

**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  $0.8\text{--}1.2 \times 10^6$  cells suspended in 0.25ml of 0.9% saline, will be administered intradermally into 1cm<sup>2</sup> 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:

| <b>Subjects enrolled per age group</b>    |   |
|---|---|
| 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 dose of 0.8–1.2 million cells suspended in 0.25ml of 0.9% saline per injection over 1 cm<sup>2</sup> of intact skin (3 intradermal injections of IMP at a single timepoint). Patients were followed up for 12 months post injection.

### Arms

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | 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

|                                       |           |
|---------------------------------------|-----------|
| <b>Number of subjects in period 1</b> | 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:<br>Patients treated with SIN LV-mediated ex vivo transduced autologous fibroblasts expressing codon-optimised COL7A1. |           |

### Primary: Adverse Events

|  |                               |
|--|-------------------------------|
| End point title  | Adverse Events <sup>[1]</sup> |
| End point description:<br>Adverse events (AEs) at each visit after screening over a 12month follow-up period |                               |
| End point type   | Primary                       |
| End point timeframe:<br>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 <sup>[2]</sup> |  |  |  |
| 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 <sup>[3]</sup> |
| End point description:<br>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:<br>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 <sup>[4]</sup> |  |  |  |
| 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 Events

|                 |                                       |
|-----------------|---------------------------------------|
| End point title | Serious Adverse Events <sup>[5]</sup> |
|-----------------|---------------------------------------|

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 <sup>[6]</sup> |  |  |  |
| 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 %

| <b>Non-serious adverse events</b>                     | 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<br>subjects affected / exposed<br>occurrences (all)   | 1 / 4 (25.00%)<br>1 |  |  |
| Occasional dizzy spells<br>subjects affected / exposed<br>occurrences (all)   | 1 / 4 (25.00%)<br>1 |  |  |
| Eye disorders<br>Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)                                     | 1 / 4 (25.00%)<br>2 |  |  |
| Sub-conjunctival haemorrhage<br>subjects affected / exposed<br>occurrences (all)  | 1 / 4 (25.00%)<br>1 |  |  |
| Gastrointestinal disorders<br>Dysphagia<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 4 (25.00%)<br>1 |  |  |
| Oesophageal dilation<br>subjects affected / exposed<br>occurrences (all)  | 1 / 4 (25.00%)<br>2 |  |  |
| Oesophageal blisters<br>subjects affected / exposed<br>occurrences (all)  | 1 / 4 (25.00%)<br>1 |  |  |
| Oesophageal spasm<br>subjects affected / exposed<br>occurrences (all)   | 1 / 4 (25.00%)<br>1 |  |  |
| Respiratory, thoracic and mediastinal disorders<br>Coryzal symptoms<br>subjects affected / exposed<br>occurrences (all) | 1 / 4 (25.00%)<br>1 |  |  |
| Dry cough<br>subjects affected / exposed<br>occurrences (all)   | 1 / 4 (25.00%)<br>1 |  |  |
| Skin and subcutaneous tissue disorders<br>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<br>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 haematuria                                |                 |  |  |

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment  |
|---------------|--|
| 10 July 2015  | <ul style="list-style-type: none"><li>• To decrease the duration of follow up from 36mths to 12mths</li><li>• 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</li><li>• 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).</li><li>• 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.</li></ul> |
| 25 April 2016 | The purpose of this amendment secondary endpoints.<br>Amend inclusion/exclusion criteria.<br>Amend IMP administration details to minimise the amount of tattooing to mark the injected sites.  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported