Clinical trial results:
Phase I study of lentiviral-mediated COL7A1 gene-modified autologous fibroblasts in adults with recessive dystrophic epidermolysis bullosa (RDEB)

Summary

EudraCT number	2014-004884-19
Trial protocol	GB
Global end of trial date	13 March 2018

Results information

Result version number	v1 (current)
This version publication date	27 March 2019
First version publication date	27 March 2019
Summary attachment (see zip file)	FINAL STUDY REPORT (FINAL STUDY REPORT.doc)

Trial information

Trial identification

Sponsor protocol code	LENTICOL-F

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02493816
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	Professor John A McGrath, King's College London and Guy's and St Thomas' NHS Foundation Trust, 44 2071886409, john.mcgrath@kcl.ac.uk
Scientific contact	Professor John A McGrath, King's College London and Guy's and St Thomas' NHS Foundation Trust, 44 2071886409, john.mcgrath@kcl.ac.uk
Sponsor organisation name	Guy's and St Thomas' NHS Foundation Trust
Sponsor organisation address	Great Maze Pond, London, United Kingdom, SE19RT
Public contact	Professor John McGrath, Guy's and St Thomas' NHS Foundation Trust and King's College London, 44 2071886409, john.mcgrath@kcl.ac.uk
Scientific contact	Professor John McGrath, Guy's and St Thomas' NHS Foundation Trust and King's College London, 44 2071886409, john.mcgrath@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	No

1901/2006 apply to this trial?	
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	13 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 March 2018
Global end of trial reached?	Yes
Global end of trial date	13 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of intradermal injections of SIN LV-mediated COL7A1 gene-modified autologous fibroblasts in adults with RDEB.

Protection of trial subjects:

Each study participant will receive three intradermal injections of ex vivo transduced autologous fibroblasts expressing codon-optimised COL7A1 as the IMP on Day 0 only. Each injection of the IMP containing 0.8–1.2x106 cells suspended in 0.25ml of 0.9% saline, will be administered intradermally into 1cm2 area of intact skin (x3). Participants will be followed up with study interventions for a 12-month period at various time points. All followups, where possible, will be co-ordinated to try to coincide with the individuals' routine clinic reviews.
Each subject will undergo an initial screening including a physical examination and assessment of disease severity. Blood analyses and skin biopsies will be performed at various time points throughout the trial. The second participant will be treated only if there is no safety concern 4 weeks after the first participant's IMP injections. All patients with RDEB are followed up on a lifelong basis, and we will therefore be able to capture any long-term possible adverse effects related to the IMP.
Subjects with positive results for HIV, Hepatitis B, Hepatitis C, HTLV or Syphilis will be excluded.
Subjects will not be included who are pregnant or of child-bearing potential who are neither abstinent nor practising an acceptable means of contraception when this is in line with the usual and preferred lifestyle of the subject, as determined by the Investigator, for 12 months after the cell injections.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	18 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 4
Worldwide total number of subjects	4
EEA total number of subjects	4

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)	4
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The participants were recruited by St John’s Institute of Dermatology at Guy's and St Thomas NHS Foundation Trust.

Pre-assignment

Screening details:

Thirty-nine RDEB adults with confirmed biallelic COL7A1 mutations by Sanger sequencing were invited to participate in the study, of which 35 patients were excluded due to failing screening.

Period 1

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

Blinding implementation details:

Open label SIN LV-mediated ex vivo transduced autologous fibroblasts expressing codon-optimised COL7A1 will be given to patients at a does of 0.8–1.2 million cells suspended in 0.25ml of 0.9% saline per injection over 1 cm2 of intact skin (3 intradermal injections of IMP at a single timepoint). Patients were followed up for 12 months post injection.

Arms

Arm title	Treatment

Arm description:

Patients treated with SIN LV-mediated ex vivo transduced autologous fibroblasts expressing codon-optimised COL7A1.

Arm type	Experimental
Investigational medicinal product name	SIN LV Mediated ex vivo transduced autologous fibroblasts expressing codon-optimised COL7A1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled injector
Routes of administration	Intradermal use

Dosage and administration details:

0.8 - 1.2 million cells in 0.25ml of 0.9% saline per injection; 2.4 - 3.6 million cells total dose

Number of subjects in period 1	Treatment
Started	4
Completed	4

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial Period

Reporting group description: -

Reporting group values	Overall Trial Period	Total	
Number of subjects	4	4	
Age categorical			
All adult patients were recruited aged between 30 and 59			
Units: Subjects			
Age range 30 to 59	4	4	
Gender categorical Units: Subjects			
Female	2	2	
Male	2	2	

End points

End points reporting groups

Reporting group title	Treatment

Reporting group description:

Patients treated with SIN LV-mediated ex vivo transduced autologous fibroblasts expressing codon-optimised COL7A1.

Primary: Adverse Events

End point title	Adverse Events[1]

End point description:

Adverse events (AEs) at each visit after screening over a 12month follow-up period

End point type	Primary

End point timeframe:

From screening to 12 months after injection

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: Please see attached report for full results and trial outcomes, including full list of adverse events

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	4[2]			
Units: Number of adverse events	4			

Notes:

[2] - There were 45 AEs (including SAEs) in total

Statistical analyses

No statistical analyses for this end point

Primary: Adverse reactions

End point title	Adverse reactions[3]

End point description:

The incidence of Adverse Reactions (ARs) and Serious Adverse Reactions (SARs) at each visit after screening over a 12-month follow-up period.

End point type	Primary

End point timeframe:

Screening over a 12-month follow-up period.

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: Please see attached report for full results and trial outcomes, including full list of adverse reactions

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	4[4]			
Units: Adverse reactions	4			

Notes:

[4] - There were 7 adverse reactions and no serious adverse reactions

Statistical analyses

No statistical analyses for this end point

Primary: Serious Adverse Evemts

End point title	Serious Adverse Evemts[5]

End point description:

End point type	Primary

End point timeframe:

From screening to 12 months post dose.

Notes:

[5] - 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: Please see attached report for full results and trial outcomes, including full list of serious adverse events

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	1[6]			
Units: Number of serious adverse events	7			

Notes:

[6] - Number of serious adverse events

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Screening to 12 months post dose of IMP	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1
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 / 4 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
Bowel obstruction			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroparesis postoperative			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			

Sepsis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Refeeding syndrome			
subjects affected / exposed	1 / 4 (25.00%)		
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	4 / 4 (100.00%)		
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Nervous system disorders			
Throbbing pain over injection site			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Increased itch over forearms			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Itch over skin biopsy site			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
General disorders and administration site conditions			

Tiredness subjects affected / exposed occurrences (all) Occasional dizzy spells subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1 1 / 4 (25.00%) 1		
Eye disorders Conjuctivitis subjects affected / exposed occurrences (all) Sub-conjunctival haemorrhage subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 2 1 / 4 (25.00%) 1		
Gastrointestinal disorders Dysphagia subjects affected / exposed occurrences (all) Oesophageal dilation subjects affected / exposed occurrences (all) Oesophageal blisters subjects affected / exposed occurrences (all) Oesophageal spasm subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1 1 / 4 (25.00%) 2 1 / 4 (25.00%) 1 1 / 4 (25.00%) 1		
Respiratory, thoracic and mediastinal disorders Coryzal symptoms subjects affected / exposed occurrences (all) Dry cough subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1 1 / 4 (25.00%) 1		
Skin and subcutaneous tissue disorders Tattoo site swollen			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Injection site erythema			
subjects affected / exposed	4 / 4 (100.00%)		
occurrences (all)	4		
Injection site bruising			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Left leg skin infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Forearm skin infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	2		
Left ear skin infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Increased blistering on elbows, shins and forearms			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Left hand skin infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pseudomonas infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Streptococcal infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Candida infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Renal and urinary disorders			
Microscopic haematuia			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Difficult micurition			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Muscle spasm causing feet deformities			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 July 2015	• To decrease the duration of follow up from 36mths to 12mths • To amend the exclusion criteria such that persons with positive serology for HIV, Hepatitis B and C, HTLV and Syphilis are excluded from the study • To amend the total number of skin biopsies to be taken at baseline (V1B) from 2 (1x6mm and 1x4mm punch) to 2-3 (1x6mm and 1-2x4mm punch). • To include two additional investigations on the skin biopsies; histology and RT-PCR to demonstrate the difference in COL7A1 gene expression between fibroblasts from treated versus untreated skin.
25 April 2016	The purpose of this amendment secondary endpoints. Amend inclusion/exclusion criteria. Amend IMP administration details to minimise the amount of tattooing to mark the injected sites.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported