Clinical trial results:
Low-dose IL-2 to expand endogenous regulatory T cells and achieve tolerance in liver transplantation

Summary

EudraCT number	2017-000177-37
Trial protocol	GB
Global end of trial date	30 January 2019

Results information

Result version number	v1 (current)
This version publication date	21 February 2020
First version publication date	21 February 2020
Summary attachment (see zip file)	FINAL STUDY REPORT (LITE - End of Study Report.pdf)

Trial information

Trial identification

Sponsor protocol code	LITE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02949492
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	King's College London
Sponsor organisation address	The Strand, London, United Kingdom, WC2R 2LS
Public contact	Prof Alberto Sanchez-Fueyo, King's College London, +44 0207848 5883, sanchez_fueyo@kcl.ac.uk
Scientific contact	Prof Alberto Sanchez-Fueyo, King's College London, +44 0207848 5883, sanchez_fueyo@kcl.ac.uk
Sponsor organisation name	King's College Hospital NHS Foundation Trust
Sponsor organisation address	Denmark Hill, London, United Kingdom, SE5 9RS
Public contact	Prof Alberto Sanchez-Fueyo, King's College Hospital, +44 0207848 5883, sanchez_fueyo@kcl.ac.uk
Scientific contact	Prof Alberto Sanchez-Fueyo, King's College Hospital, +44 0207848 5883, sanchez_fueyo@kcl.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	30 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 January 2019
Global end of trial reached?	Yes
Global end of trial date	30 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine the capacity of a short course of low-dose IL-2 to facilitate the complete discontinuation of immunosuppressive drugs in liver recipients 2-6 years after transplantation.

Protection of trial subjects:

To assess safety during the administration of IL-2 and the discontinuation of IS, participants will undergo frequent blood tests that will include full blood cell count, Na, K, creatinine, AST, ALT bilirubin, GGT and alkaline phosphatase as follows: • Between Baseline Visit and Treatment Visit 2 patients will undergo blood tests every week. • Between Treatment Visit 2 and Treatment Visit 4 patients will undergo blood tests at least every 2 weeks. • Between Treatment Visit 4 and Treatment Visit 5 patients will require performance of blood tests at least every 3 weeks.
Adverse events will be monitored from screening to last visit. Patients will also be contacted by telephone after each blood test to discuss the results and enquire about potential adverse events. Furthermore, patients will undergo a full physical examination and vital signs at the time of each trial visit. Finally, patients will undergo protocol liver biopsies during the Screening Visit 2, following 4 weeks of IL-2 treatment (Treatment Visit 2), 12 months following IS discontinuation (Treatment Visit 5), and at any time during the duration of the study if they develop allograft dysfunction.

Background therapy:

At the time of enrolment participants will be treated with tacrolimus or cyclosporine A with/without mycophenolate mofetil/mycophenolic acid or azathioprine. All these specified immunosuppressive pharmacological drugs are commercially available and are licensed and have marketing authorisations as part of the standard of care in liver transplantation. These drugs therefore constitute a background therapy.

Evidence for comparator: -

Actual start date of recruitment	18 December 2017
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: 6
Worldwide total number of subjects	6
EEA total number of subjects	6

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)	6
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who underwent liver transplantation at Kings College Hospital and who are 6 to 12 months post liver transplantation will be selected according to the inclusion criteria. The trial specifically excludes transplant recipients that are at increased risk of acute cellular rejection and, recurrent disease.

Period 1

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

Blinding implementation details:

The trial was not blinded

Arms

Arm title	Proleukin

Arm description:

llver recipients ≤50 years old and 2-6 years after transplantation will receive IL-2 and gradually discontinue their immunosuppressive medication.

Arm type	Experimental
Investigational medicinal product name	Proleukin
Investigational medicinal product code	
Other name	Aldesleukin
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 - 2 million IU million international units per day. Subcutaneous Use

Number of subjects in period 1	Proleukin
Started	6
Completed	0
Not completed	6
Trial was terminated early	6

Baseline characteristics

End points

End points reporting groups

Reporting group title	Proleukin

Reporting group description:

llver recipients ≤50 years old and 2-6 years after transplantation will receive IL-2 and gradually discontinue their immunosuppressive medication.

Primary: Successful IS withdrawal at 1 year

End point title	Successful IS withdrawal at 1 year[1]

End point description:

Primary efficacy outcome measure was successful IS withdrawal as defined by the absence of rejection and a rejection free biopsy at 1year following IS discontinuation.

End point type	Primary

End point timeframe:

Successful IS withdrawal at 1 year

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: The trial was ended early and no statistical analysis was possible. Please see attached results.

End point values	Proleukin			
Subject group type	Reporting group			
Number of subjects analysed	6[2]			
Units: Successful IS withdrawal at 1 year	0			

Notes:

[2] - No subjects reached the primary endpoint

Attachments (see zip file)	Summary data/LITE summary of results.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Allograft dysfunction

End point title	Allograft dysfunction

End point description:

End point type	Secondary

End point timeframe:

Between baseline and visit 5

End point values	Proleukin			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number of subjects	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Allograft rejection

End point title	Allograft rejection

End point description:

End point type	Secondary

End point timeframe:

Between baseline and visit 5

End point values	Proleukin			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Number of subjects	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient graft survival

End point title	Patient graft survival

End point description:

End point type	Secondary

End point timeframe:

Between baseline and visit 5

End point values	Proleukin			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number of subjects	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Patients underwent IS withdrawal

End point title	Patients underwent IS withdrawal

End point description:

End point type	Secondary

End point timeframe:

Between baseline and visit 5

End point values	Proleukin			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Number of subjects	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Failure of IS withdrawal

End point title	Failure of IS withdrawal

End point description:

End point type	Secondary

End point timeframe:

Between baseline and visit 5

End point values	Proleukin			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Number of subjects	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from consent to last patient visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Whole trial

Reporting group description: -

Serious adverse events	Whole trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Severe Rejection Episode			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic artery pseudoaneurysm			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Whole trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Surgical and medical procedures			
Teeth extraction			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

Nervous system disorders Headache1 subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1		
Blood and lymphatic system disorders Hypereosinophilia subjects affected / exposed occurrences (all)	 6 / 6 (100.00%) 6		
Gastrointestinal disorders Loose stools subjects affected / exposed occurrences (all)	 2 / 6 (33.33%) 2		
Respiratory, thoracic and mediastinal disorders Coryzal symptoms subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 1		
Skin and subcutaneous tissue disorders Injection site reaction subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 5 / 6 (83.33%) 5 1 / 6 (16.67%) 1		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	 3 / 6 (50.00%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2018	Inclusion criteria Inclusion criteria has been updated to include subjects less than and including 50 years of age to include more potential participants. Addition of fine needle aspiration Fine needle aspiration is required as an extra purely mechanistic sample, as it is a good representation of liver health. It is easy to obtain and is very low risk to the patients. Additional visit at 7 (+/- 2 days) after baseline visit Added for safety reasons to quantify the number of circulating Tregs. Patients in whom the increase in Tregs is <2-fold as compared to baseline will increase their dose of IL-2 to 1 million IU twice daily, whilst those in whom Tregs increase ≥ 2-fold will remain on 1 million IU daily. Stool and urine samples made non-mandatory The stool and urine samples were changed to optional to avoid protocol violations in case of non-collection. Addition of whole blood gene expression as part of mechanistic lab assessments Update of TSC/DMC meeting timelines TSC/DMC meetings to take place every 6 months. Update to SmPC (RSI)
25 June 2018	IL-2 dose reduced to 0.5M IU/day after 4 weeks

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
17 October 2018	The trial was halted temporarily due to a participant experiencing chronic rejection which was not anticipated. The trial was not re-started.	-

Notes:

Limitations and caveats

None reported