor organisation address	5 Walden Street, London, United Kingdom, E1 2EF
Public contact	Dr Mays Jawad, Queen Mary University of London, +44 020 7882 7252, research.governance@qmul.ac.uk
Scientific contact	Dr Mays Jawad, Queen Mary University of London, +44 020 7882 7252, research.governance@qmul.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 November 2020
Global end of trial reached?	Yes
Global end of trial date	29 November 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to assess whether autologous haematopoietic stem call transplantation (HSCT) with a low intensity treatment regimen (lite) is safe and effective in inducing regression of ileo-colonic ulceration in Crohn's Disease, where previous treatments have been unsuccessful, compared with standard care.

Definitions:
Autologous - cells or tissue obtained from the same individual
Hematopoietic - cells that give rise to blood cells

Protection of trial subjects:

Patients who were not randomised to receive HSCTlite (study intervention) were treated as per standard care. Patients who were randomised to receive HSCTlite received standard clinical haematology follow up during and following their stem cell transplant.
Patients were free to withdraw from the study at any time without giving a reason and without this affecting their ongoing treatment. Safety events were regularly reviewed by an independent Data Monitoring and Ethics Committee, and the decision to pause recruitment on safety grounds was taken following review of this safety data.

Participants were provided with a contact card and encouraged to get in touch with their local trial team if they had experienced any adverse events.

Background therapy:

The control group were permitted any current available treatment for Crohn’s disease, except stem cell transplant.

Evidence for comparator:

The comparator included all treatments available to patients with Crohn's disease, under non-trial circumstances. These could include: (1) biologic therapy, (2) nutritional therapy, (3) corticosteroids and (4) conventional immune modulators. The study evaluated the intervention to investigate if this could potentially be offered as routine care in the future.

Actual start date of recruitment	09 May 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 23
Worldwide total number of subjects	23
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	23
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study opened to recruitment on 9th May 2018 and the last patient was randomised on 26th September 2019. The decision was made by the TSC and DMEC to pause recruitment on 30th December 2019 and no further patients were recruited to the study after this time. In total 49 patients were consented, with 23 randomised.

Pre-assignment

Screening details:

Potentially eligible patients were asked for consent to be discussed at the trial MDT. Once MDT had confirmed the patient seemed appropriate for the trial, full consent was taken and screening investigations completed.
Referral to trial MDT – 77
MDT confirmed could proceed – 74
Screening completed – 49
Baseline completed - 27
Randomised - 23

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Usual care

Arm description:

Standard care for Crohn's disease

Arm type	Control

No investigational medicinal product assigned in this arm

Arm title	HSCTlite

Arm description:

Autologous stem cell transplant

Arm type	Experimental
Investigational medicinal product name	Cyclophosphamide, Fludarabine, Rabbit ATG, G-CSF (filgrastim)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Mobilisation
Cyclophosphamide, 1 hour infusion 1g/m2 on day 1, G-CSF (filgrastim) 5mcg/kg subcutaneously 4 days following cyclophosphamide until the day of stem cell harvest
Conditioning
Fludarabine: IV fludarabine 25mg/m2, given on days -6, -5, -4, -3 and -2. Reduced doses in the presence of impaired renal function, cyclophosphamide 60mg/kg/day IV over 1 hour, given in 500ml of normal saline on days -3 and -2. Rabbit ATG IV 2.5mg/kg was given on days -3, -2 and -1. A test dose was given as per standard local practice. G-CSF: Stem cells were re-infused at day 0. G-CSF 5mcg/kg/day (to the nearest vial) began on day +5 and continued until absolute neutrophil counts reached >1.0x109/L for two consecutive days.

Number of subjects in period 1[1]	Usual care	HSCTlite
Started	9	13
Completed	9	9
Not completed	0	4
Adverse event, serious fatal	-	1
Consent withdrawn by subject	-	1
Withdrawn due to early study closure	-	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One person was withdrawn post-randomisation after being found ineligible and therefore didn't make the ITT criteria.

Baseline characteristics

Reporting groups	
Reporting group title	Usual care
Reporting group description:	
Standard care for Crohn's disease	
Reporting group title	HSCTlite
Reporting group description:	
Autologous stem cell transplant	

Reporting group values	Usual care	HSCTlite	Total
Number of subjects	9	13	22
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	13	22
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	5	7	12
Male	4	6	10
Smoking status Units: Subjects			
Never smoked	7	7	14
Current smoker	1	2	3
Previous smoker (stopped 5+ years)	1	3	4
Not recorded	0	1	1
Presence of perianal Crohn's disease Units: Subjects			
Yes	5	3	8
No	4	10	14
Stoma Units: Subjects			
Yes - ileostomy	2	3	5
Yes - end ileostomy	0	3	3
Yes - loop colostomy	0	1	1
No	7	6	13
Disease location Units: Subjects			
L1 - ileal	0	3	3
L2 - colonic	1	1	2

L3 - ileocolonic	3	5	8
L4 - isolated upper disease	1	0	1
L1 L4	2	3	5
L3 L4	2	1	3
Previous surgery for Crohn's disease Units: Subjects			
Intestinal surgery	5	8	13
Perianal surgery	1	0	1
Both intestinal and perianal surgery	3	4	7
No previous surgery	0	1	1
Duration of disease Units: years			
arithmetic mean	14.1	13.6	
standard deviation	± 7.8	± 6.7	-
Baseline CDAI Units: score			
arithmetic mean	271.5	381.5	
standard deviation	± 115.2	± 209.1	-
Baseline SES-CD Units: score			
arithmetic mean	10.1	11.8	
standard deviation	± 5.7	± 8.7	-
Number of previous biologics Units: number			
arithmetic mean	3.33	3.08	
standard deviation	± 0.50	± 0.76	-

End points

End points reporting groups

Reporting group title	Usual care
Reporting group description:	
Standard care for Crohn's disease	
Reporting group title	HSCTlite
Reporting group description:	
Autologous stem cell transplant	

Primary: Absence of ulceration

End point title	Absence of ulceration[1]
End point description:	
Treatment success at week 48 defined as mucosal healing (no endoscopic ulceration (SES CD ulcer size sub score = 0, assessed by adjudication panel blind to allocation and time of assessment)) without surgery or death.	
End point type	Primary
End point timeframe:	
at 48 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the early study closure and low numbers, the original statistical analysis plan was amended and an addendum to the SAP was written, in which it was decided that a mixed effects logistic regression model would be used for the primary outcome, however upon receiving the data and fitting the model, the model did not converge. Therefore, it was decided only descriptive statistics were to be reported for the primary endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical remission (CDAI<150)

End point title	Clinical remission (CDAI<150)
End point description:	
End point type	Secondary
End point timeframe:	
At 48 weeks	

Statistical analyses

No statistical analyses for this end point

Secondary: Steroid free clinical remission (CDAI <150)

End point title	Steroid free clinical remission (CDAI <150)

End point description:

End point type	Secondary

End point timeframe:

At 48 weeks

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical remission (Harvey Bradshaw Index <4)

End point title	Clinical remission (Harvey Bradshaw Index <4)

End point description:

End point type	Secondary

End point timeframe:

At 48 weeks

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical remission (PRO2 - abdominal pain <1 and stool frequency <1.5)	
End point title	Clinical remission (PRO2 - abdominal pain <1 and stool frequency <1.5)
End point description:	
End point type	Secondary
End point timeframe:	
At 48 weeks	

Statistical analyses

No statistical analyses for this end point

Secondary: Complete endoscopic remission (SES-CD score=0)	
End point title	Complete endoscopic remission (SES-CD score=0)
End point description:	
End point type	Secondary
End point timeframe:	
At 48 weeks	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the point of patient consent to the trial, until patients completed their participation in the trial. Ongoing adverse events at trial completion were followed up where possible until the study database was frozen.

Adverse event reporting additional description:

During this follow up of ongoing adverse events, it was discovered that a participant had died following completion of their participation in the trial. This death has been included in the figures reported here.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Usual care

Reporting group description:

All participants randomised to usual care (control group), including one participant found to be ineligible post randomisation.

Reporting group title	HSCTlite

Reporting group description:

All participants randomised to HSCTlite (trial intervention).

Serious adverse events	Usual care	HSCTlite	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	13 / 13 (100.00%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
Investigations			
C-reactive protein abnormal			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Optic neuritis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombotic microangiopathy			

subjects affected / exposed	0 / 10 (0.00%)	3 / 13 (23.08%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Methaemoglobinaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse reaction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adverse drug reaction			
subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	3 / 10 (30.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary veno-occlusive disease			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 10 (0.00%)	3 / 13 (23.08%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal abscess			
subjects affected / exposed	1 / 10 (10.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 10 (10.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 10 (10.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Usual care	HSCTlite	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 10 (30.00%)	11 / 13 (84.62%)	
Vascular disorders			
Thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Catheter site discharge			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Hypoxia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	

Hallucination			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Mental disorder			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Oxygen saturation			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Investigation			
subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood glucose increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Liver function test abnormal			
subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	3	
Antimicrobial susceptibility test resistant			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Mycobacterium tuberculosis complex test positive			

subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Neuropathy peripheral			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Pineal gland cyst			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Mouth ulceration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	3	
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Rectal haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Crohn's disease			
subjects affected / exposed	2 / 10 (20.00%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 10 (10.00%)	2 / 13 (15.38%)	
occurrences (all)	1	2	
Rash papular			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Infections and infestations			
Tonsillitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Eye infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Epstein-Barr virus infection			
subjects affected / exposed	0 / 10 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
Fungal infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Anal abscess			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
Bronchitis viral			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 13 (0.00%)	
occurrences (all)	2	0	

Viral infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0	
Metabolism and nutrition disorders Fluid overload subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2018	• Clarity added to protocol around procedures relating to mechanistic studies • Corrections/typos where required • Increased window for some screening investigations prior to randomisation, and timing of CDAI in relation to colonoscopy • Inclusion of the use of the IBD BioResource to identify potential participants • Addition of HBI between mobilisation and conditioning, CDAI and HBI at both screening and baseline, added stoma version of IBDQ for participants where this is required • Updates to PIS on advice from TSC – timing of discussion with both specialties, noted that most common side effects likely to occur in almost all patients • Submitted reformatted versions of the validated participant questionnaires • Minor updates to formatting for healthcare resource use questionnaire, symptom diary and vaccination proforma
01 June 2018	• Changes to PI at Edinburgh and Nottingham sites • Secondary outcome added in relation to MRI and MaRIA score • Additional mechanistic serum sample added at week 40 visit • Addition of potential storage of stem cell samples for use in future research • Added Karnofsky performance status at screening and week 48 for all participants • Information added in relation to press release to aid recruitment, and potential use of a study Twitter account • Participant allocation letter submitted which can be used to follow up informing participants of their allocation where face to face is not possible • Addition of a vaccination advice sheet for GPs
05 June 2018	• To allow the use of PICs, and to add Nottingham NHS Treatment Centre as a PIC for the Nottingham site
02 August 2018	• The removal of details of MA holder for each IMP in section D2-1 of the application. The intention has always been for sites to use any brand of the IMPs in this study, and whilst the correct section of the application was completed to reflect this, details from the sample SmPCs submitted originally was also included, which implied that those brands were specified.
05 September 2018	• To add King's College Hospital London as a non-recruiting site, and to change the site type for Guy's & St Thomas' to a non-treatment site.
02 November 2018	• Administrative changes to the protocol to update the organisations for two collaborators, Sponsor contact email address, CI deputy details • Increase the window for screening investigations from within 4 weeks to 8 weeks of randomisation • Provided clarity on how the primary outcome will be assessed for patients who have had ileo and/or colonic resection, but are still eligible to take part in the trial • Correction to DMEC meeting frequency in line with the DMEC Charter • Correction to treatment section in the PIS to note that mobilisation cyclophosphamide will be given on one day, rather than two. • Clarification in the PIS that endoscopy might be undertaken if the bowel cannot be examined using ileocolonoscopy. • The SmPC for filgrastim has been updated since the start of the study; the revised version has been submitted with this amendment to update the RSI. • The SmPC for cyclophosphamide has been updated since the start of the study; although there have been no changes to the safety aspects, the updated version has been included with this amendment so that sites can have access to the latest information relating to the IMP.

25 July 2019	• Addition of genetic and or functional tests during screening to exclude monogenic cause of intestinal inflammation in patients with predictive clinical phenotype • To allow possibility of second attempt at mobilisation with reduced or no cyclophosphamide in patients who fail to mobilise first time • Admin changes and updates to protocol • Clarified definition of SES-CD ulcer size subscore for eligibility and outcomes • Updates to PIS for GDPR requirements, and genetic testing as above • Additional two flowcharts to help explain trial to participants
12 August 2019	Increase in dose of methylprednisolone (NIMP) from 1mg/kg/day to 2mg/kg/day, with scope to increase further up to 500-1000mg in the setting of an ATG reaction. Amendment in response to Urgent Safety Measure (July 2019).
08 February 2020	Administrative changes to reflect change in trial manager and research assistant. Removal of the circle Nottingham as this is now part of Nottingham University Hospitals NHS Trust. Allow the use of an alternative to MRI such as a CT scan for screening if patients are unable to have an MRI. Addition that MRI will not be carried out at week 4, week 24 or week 48 if this is contraindicated. At week 24 an assessment of whether anti-TNF therapy is indicated will be based on endoscopic evidence and if needed, abdominal ultrasound. Addition that any laboratory test result which is out of range, and clinically significant, will be recorded as an adverse event, unless it is expected as part of the patient's disease presentation, or reflects the status of their baseline disease. Consideration about reintroducing anti-TNF at week 24 for patients with multiple sclerosis. Anti-TNF therapy may not be appropriate for these patients therefore it will be reviewed on a case by case basis and discussed at MDT. Suitable alternative such as vedolizumab may be offered. Changes to the SmPC for filgrastim and thymoglobulin.
30 March 2020	Temporary Halt following fatal SUSAR
22 September 2020	Addition of letter to update patients on the closure to the ASTIClite trial.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 December 2019	The trial was paused in December 2019 whilst a number of SUSARs were investigated. Two further SUSARs were reported in May 2020. In June 2020, the DMEC and TSC held a joint meeting to discuss the events, the outcomes of investigations and the impact of the coronavirus pandemic. The DMEC and TSC agreed that recruitment to the trial should stop. Patients already in follow up, either having completed the intervention, or in the control group, were followed up as normal. Patients randomised to the intervention who had not yet received this, were withdrawn from the study. In addition, the coronavirus pandemic affected the ability of trial sites to conduct all aspects of patient visits. Some visits were delayed, and some procedures had to be omitted.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the early closure of the trial, participant numbers included in the final analysis are lower than anticipated. An addendum was written for the Statistical Analysis Plan to document the changes to the planned analyses given the reduced numbers.

Notes: