Clinical trial results:
A Single-Arm, Open-Label, Multi-Centre, Phase I/II Study Evaluating the Safety and Clinical Activity Of AUTO3, a CAR T Cell Treatment Targeting CD19 And CD22 in Paediatric And Young Adult Patients With Relapsed or Refractory B Cell Acute Lymphoblastic Leukaemia

Summary

EudraCT number	2016-004680-39
Trial protocol	GB
Global end of trial date	18 May 2020

Results information

Result version number	v1 (current)
This version publication date	04 December 2020
First version publication date	04 December 2020

Trial information

Trial identification

Sponsor protocol code	AUTO3-PA1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03289455
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Autolus Ltd
Sponsor organisation address	58 Wood Lane, White City, London, United Kingdom, W12 7RZ
Public contact	Clinical Project Manager, Autolus Ltd, +44 1483 920748, clinicaltrials@autolus.com
Scientific contact	Clinical Project Manager, Autolus Ltd, +44 1483 920748, clinicaltrials@autolus.com

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	18 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2020
Global end of trial reached?	Yes
Global end of trial date	18 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objectives of Phase 1 of this trial were to assess the overall safety and tolerability of AUTO3 administration and to confirm and evaluate the recommended Phase II dose (RP2D) and dosing schedule, and confirm maximum tolerated dose (MTD), if an MTD exists, of AUTO3 in both paediatric and adult patients. The main objective of Phase 2 of this trial was to evaluate the anti-leukaemic effect of AUTO3 in paediatric and young adult patients (aged 1-24 years).

Protection of trial subjects:

This study was conducted in accordance with standards of Good Clinical Practice (as defined by the International Council on Harmonisation), ethical principles that have their origin in the Declaration of Helsinki and all applicable national and local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 July 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
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	23

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)	17
Adolescents (12-17 years)	6
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited at three study centres in the United Kingdom.

Pre-assignment

Screening details:

Screening procedures were performed up to 12 weeks before study drug was administered. After screening subjects went through the sequential stages of leukapheresis, and pre conditioning before subjects were treated with actual doses of 0.3 to 5.0 x 10^6 /kg CD19/CD22 CAR-positive T cells.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AUTO3

Arm description:

Paediatric subjects with relapse or refractory B-cell acute lymphoblastic leukaemia (ALL).

Arm type	Experimental
Investigational medicinal product name	AUTO3 (CD19/22 CAR T cells)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Following preconditioning with chemotherapy (cyclophosphamide and fludarabine) subjects were treated with actual doses of 0.3 to 5.0 x 10^6 /kg CD19/CD22 Chimeric Antigen Receptor (CAR) positive T cells

Number of subjects in period 1	AUTO3
Started	23
Leukapheresed	20
Started Preconditioning Therapy	15
Received Study Treatment	15
Completed	0
Not completed	23
Death	1
Other	2
Progressive Disease	12
Not infused with AUTO3	8

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	23	23	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	9.0		
standard deviation	± 4.38	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	15	15	
Race Units: Subjects			
Asian	4	4	
White	19	19	
Karnofsky/Lansky score Units: Percentage			
median	90		
full range (min-max)	70 to 100	-	

Subject analysis sets

Subject analysis set title	Received Study Treatment
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients who received at least 1 (complete or partial) dose of AUTO3 (infused set)

Reporting group values	Received Study Treatment		
Number of subjects	15		

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	9.6		
standard deviation	± 4.36		
Gender categorical Units: Subjects			
Female	4		
Male	11		
Race Units: Subjects			
Asian	1		
White	14		
Karnofsky/Lansky score Units: Percentage			
median	90		
full range (min-max)	80 to 100		

End points

End points reporting groups

Reporting group title	AUTO3
Reporting group description:	
Paediatric subjects with relapse or refractory B-cell acute lymphoblastic leukaemia (ALL).	
Subject analysis set title	Received Study Treatment
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients who received at least 1 (complete or partial) dose of AUTO3 (infused set)	

Primary: Incidence of Grade 3-5 Toxicities Occurring Within the Dose Limiting Toxicity (DLT) Period of AUTO3 Infusion

End point title	Incidence of Grade 3-5 Toxicities Occurring Within the Dose Limiting Toxicity (DLT) Period of AUTO3 Infusion[1]
End point description:	
End point type	Primary
End point timeframe:	
Within 30 days (+/- 3 days) after the last dose of AUTO3	

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: Only summary statistics were planned for this endpoint.

End point values	AUTO3			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Subjects	14			

Statistical analyses

No statistical analyses for this end point

Primary: Frequency of Dose Limiting Toxicity (DLT) of AUTO3

End point title	Frequency of Dose Limiting Toxicity (DLT) of AUTO3[2]
End point description:	
DLT was defined as i) any new non-hematological AE of Grade 3 or higher toxicity using the NCI CTCAE (version 5.0), which is probably or definitely related to AUTO3 therapy, which occurs within the DLT evaluation period, and which fails to resolve to Grade 2 or better within 14 days, despite appropriate supportive measures; ii) Grade 4 CRS or neurotoxicity, cerebral edema, or Grade 3 neurotoxicity (including cerebral edema) that lasts >72 hours; iii) Grade >3 disseminated intravascular coagulation; iv) Grade >2 infusion reaction; v) Any other fatal event (Grade 5) or life-threatening event (Grade 4) that cannot be managed with conventional supportive measures or which in the opinion of the SEC necessitates dose reduction or other modification to trial treatment to avoid a similar hazard in future subjects.	
End point type	Primary
End point timeframe:	
Within 30 days (+/- 3 days) after the last dose of AUTO3	

Notes:

[2] - 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: Only summary statistics were planned for this endpoint.

End point values	AUTO3			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Subjects	0			

Statistical analyses

No statistical analyses for this end point

Primary: Proportion of Patients Achieving Morphological Remission (Complete Response(CR) or Complete Response With Incomplete Count Recovery (CRi) and Minimal Residual Disease (MRD)-Negative Response in the Bone Marrow (PCR)).

End point title	Proportion of Patients Achieving Morphological Remission (Complete Response(CR) or Complete Response With Incomplete Count Recovery (CRi) and Minimal Residual Disease (MRD)-Negative Response in the Bone Marrow (PCR)).[3]

End point description:

End point type	Primary

End point timeframe:

Within 30 days (+/- 3 days) post AUTO3 infusion

Notes:

[3] - 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: Only summary statistics were planned for this endpoint.

End point values	AUTO3			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Subjects	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Feasibility of Generating AUTO3: Number of Subjects' Cells Successfully Manufactured as a Proportion of the Number of Subjects Undergoing Leukapheresis

End point title	Feasibility of Generating AUTO3: Number of Subjects' Cells Successfully Manufactured as a Proportion of the Number of Subjects Undergoing Leukapheresis

End point description:

Feasibility of product generation was examined by assessing the number of AUTO3 successfully manufactured as a fraction of the number of subjects undergoing leukapheresis (all subjects screened).

End point type	Secondary

End point timeframe:

Up to 8 weeks post leukapheresis

End point values	AUTO3			
Subject group type	Reporting group			
Number of subjects analysed	20[4]			
Units: Subjects	19			

Notes:

[4] - This endpoint includes all patients who were screened and underwent leukapheresis.

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS) by Morphological Analysis

End point title	Event-Free Survival (EFS) by Morphological Analysis

End point description:

Time from date of first AUTO3 infusion until the earliest of treatment failure (defined as not achieving CR/CRi post AUTO3 infusion / no response), morphological relapse, or death due to any cause, whichever occurred first.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	AUTO3			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Months				
median (confidence interval 95%)	4.90 (1.64 to 12.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of CD19- and/or CD22-negative Relapse

End point title	Incidence of CD19- and/or CD22-negative Relapse

End point description:

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	AUTO3			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Subjects	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse-Free Survival (RFS) by Morphological Anlaysis

End point title	Relapse-Free Survival (RFS) by Morphological Anlaysis

End point description:

Time from first achievement of morphological CR/CRi post AUTO3 treatment until the earliest of morphological relapse, or death due to any cause, whichever occurred first.

99999 is used as the upper limit of the confidence interval was not reached.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	AUTO3			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Months				
median (confidence interval 95%)	9.53 (1.87 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Calculated from the date of AUTO3 treatment to the date of death anytime post AUTO3 infusion. Patients who had not died were censored at the date of last contact.

99999 is used where the upper limit of the confidence interval had not been reached.

End point type	Secondary

End point timeframe:

Up to last patient last visit

End point values	AUTO3			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Months				
median (confidence interval 95%)	14.55 (4.34 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Expansion of AUTO3 Following Adoptive Transfer

End point title	Expansion of AUTO3 Following Adoptive Transfer

End point description:

Expansion of AUTO3 was measured as the median peak (Cmax) of transgene levels in the peripheral blood after AUTO3 infusion.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	AUTO3			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Vector copies/ug DNA				
median (full range (min-max))	56100 (5690 to 127000)			

Statistical analyses

No statistical analyses for this end point

Secondary: Persistence of AUTO3 Following Adoptive Transfer

End point title	Persistence of AUTO3 Following Adoptive Transfer

End point description:

Persistence of AUTO3 was measured by qualitative polymerase chain reaction (PCR) and/or flow cytometry at a range of time points in the peripheral blood and the bone marrow.

Persistence was defined as the timepoint in days of last detectable CAR T cell by qPCR or last assessment if zero copies per µg DNA (whichever occurred later) before morphological relapse (Tlast).

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	AUTO3			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Days				
median (full range (min-max))	62.7 (18.8 to 570.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of B Cell Aplasia

End point title	Duration of B Cell Aplasia

End point description:

Depletion of circulating B cells assessed by flow cytometry at a range of time points in the peripheral blood.

99999 is entered as B cell aplasia from the database was inconclusive because the total lymphocytes from the peripheral blood analyzed by flow cytometry were not collected systematically.

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	AUTO3			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From AUTO3 infusion (Day 0) to until the end of study or withdrawal, whichever occurred first.	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0
Reporting groups	
Reporting group title	AUTO3
Reporting group description:	
Paediatric subjects with relapse or refractory B-cell acute lymphoblastic leukaemia (ALL).	

Serious adverse events	AUTO3		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 15 (40.00%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events			
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		

Thrombocytopenia			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	AUTO3		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		

Fatigue			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	9 / 15 (60.00%)		
occurrences (all)	31		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypoxia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Painful respiration			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Psychiatric disorders			
Hallucination			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Human herpes virus 6 serology positive			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		

Lymphocyte count decreased			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	4		
Neutrophil count decreased			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	28		
Platelet count decreased			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	6		
Staphylococcus test positive			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Soft tissue injury			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		

Paraesthesia subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Syncope subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 6		
Febrile neutropenia subjects affected / exposed occurrences (all)	6 / 15 (40.00%) 6		
Neutropenia subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 8		
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 3		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	4 / 15 (26.67%) 5		
Anal haemorrhage			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Lip dry			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	5		
Stomatitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Rash erythematous			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Rash maculo-papular subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Rash papular subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Epistaxis subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Musculoskeletal and connective tissue disorders Aphasia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Neck pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Pain in extremity subjects affected / exposed occurrences (all)	5 / 15 (33.33%) 5		
Infections and infestations Catheter bacteraemia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Enterococcal infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Device related infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2		
Folliculitis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		

Gingival abscess subjects affected / exposed occurrences (all) Infectious pleural effusion subjects affected / exposed occurrences (all) Parvovirus infection subjects affected / exposed occurrences (all) Staphylococcal infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Gout subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all)	5 / 15 (33.33%) 6 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 June 2017	Protocol version 2 - Summary of Changes: - Typographical and administrative changes - Changed dose escalation to dose evaluation/escalation - Expanded inclusion criterion 1c with broader definitions extreme hyperdiploidy or hypodiploidy - Added further clarity for high-risk CNS relapse subjects in inclusion criterion 1i and exclusion criterion 1 - Clarified screening window i.e. Day -84 to Day -35 - Clarified the inpatient period in the case of a split dose i.e. 30 (-3/+5) days post-AUTO3 infusion and up to 14 days after the second split dose - Added text to clarify when the second split dose can be administered i.e. only at ≤ Grade 1 CRS and no ongoing CRS or neurotoxicity at Day 7 - Clarified the procedure for re-starting the trial following a halt as per the safety stopping criteria - Clarified DLT period of 30 days (±3 days) after last dose or until start of a new ALL therapy - Added hypoxia risks and mitigation strategy, respiratory toxicity guidelines - Added GVHD risks and mitigation strategy as per the Investigator's Brochure - Clarified early use of tocilizumab for CRS safety management - Added text to note patients will be monitored for CMV weekly during admission or as necessary - Updated frequency of IDMC meetings to every 6 months in Phase II. Added text regarding the information received and the decision(s) that can be taken by the IDMC, particularly with regards to opening Phase II - Updated the withdrawal of consent for patient samples stored for research
24 October 2017	Protocol version 3 - Summary of Changes: - Typographical and administrative changes - Updated and added new exclusion criteria - Clarified Rolling 6 Dose Evaluation Decision Rules - Added details on which blast count will be used to choose the cohort for a subject - Added that subjects must have a full neurological assessment prior to pre-conditioning (Day -7) - Amended central laboratory for MRD analysis from Great Ormond Street to Bristol Genetics Laboratory - Updated Management of CRS text - Updated concomitant medications and therapies

02 February 2018	Protocol version 4 - Summary of Changes: - Typographical and administrative changes - Updated schedule of events - Added up to 3 dose levels for Phase 1 and clarified that each dose level will have 2 cohorts - Added interim analysis on safety and preliminary efficacy - Updated study product wording for AUTO3 - Changed dose evaluation to dose escalation - Increased the number of patients needed for Phase I from 12-18 to 18-30. And increased the total number of patients needed for the whole study from 50 to 62 - Modified pre-conditioning regimen - Timing of 2nd split dose reduced from 14 days (+/- 7d) to 5-10 days - Updates to inclusion and exclusion criteria - Addition of available clinical data in the first 3 patients treated with CD19/CD22 CAR-positive T cells - Clarification of use of data from re-treated patients - SEC recommended to declared the Cohort 1 dose as safe and escalate dose for subsequent patients to 3x10^6 CD19/CD22-positive CAR-T cells/kg and further if needed to establish a RP2D - Modified text based on recently published data indicating that patients at risk of severe CRS or neurotoxicity develop signs and symptoms very early and early dosing of the second fraction between day 5-10 is likely to maximise the potential effect of pre-conditioning induced cytokines on AUTO3 without increasing the risk of severe toxicity - Updated DLT criteria - Clarified text regarding patients with ≥25% blasts can be treated with single doses if both single and split doses are determined to be safe - Revised Safety Stopping Criteria - Dosing caveat added to increase patient safety - Updated text regarding re-treatment of patients - Updated the CRS management guidelines - Update the tocilizumab dosing guidelines to match the current label - Revised concomitant medications text - Updated dietary and lifestyle restrictions - Clarified interim analysis text - Clarified study discontinuation text - Clarified monitoring text
11 May 2018	Protocol version 5 - Summary of Changes: - Clarified exclusion criteria - Updated schedule of events
10 October 2018	Protocol version 6 - Summary of Changes: (US only; not implemented) - Typographical changes - Revised text regarding single or split doses based on disease burden, but clarified they will be analysed as one group - Updated DLT definition based on FDA recommendation - Made corrections to the risks and mitigations section

29 March 2019	Protocol version 7 - Summary of Changes: (implemented in v. 8) - 'Young adult' has been replaced by 'adult' - Inclusion of a potential 4th dose level, that increases the total number of paediatric/young adult patients required for Phase I to 24-36 - Inclusion of an adult cohort (≥25 years), which adds 12-24 patients into Phase I - Update to Infectious Disease Screening - Reduction of blood volume required for RCR testing and insertional mutagenesis from 10ml to 5 - Update to paediatric/young adult exclusion criteria - Update of window for DLT period at Day 30 to ±3 days - The recommended in-patient stay after AUTO3 dosing in Phase I has been reduced from 30 (-3/+5) days to 14 days, or longer if necessary. In Phase II the duration of admission to hospital will be based on emerging data and the patient's condition. Patient may be discharged before 14 days or treated as out patients - MRD will now be analysed at all time points by both PCR and flow - Bone marrow and cerebrospinal fluid tests at Day 0 removed - Frequency of blood tests for cytokines and CAR T cells reduced - Immunological profiling will be done in Phase I only - Schedule of assessments updated - Update to the clinical data in AUTO3-PA1 to new data - Update to secondary objectives and endpoints - The SEC has agreed that Cohort 2b (3x10^6/kg split dose) should be closed after 1 patient as it is deemed sub-therapeutic - A minimum of 6 patients need to be treated in a cohort before it can be declared as the phase 2 dose - Updated DLT definition - Updated text in risks and mitigation section - Clarification of patients going on hold before dosing - Update to information on the administration of AUTO3 - New text added to Monitoring During and After Drug Administration section - Definitions of relapse disease have been clarified - New text added for HRQOL measures and bridging therapy - New CRS/MAS treatment option - Updated Lee et al, 2018 guidance - CTCAE version updated to v5.
10 May 2019	Protocol version 8 - Summary of Changes: - The recommended in-patient stay after AUTO3 dosing has been returned from 14 days to 30 days (±3), or longer if necessary for monitoring and management, per MHRA request - The following text was deleted: AEs such as severe cytopenias that require re-hospitalization within 30 (±3) days of AUTO3 because the patient was discharged early should not be automatically reported as SAEs unless clinically indicated ex febrile neutropenia - Reporting of prolonged Grade 4 cytopenia lasting more than 60 days: text moved and clarification added - BMA immunophenotyping and flow MRD tests at screening

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
29 September 2019	Recruitment halted on 29-Sep-2019 and not reopened. Patients were followed to completion (withdrawal).	-

Notes:

Limitations and caveats

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

Early completion of the study leading to small numbers of patients analyzed from the Phase I part of the study.

Notes: