Clinical trial results:
A phase I/II study evaluating allogeneic mesenchymal stromal cells in adults with recessive dystrophic epidermolysis bullosa

Summary

EudraCT number	2014-004500-30
Trial protocol	GB
Global end of trial date	10 October 2017

Results information

Result version number	v1 (current)
This version publication date	28 February 2019
First version publication date	28 February 2019

Trial information

Trial identification

Sponsor protocol code	ADSTEM001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02323789
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, 44 207188 6409, john.mcgrath@kcl.ac.uk
Scientific contact	Professor John A. McGrath, King's College London, 44 207188 6409, 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 A. McGrath, Guy's and St Thomas NHS Foundation Trust, 44 207188 6409, john.mcgrath@kcl.ac.uk
Scientific contact	Professor John A. McGrath, Guy's and St Thomas NHS Foundation Trust, 44 207188 6409, 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 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	12 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 July 2017
Global end of trial reached?	Yes
Global end of trial date	10 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety of allogeneic intravenously administered MSCs in adults with RDEB over a 12-month period

Protection of trial subjects:

Study participants will be instructed that further information can be obtained at any time from the Investigator, and that they are free to withdraw their consent and to discontinue participation in the study at any time without prejudice

Background therapy:

The study subjects can continue to receive their regular medication(s).

Evidence for comparator:

n/a

Actual start date of recruitment	12 June 2015
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: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	10
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Guy“s and St Thomas“ NHS Trust is a local, regional and national referral centre for adults with EB with an extensive database. Trial participants were recruited from this one site during 2017-2017.

Pre-assignment

Screening details:

The screening assessments (V1) will be conducted up to 200 days prior to Day 0.
Inclusion Criteria
1) Individuals with a diagnosis of RDEB confirmed by DNA analysis.
2) Individuals 18 years of age or above, and under the age of 65, both male and female
3) Individuals that have voluntarily signed and dated an informed consent form (ICF) prior to

Period 1

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

Blinding implementation details:

Phase I/II, non-randomised, open-label trial.

Arms

Arm title	Full study

Arm description:

8 visits over 12 months are planned for the first eight eligible patients, and over 8 months for the last two eligible patients. Each study subject will receive two intravenous infusions (day 0 and day 14).

Arm type	Experimental
Investigational medicinal product name	TC-MSC (mesenchymal stem cells)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

TC-MSC (mesenchymal stem cells received two intravenous infusions (day 0 and day 14).

Number of subjects in period 1	Full study
Started	10
Completed	9
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	10	10	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	5	5	
Male	5	5	

End points

End points reporting groups

Reporting group title	Full study

Reporting group description:

8 visits over 12 months are planned for the first eight eligible patients, and over 8 months for the last two eligible patients. Each study subject will receive two intravenous infusions (day 0 and day 14).

Primary: Safety

End point title	Safety[1]

End point description:

Lack of serious and severe adverse events (SAEs) related to the administration of the investigational medicinal product over a 8 or a 12 month period. SAEs are defined as any occurrence related to the administration of the IMP that results in death, or is life threatening or requires hospitalization or prolongation of existing hospitalization.

End point type	Primary

End point timeframe:

Up to 12 months post first infusion

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: See attached document for all results and charts for both primary and secondary endpoints.

End point values	Full study			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: whole	9			

Attachments (see zip file)	RESULTS/ADSTEM Final Study Report V1 5Jul18.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoints

End point title	Secondary Endpoints

End point description:

1. Presence of new type VII collagen at the dermal-epidermal junction post treatment on Day 28, Day 60, and Month 6.
2. Changes in general markers of inflammation at Day 14, Day 28, Day 60, Day 100, Month 6 (for all patients) and Month 12 (for the first eight eligible patients) or Month 8 (for the last two eligible patients) compared to baseline.
3. Changes in specific markers of inflammation on Day 14, Day 28, Day 60 and Month 6 compared to baseline using ELISA and LUMINEX platforms. Specific inflammatory markers include: HMGB-1, TNF α, IFN γ, IL-17A, IL1 β, IL-10, MMP-2, MMP-9, MMP-11 and TIMP-1.
4. Changes in the clinical appearance of the skin assessed with clinical photographs
5. Differences in quality of life data at Day 28, Day 60, Day 100, Month 6 (for all patients) and Month 12 (for the first eight eligible patients) or Month 8 (for the last two eligible patients) compared to baseline.
6 Changes in BEBSS & EBDASI scores at Day 28 60 100 & month 6 & 12 (8 for final 2 pts)

End point type	Secondary

End point timeframe:

Up to 12 months post first infusion

End point values	Full study			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: whole	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoints continued

End point title	Secondary Endpoints continued

End point description:

Change in pruritus score using the Leuven Itch Scale (LIS) at Day 28, Day 60, Day 100, Month 6 (for all patients) and Month 12 (for the first eight eligible patients) or Month 8 (for the last two eligible patients) compared to baseline.
8. Quantification of total blister numbers over the entire body surface area at Day 28, Day 60, Day 100, Month 6 (for all patients) and Month 12 (for the first eight eligible patients) or Month 8 (for the last two eligible patients) compared to baseline.
9. Increase in the skin strength measured by time to blister formation after negative pressure skin suction test at Day 28, Day 60, Day 100, Month 6 (for all patients) and Month 12 (for the first eight eligible patients) or Month 8 (for the last two eligible patients) compared to baseline

End point type	Secondary

End point timeframe:

Up to 12 months post infustion

End point values	Full study			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: whole	9			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 months post first infustion for the first 8 participants and 8 months post first infusion for the final 2 participants.

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	3 / 10 (30.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Skin and subcutaneous tissue disorders			
Squamous cell carcinoma (SCC) lower leg	Additional description: Squamous cell carcinoma identified on lower leg of two patients - both admitted to hospital for excision of SCC. Classed as important medical event (disease progression) bet met SAE criteria due to hospitalization of more than 24 hours		
subjects affected / exposed	2 / 10 (20.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Deranged renal funcion			
subjects affected / exposed	1 / 10 (10.00%)		
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	3 / 10 (30.00%)		
General disorders and administration site conditions			

Nightmares			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Loose & frequent stools	Additional description: Known history of IBS		
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Skin infection affecting back			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Infections and infestations			
Sore Throat			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Ear Infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Chest Infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2015	• A change to the exclusion criteria, to exclude subjects with both a) positive C7 ELISA and b) a positive indirect immunofluorescence (IIF) with binding to the base of salt split skin. • The removal of a secondary end point relating to quality of life data, which will now be captured as part of a nested study with an independent application to an Ethics Committee. • A new secondary end point to perform flow cytometry to evaluate the cytotoxic T-cell signature at 24 to 48 hours post first infusion. This will involve an optional blood test and for all patients who partake in this an additional visit will be required, which has also been added to the protocol (visit 2a). • The number of skin biopsies have also been reduced from 6 to 4, so the visit schedule has been updated accordingly to reflect these changes and a new table has been included in v3.0 to make the procedures per visit easier to see. • The removal of the data monitoring committee section as this study only has a trial steering committee. • The statistics section has been updated to explain that attempts will be made to replace patients that do not completed at least 6 months of the trial and No interim analysis will now be performed.
27 January 2016	It includes a change to one of the inclusion criteria, as highlighted below: Protocol v3.0 wording: 'Individuals with a diagnosis of RDEB confirmed by DNA analysis and skin immunofluorescence for partial or complete absence of type VII collagen.' Protocol v4.0 New wording: 'Individuals with a diagnosis of RDEB confirmed by DNA analysis.'
03 April 2017	The protocol has been amended to change the conduct and management of the trial by removing visit 2a and reducing the follow up for the final two patients in the trial from 12 to 8 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported