KING'S College LONDON
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Guy's and St Thomas' NHS
NHS Foundation Trust

STATISTICAL ANALYSIS PLAN

LENTICOL-F

Phase I study of lentiviral-mediated *COL7A1* gene-modified autologous fibroblasts in adults with recessive dystrophic epidermolysis bullosa (RDEB).

TRIAL IDENTIFIERS

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APPROVAL

The undersigned hereby declare that they have prepared/examined the Statistical Analysis Plan and agree to its form and content.

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Prof. John McGrath

REVISION HISTORY

Version	Author	Date of Implementation	Description of Modification
1.0	Rachel Phillips/Fiona Reid	28/11/2016	Original version of SAP.

Table of Contents

1 Description of the trial

See protocol for full details.

1.1 Trial objectives

1.1.1 Primary objective

To evaluate the safety of intradermal injections of SIN LV-mediated *COL7A1* gene-modified autologous fibroblasts in adults with recessive dystrophic epidermolysis bullosa (RDEB).

1.1.2 Secondary objectives

i. To evaluate the potential efficacy of intradermal injections of SIN LV-mediated *COL7A1* gene-modified autologous fibroblasts in adults with RDEB at week (W) 2, month (M) 3 and 12 after the IMP injections.

ii. To screen for immune response against the recombinant C7 at W2, M1, M3, M6 and M12 after the IMP injections compared to baseline.

1.2 Trial design

This is a prospective phase 1, non-randomised, open label, single-centre, proof-of-concept study.

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 0.8–1.2x10^6 cells suspended in 0.25ml of 0.9% saline, will be administered intra-dermally into 1cm^2 area of intact skin (x3). Participants will be followed up with study interventions for a 12-month period at various time points as outlined in the trial timeline (Figure 1). All follow-ups, 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 as per the monitoring schedule (Table 1 and Figure 1**)**. 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 it will therefore be possible to capture long-term possible adverse effects related to the IMP.

1.3 Trial timeline

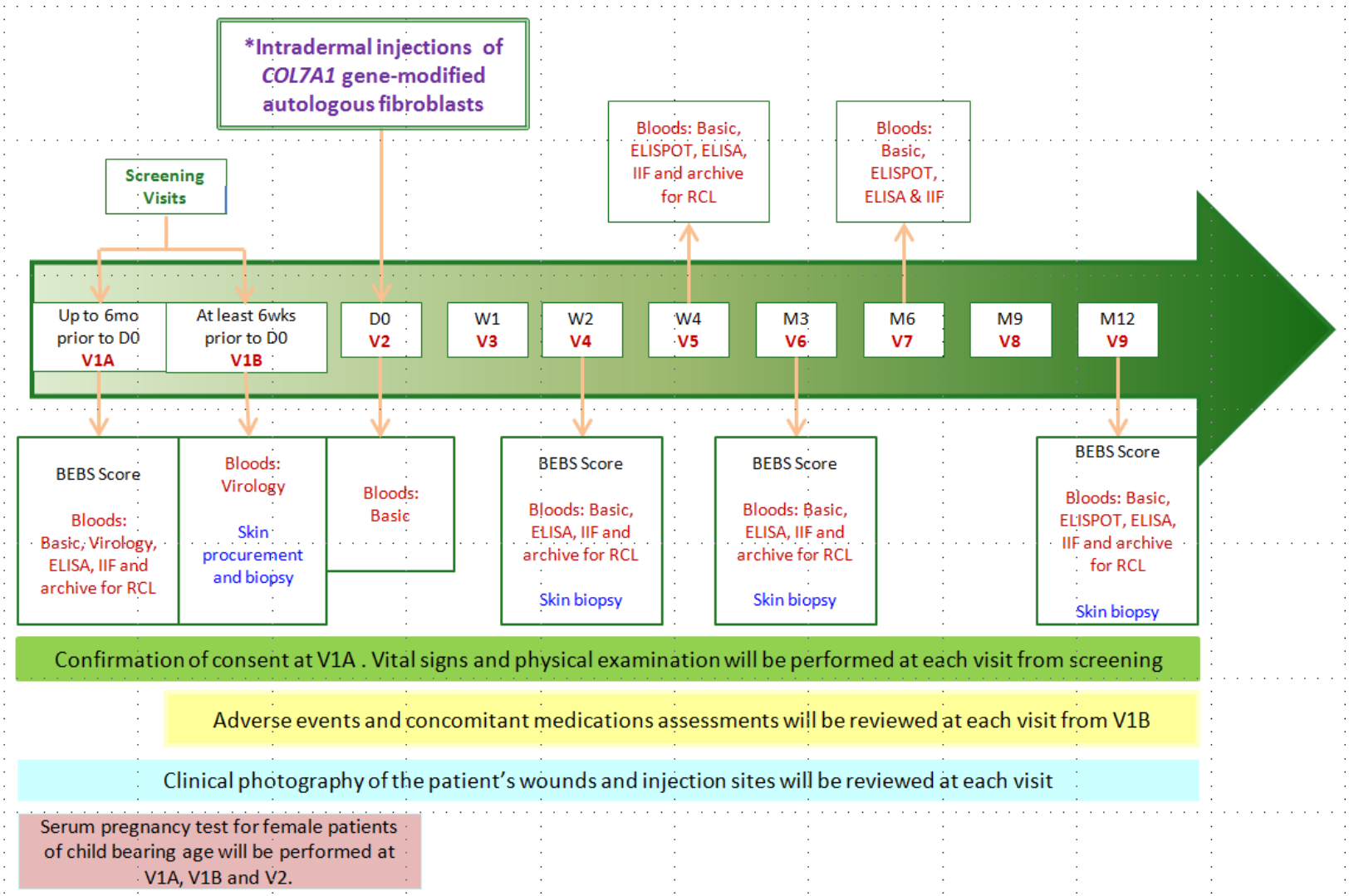


Figure 1: LENTICOL-F trial timeline.

*Each injection consists of 0.8–1.2 million cells suspended in 0.25ml of 0.9% saline. Each of three syringes containing the IMP will be administered over 1 cm^2 area of intact skin. . Virology tests done at V1A & V1B = HIV, HepBsAg, HepBcAb, HepCIgG, HTLV 1&2 and Treponema pallidum serology; Skin procurement and biopsy at V1B = 2 to 3 biopsies (one 6mm procurement for tissue culture for IMP production; and one to two 4mm for C7IF, TEM, qPCR and histology); Skin biopsy @ W2, M3 and M12 = Two 6-8mm biopsies for C7 IF, TEM, qPCR and histology (one from injected site and one from non-injected site). All skin biopsies will be archived for integration site analyses in the rare event of clinically indicated serious adverse events. Pregnancy tests at V1A, V1B and V2: if serum is not obtainable, urine pregnancy test may be performed instead. Historical samples/ results may be used for C7 ELISA & IIF, ELISPOT, C7 IF microscopy & TEM and virology tests.

NB: If W2 and M3 skin biopsy results are negative then M12 biopsy may not be performed.*Abbreviations: BEBS score=Birmingham Epidermolysis Bullosa Severity Score; IMP=Investigational medicinal product.*

1.4 Method of allocation of groups / randomisation procedure

This is a phase 1, non-randomised, single group, proof-of-concept study. All participants will receive the IMP. Therefore method of allocation to groups and randomisation procedure are not applicable.

1.5 Dosing regimen

Each trial participant will receive three intradermal injections of gene-modified autologous fibroblasts on Day 0. Each 1cm^2 of intact skin will be injected with 0.8–1.2x10^6 cells/ 0.25ml of normal saline. Once all 3 syringes are received, they will be injected over 3x1cm^2 areas.

1.6 Visit schedule

Subjects will be required to visit the clinic 10 times in 12 months. The screening assessment visit (V1A) will be conducted up to 6 months prior to D0 – the day of the IMP injections. The timings of the subsequent visits will be relative to D0 (V2) (Table 1). Timing of screening, treatment and follow-up visits are summarised in the trial flowchart and monitoring schedule.

The end of the trial will be defined as the final study participant's last scheduled follow-up visit according to the protocol, which will be the 12 month follow-up visit after the intradermal injections of the IMP of the last subject entering the trial.

1.7 Procedures by visit

Visit number		**V1A**	**V1B**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Timeline of each visit relative to the day of gene-modified fibroblast injections (D0)		Up to 6M prior to D0	At least 6W prior to D0	**D0**	**W1** (±3D)	**W2** (±3D)	**W4** (±14D)	**M3** (±1M)	**M6** (±1M)	**M9** (±1M)	**M12** (±1M)
Approximate duration of each visit (hours)		**2**	**2**	**1.5**	**1.5**	**2**	**1.5**	**2**	**1.5**	**1.5**	**2**
Informed consent		X									
Inclusion / exclusion		X	X								
Demographics		X									
Medical history		X									
Vital signs		X	X	X	X	X	X	X	X	X	X
Physical examination		X	X	X	X	X	X	X	X	X	X
Serum pregnancy test for female participants with child-bearing potential (if serum is not obtainable, urine pregnancy test may be used)		X	X	X							
[a]BEBS Score		X				X		X			X
[b]Clinical photography		X	X	X	X	X	X	X	X	X	X
Blood samples	[c]Basic bloods	X		X		X	X	X	X		X
	[d]Virology	X	X								

Visit number		**V1A**	**V1B**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Timeline of each visit relative to the day of gene-modified fibroblast injections (D0)		Up to 6M prior to D0	At least 6W prior to D0	**D0**	**W1** (±3D)	**W2** (±3D)	**W4** (±14D)	**M3** (±1M)	**M6** (±1M)	**M9** (±1M)	**M12** (±1M)
	C7 ELISA & IIF	X				X	X	X	X		X
	ELISPOT			X			X		X		X
	[e]RCL	X				X	X	X			X
Skin biopsies	C7 IF microscopy & TEM		X			X		X			X
	[f]qPCR		X			X		X			X
	[g]Integration site analysis		X			X		X			X
Skin procurement (1x6mm)	Tissue culture for IMP production		X								
[h]Intradermal injections of IMP				X							
Adverse event(s) assessment			X	X	X	X	X	X	X	X	X
Concomitant medications assessment			X	X	X	X	X	X	X	X	X

Table 1: LENTICOL-F trial flowchart with details of interventions at each visit.

Abbreviations: V=Visit; D=Day; W=Week; M=Month.

Consent will be obtained at each visit. On Day 0, your vital signs will be monitored every 15mins for 30mins after the gene-modified fibroblast injections. There will be one-off readings of the vital signs on the rest of the other visits during the study. Historical samples/ results may be used for C7 ELISA & IIF, ELISPOT, C7 IF microscopy & TEM. Historical virology results performed within the last 3 months may be used. NB: If W2 and M3 skin biopsy results are negative then M12 biopsy may not be performed.

[a]Birmingham Epidermolysis Bullosa Severity Score;

[b]Clinical photography of potential injection sites over an area of the intact skin will be taken at screening on visit 1, post-IMP injections on visit 2 and at each visit thereafter;
[c]Includes FBC, U&Es, LFTs, ESR and CRP;
[d]Includes HIV, HepBcAb, HepBsAg, HepCIgG, HTLV 1&2 and Treponema pallidum serology;
[e]Blood samples will be archived for replication-competent lentivirus (RCL) - may be archived for at least 15 years and analysed in the event of relevant serious adverse reactions (SAEs) as clinically indicated;
[f]Vector copy number and *COL7A1* gene expression will be measured using quantitative polymerase chain reaction (qPCR) and some skin samples retained for integration site analysis in the event of clinically indicated SAEs;
[g]DNA will be extracted from part of the skin biopsy and archived for integration site analysis in the event of relevant adverse reactions as clinically indicated;
[h]Each of 3 intradermal injections of IMP (*COL7A1* gene-modified autologous fibroblasts) will be administered to $1cm^2$ of intact skin

1.8 Long-term follow-up

Patients with RDEB are regularly reviewed, often for life, by the consultant Dermatologists in the multi-disciplinary setting at the regular epidermolysis bullosa (EB) clinics at GSTT, providing opportunities for detection of late adverse events. Once these studies are officially closed, serious events related to the IMP (SARs and SUSARs) will continue to be reported to the MHRA and London – West London & Gene Therapy Advisory Committee (GTAC) in the same way as during the study.

1.9 Selection of participants

The patient population is under the care of the specialist EB team at St John's Institute of Dermatology, GSTT. As a tertiary care centre, patients may have been referred from other regional district hospitals in the first instance. Potential study subjects will be identified from the National EB database that includes patients from both GSTT and nationally and an initial approach made by members of the clinical team. Potential participants may also be recruited from Patient Identification Centres. Study information sheets will be provided and individuals interested will be invited for further consultation and screening, assessed for eligibility, and consented as necessary. All individuals invited to participate in the study will have a minimum of 24 hours to make their decision.

1.10 Inclusion criteria

1. Clinical and genetic diagnosis of RDEB with confirmed bi-allelic *COL7A1* mutations.
2. A reduced number or morphologically abnormal anchoring fibrils confirmed by TEM.
3. At least 5x3cm of intact skin on the trunk and/or extremities that is suitable for cell injections.
4. Able to undergo local anaesthesia.
5. Subjects aged ≥ 17 years and able to give informed consent prior to the first study intervention.

1.11 Exclusion criteria

1. Subjects who received other investigational medicinal products within 6 months prior to enrolment into this study.
2. Past medical history of biopsy proven skin malignancy.
3. Subjects who have received immunotherapy including oral corticosteroids (Prednisolone >1mg/kg) for more than one week (intranasal and topical

preparations are permitted) or chemotherapy within 60 days of enrolment into this study.

4. Known allergy to any of the constituents of the investigational medicinal product (IMP).
5. Subjects with **BOTH**:
    i. positive serum antibodies to C7 confirmed by ELISA **and**
    ii. positive IIF with binding to the base of salt split skin.
6. Subjects with positive results for HIV, Hepatitis B, Hepatitis C, HTLV or Syphilis.
7. Subjects 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.

1.12 Outcome measures

1.12.1 Primary outcome measures

Adverse events (AEs), Serious Adverse Events (SAEs), Adverse Reactions (ARs) and Serious Adverse Reactions (SARs) at each visit after screening over a 12-month follow-up period.

1.12.2 Secondary outcome measures

- Skin biopsy analysis of treated skin at W2, M3 and M12 compared to untreated skin:

    i. C7 protein expression by direct immunofluorescence microscopy (DIF)
        a. C7 IF microscopy
        b. C7 immunofluorescence intensity

    ii. Morphology of anchoring fibrils at the dermal-epidermal junction (DEJ) by transmission electron microscopy (TEM)
        a. Number of anchoring fibrils

    iii. Vector copy number by quantitative polymerase chain reaction (qPCR)

- Serum analysis post-injections compared to baseline for:

iv. Detection of anti-C7 antibodies by enzyme-linked immunosorbent assay (ELISA) (against NC1 and NC2 domains of C7) and indirect immunofluorescence (IIF) at W2, M1, M3, M6 and M12:
    a. C7 ELISA - positive or negative
    b. C7 ELISA value
    c. IIF – positive or negative

v. Detection of T-cell responses to the full length C7 by enzyme-linked immunosorbent spot (ELISPOT) assay at M1, M6 and M12 post-injections.
    a. C7 ELISPOT - positive or negative
    b. C7 ELISPOT value

1.13 Adverse events

Adverse events and concomitant medications will be reviewed at every visit after V1A. Clinical photographs will be taken at each visit in order to monitor changes in the injection sites especially with regards to any suspicious lesions or adverse reactions locally. If suspicious lesions are detected then, the participant will be immediately assessed and managed by a consultant dermatologist and if found malignant then, the lesion will be excised as per GSTT guidelines. Physical examination and vital signs will be performed at every visit in order to assess any potential systemic adverse effects and treated as appropriate as per GSTT guidelines.

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Investigator's Brochure (IB) relating to the trial in question (for any other investigational product).

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

- Results in death;
- Is life-threatening;

- Required hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect.

Suspected Unexpected Serious Adverse Reaction (SUSAR): Is defined as a serious adverse drug reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the IB relating to the trial in question, and which results in any of the outcomes set above.

Important Medical Events (IME) & Pregnancy: Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system (please see protocol version 4.0, section 9.4 for more details).

- Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

1.13.1 Reporting responsibilities

Please see protocol version 4.0, section 9.4 for detailed reporting responsibilities.

Adverse Events and Serious Adverse Events that do not require reporting

The following will not require reporting although will be documented on the eCRF and will be included in the primary outcome.

Adverse event as a result of venesection and cannulation include:

i) Mild bruising at site of needle puncture

Adverse event as a result of the skin biopsy include:

i) Mild bruising at the site of the skin biopsy
ii) Cutaneous skin infection requiring oral course of antibiotics
A small scar will result after each skin biopsy, resembling an old chickenpox scar.

All hospitalisations which are expected to take place as a result of disease progression including any planned elective surgeries will not be documented on the eCRF and will not be reported at the interim and the end-of-trial safety data analysis however they will be documented in the patient notes. This may include but not limited to:

- Skin
    - Skin infection
    - Review of a wound
    - Skin blisters/ erosions as part of EB wound
- Teeth

  - Dental extractions/ abscess
- Hand
  - Hand surgery
  - De-gloving injury
  - Occupational Therapy review and splints
- Transfusions
- Overnight hospital stay for reviews
- Blood monitoring, routine blood tests
- Corneal abrasions
- Eye Infections
- Chronic eye problems due to EB
- Gastrointestinal problems
  - Dysphagia, oesohageal stricture and dilation
  - Gastrostomy insertion, leakage or blockage/ jejunal tube insertion leakage/ blockage
  - Regurgitation or vomiting as a result of oesophageal blisters/ stricture
  - NG tube insertion
  - Constipation
- Vertebral or other fractures
- IV bisphosphonates
- IV iron infusion
- Contractures requiring physiotherapy
- Hydrotherapy
- ENT
  - Tonsillitis
  - Otitis externa
  - Otitis media
- Pain
  - pain assessment for acute or chronic pain
  - pain from ongoing EB wounds
- Accidental injuries causing minor skin wounds

Thus, any hospitalisation that is not associated with the IMP will not be reported, unless the IMP results in a prolongation of existing hospitalisation. Unscheduled and/or emergency hospitalisations that are not expected due to the natural course of the disease will be reported via the sponsor's normal serious adverse event (SAE) reporting practice. AEs will be reviewed at each visit both from the patient's report as well as documentation from medical notes.

1.14 Sample size

The aim of this phase 1 trial will be to recruit approximately 5–10 patients from GSTT EB clinical database. This is a rare disease with an incidence of 1 in 17,000 live births. As per our statistician's advice, even if no subjects experienced adverse reactions (i.e. 0% AR), a sample size of 10 would give a 95% confidence interval of 0% to 31% (exact CI from Stata®). A sample of 10 could still potentially provide reassurance that no more than 3 in 10 subjects should experience a given side-effect.

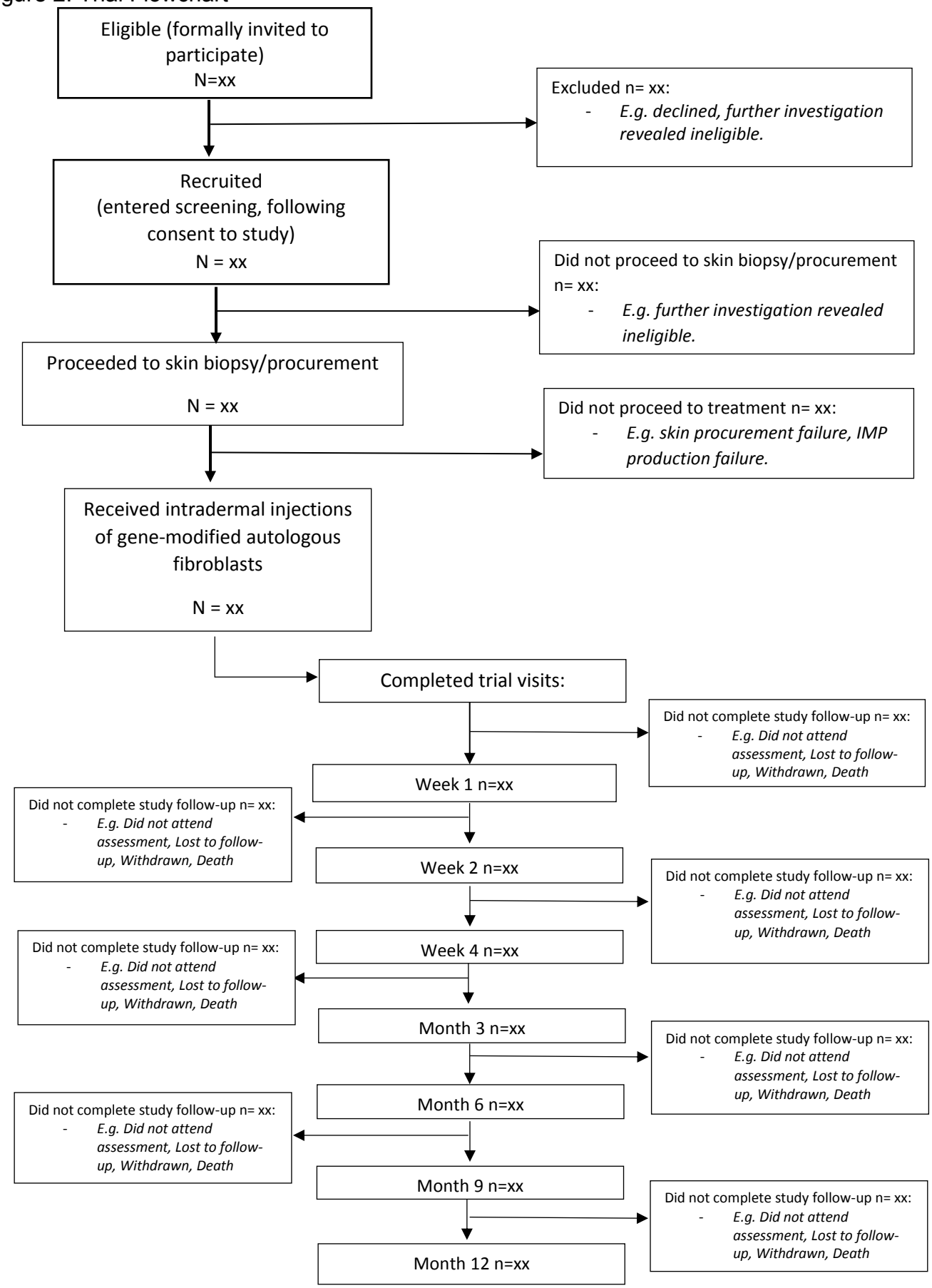
2 Data analysis plan

2.1 Recruitment of patients

A flow chart in accordance with the requirements of the CONSORT statement will be presented (Figure 2). This will include the number of eligible patients formally invited to participate in the study, number of patients agreeing to enter the trial, the number who proceed to skin biopsy/procurement, the number of patients receiving treatment (intradermal injections of gene-modified autologous fibroblasts) and the number of patients, with reasons, not proceeding to the next stage. It will also include the number of patients who complete each visit, and the number not completing (including those not completing due to withdrawal, loss to follow-up, and death).

A table of the number of patients consenting to enter the trial, the number who proceed to skin biopsy/procurement and the number of patients receiving treatment (intradermal injections of gene-modified autologous fibroblasts) will be presented by month (appendix - table 2). A table of visit completion status for each patient will be reported, including date enrolled (appendix - table 3).

Figure 2: Trial Flowchart



2.2 Baseline characteristics

The baseline characteristics of each patient will be reported, including demographics and clinical characteristics (appendix - table 4).

2.3 Treatment delivery

The number of patients who receive treatment will be reported (appendix - table 2).

Treatment related characteristics such as site of treatment and cell numbers injected will be summarised for each patient (appendix - table 5).

2.4 Loss to follow-up

The reasons for withdrawal from the trial will be reported (Figure 2).

All study participants will be included in all analyses unless they have withdrawn consent. For subjects who drop out rather than withdraw consent, a request will be made to use data collected prior to drop-out.

2.5 Adverse event reporting (primary outcome)

Adverse events (AE), serious adverse events (SAE) and serious adverse reactions (SAR) as specified in the protocol will be reported to the data monitoring committee (DMC). Total number of events (AE, SAE, SUSAR and SARs) and number of patients experiencing at least one of each event (AE, SAE, SUSAR and SARs) will be tabulated (appendix - table 6). Individual listings of all adverse events will also be presented (appendix - table 7).

2.6 Descriptive statistics for secondary outcomes

Means (or medians) and ranges will be reported for continuous outcomes and frequencies will be reported for categorical outcomes.

2.7 Comparative analyses for secondary outcomes

2.7.1 Skin biopsy

Skin biopsy results will be compared between treated skin and untreated skin at each of W2, M3 and M12, for the following variables:

- C7 protein expression by direct immunofluorescence microscopy (DIF)
  a. C7 IF microscopy

b. C7 immunofluorescence intensity

- Morphology of anchoring fibrils at the dermal-epidermal junction (DEJ) by transmission electron microscopy (TEM)
  a. Number of anchoring fibrils

- Vector copy number by quantitative polymerase chain reaction (qPCR)

No hypothesis tests will be performed. Individual listings of all outcomes will be presented (appendix - table 8, 9 and 10). For continuous outcomes, differences in means or medians will be presented. For categorical outcomes, frequencies will be presented for descriptive purposes only (appendix - table 11).

Additionally graphical representations of continuous outcome measures for each patient at different time points will be presented.

2.7.2 Serum test

Serum test results at various time-points post-injections will be compared to baseline, for the following variables:

- Detection of anti-C7 antibodies by enzyme-linked immunosorbent assay (ELISA) (against NC1 and NC2 domains of C7) and indirect immunofluorescence (IIF) at W2, M1, M3, M6 and M12 post-injections:
  a. C7 ELISA - positive or negative
  b. Number of C7 ELISA
  c. IIF – positive or negative

- Detection of T-cell responses to the full length C7 by enzyme-linked immunosorbent spot (ELISPOT) assay at M1, M6 and M12 post-injections:
  a. C7 ELISPOT - positive or negative
  b. Number of C7 ELISPOT

No hypothesis tests will be performed. Individual listings of all outcomes will be presented (appendix - table 12, 13 and 14). For continuous outcomes, differences in means or medians will be presented. For categorical outcomes, frequencies will be presented for descriptive purposes only (appendix - table 15).

Additionally graphical representations of continuous outcome measures for each patient at different time points will be presented.

2.8 Interim and final analyses

Adverse events will be monitored throughout the trial by the data monitoring committee (DMC). (See DMC charter)

When all participants complete Visit 7 (Month 6), an interim analysis of the collected data will be performed. There will be another analysis at the end of the trial (12 months after the last participant's cell injections).

2.9 Software

Data management: the BRC secure data management system MedScinet will be used.

Statistical analysis: Stata version 13.1 (Stata Corp LP, Texas, US) or later, will be used for data description and analysis.

Appendix

LIST OF TABLES

Table 2: Summary of recruitment and treatment, by month

Month	**Recruited***	**Skin biopsy/procurement performed**	**Treated**
2015:			
September	xx	xx	xx
October	xx	xx	xx
November	xx	xx	xx
December	xx	xx	xx
2016:			
January	xx	xx	xx
…			
…			
…			
Total			

* Recruited – i.e. consented into screening

Table 3: Study visits completed per patient

Visit Number		**V1A**	**V1B**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Timeline of each visit relative to the day of gene-modified fibroblast injections (D0)		**Up to 6M3 prior to D0**	**<3W after 1A**	**D0**	**W1** (±3D)	**W2** (±3D)	**W4** (±14D)	**M3** (±1M)	**M6** (±1M)	**M9** (±1M)	**M12** (±1M)
Patient ID	**Date recruited (V1A)** dd/mm/yyyy										
001		X	X	…							
002											
003											
004											
005											
006											
007											
008											
009											
010											

Note: X indicates a completed study visit

Notation:V1A – Screening (up to 6 months prior to treatment day: Day 0); V1B – Screening and skin procurement (<3 weeks after V1A); V2 (D0) – Intradermal injections of gene-modified autologous fibroblasts; V3 (W1) – 1 week after the injections ± 3 days; V4 (W2) – 2 weeks after the injections ± 3 days; V5 (W4) – 4 weeks after the injections ± 14 days; V6 (M3) – 3 months after the injections ± 1 month; V7 (M6) – 6 months after the injections ± 1 month; V8 (M9) – 9 months after the injections ± 1 month; V9 (M12) – 12 months after the injections ± 1 month

Table 4: Baseline demographic and clinical characteristics per patient

		Patient ID									
		001	**002**	**003**	**004**	**005**	**006**	**007**	**008**	**009**	**010**
Demographics											
Age (years)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Sex (Male/Female)											
Ethnicity											
BMI (kg/m2)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
RDEB characteristics											
Type of RDEB[1]											
COL7A1 mutations											
C7 immunofluorescence											
	C7 IF microscopy[2]										
	C7 MII ± SE[3]	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x
Anchoring fibrils											
	AF number ± SE[4]	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x	xx.x ±xx.x
	Integrity (free text)										
Vector copy number		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
BEBSS		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Immune profile											
C7 IIF											
	(Pos/Neg)										
C7 ELISA											
	(Pos/Neg)										
	Titres (U)	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
C7 ELISPOT											
	(Pos/Neg)										
	Number of spots	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Patient Clinical Information											
Suitable site for injections											
Significant co-morbidities											
Blood test results											
Hb (g/L)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
MCV (fl)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
WCC ($x10^9$)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Neutrophils (g/L)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Platelets ($x10^9$ g/L)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
CRP (mg/L)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
ESR (mm/hr)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Sodium (mmol/L)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Potassium (mmol/L)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Creatinine (g/L)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Bilirubin (µmol/L)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
ALP (iu/L)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
ALT (iu/L)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Albumin (g/L)		xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Acronyms: RDEB=recessive dystrophic epidermolysis bullosa; IF= immunofluorescence; MII= mean immunofluorescence intensity; SE=standard error; AF=anchoring fibrils; BEBSS=Birmingham epidermolysis bullosa severity score (0-100); IIF=indirect immunofluorescence; ELISA= enzyme-linked immunosorbent assay; ELISPOT=enzyme-linked immunosorbent spot; Hb=Haemoglobin; MCV=mean corpuscular volume;

WCC=White cell count; CRP=C-reactive protein; ESR=Erythrocyte sedimentation rate; ALP=alkaline phosphatase; and ALT=alanine aminotransferrase.

[1]Type of RDEB: *GS=Generalised severe, GI=Generalised intermediate, In=Inversa, Lo=Localised, PT=Pretibial, Pru=Pruriginosa, Cen=Centripetalis, BDNB=Bullous dermolysis of the new born*.

[2]C7 IF microscopy: CD=Complete deficiency, PD=Partial deficiency, ND=No deficiency.

[3]C7 MII ± SE = Type VII collagen mean immunofluorescence intensity ± standard error

[4]AF ± SE = anchoring fibrils ± standard error

Note: All baseline values are taken from visits 1A or 1B which are up to 6 months and 6 weeks prior to administration of IMP, respectively. With the exception of the ELISPOT values which are taken at visit 2 prior to administration of the IMP.

Table 5: Treatment related data per patient

Patient ID	Time from treatment of previous patient (days)	Date of treatment	Site of treatment	Cell numbers injected in Square 1 ($x10^6$ cells in 0.25ml of 0.9% saline)	Cell numbers injected in Square 2 ($x10^6$ cells in 0.25ml of 0.9% saline)	Cell numbers injected in Square 3 ($x10^6$ cells in 0.25ml of 0.9% saline)
001	xx	dd/mm/yyyy		xx.x	xx.x	xx.x
002						
003						
004						
005						
006						
007						
008						
009						
010						

Table 6: Summary of adverse events and reactions, including SAEs

		Number of events nAE	**Number of patients** n
Overall			
Adverse events (AE)		xx	xx
Serious adverse events (SAE)		xx	xx
	Suspected unexpected serious adverse reactions (SUSAR)	xx	xx
	Serious adverse reactions (SAR)	xx	xx
Severity Grade[1]			
	1	xx	xx
	2	xx	xx
	3	xx	xx
	4	xx	xx
	5	xx	xx

NOTE: nAE = number of adverse events (or SAE/SUSAR/SAR); n =number of patients experiencing at least one event.

[1] **Severity grade**: 1=mild: awareness of signs or symptoms, but easily tolerated; 2=moderate: uncomfortable enough to cause interference with usual activity; 3=severe: incapacity with inability to work or do usual activity; 4=life-threatening; 5=death.

Table 7: Adverse events and reactions, including SAEs, per patient

Patient ID	**Event**	**Days from treatment to onset**	**Start date**dd/mm/yyyy	**End date**dd/mm/yyyy	**Serious?[1] Y/N**	**Severity Grade[2] (1-5)**	**Causality[3]**	**Outcome[4]**	**Treatment (free text)**	**Medications received if any**

[1] **Serious:** yes/no. *NOTE: If yes, qualifies an AE/R as Serious (SAE/R)*
[2]**Severity grade:** 1=mild: awareness of signs or symptoms, but easily tolerated; 2=moderate: uncomfortable enough to cause interference with usual activity; 3=severe: incapacity with inability to work or do usual activity; 4=life-threatening; 5=death;
[3]**Causality:** unlikely to be related / possibly related / probably related / definitely related. *NOTE: Causality of 'possibly' or greater qualifies an AE as an Adverse Reaction (AR*).
[4]**Outcome:** fully recovered/recovered with sequelae/no recovery/fatal

Table 8: Type VII collagen immunofluorescence microscopy and mean immunofluorescence intensity ± standard error from skin biopsies per patient

		Baseline	Week 2		Month 3		Month 12	
Patient ID	C7 IF		**Treated**	**Untreated**	**Treated**	**Untreated**	**Treated**	**Untreated**
001	Microscopy[1]							
	Intensity[2]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
002	Microscopy[1]							
	Intensity[2]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
003	Microscopy[1]							
	Intensity[2]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
004	Microscopy[1]							
	Intensity[2]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
005	Microscopy[1]							
	Intensity[2]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
006	Microscopy[1]							
	Intensity[2]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
007	Microscopy[1]							
	Intensity[2]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
008	Microscopy[1]							
	Intensity[2]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
009	Microscopy[1]							
	Intensity[2]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
010	Microscopy[1]							
	Intensity[2]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x

Acronyms: IF= immunofluorescence.
[1]C7 IF microscopy: CD=Complete deficiency, PD=Partial deficiency, ND=No deficiency.

[2]C7 MII ± SE = Type VII collagen mean immunofluorescence intensity ± standard error

Table 9: Morphology of anchoring fibrils at the dermal-epidermal junction (DEJ) by transmission electron microscopy (TEM): anchoring fibrils ± standard error and integrity from skin biopsies per patient

		Baseline	Week 2		Month 3		Month 12	
Patient ID			**Treated**	**Untreated**	**Treated**	**Untreated**	**Treated**	**Untreated**
001	AF number[1]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
	Integrity							
002	AF number[1]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
	Integrity							
003	AF number[1]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
	Integrity							
004	AF number[1]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
	Integrity							
005	AF number[1]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
	Integrity							
006	AF number[1]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
	Integrity							
007	AF number[1]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
	Integrity							
008	AF number[1]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
	Integrity							
009	AF number[1]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
	Integrity							
010	AF number[1]	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x	xx.x ± xx.x
	Integrity							

Acronyms: AF= anchoring fibrils.

[1]AF ± SE = anchoring fibrils ± standard error.

Table 10: Vector copy number by quantitative polymerase chain reaction (qPCR) from skin biopsies per patient

	Baseline	Week2		Month 3		Month 12	
Patient ID		**Treated**	**Untreated**	**Treated**	**Untreated**	**Treated**	**Untreated**
001	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
002	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
003	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
004	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
005	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
006	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
007	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
008	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
009	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
010	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Table 11: Summary of changes between treated and untreated skin – skin biopsy outcomes

		Treated skin	Untreated skin
		N	N
C7 IF microscopy			
Baseline			
	Complete deficiency	xx	
	Partial deficiency	xx	
	No deficiency	xx	
Week 2			
	Complete deficiency	xx	xx
	Partial deficiency	xx	xx
	No deficiency	xx	xx
Month 3			
	Complete deficiency	xx	xx
	Partial deficiency	xx	xx
	No deficiency	xx	xx
Month 12			
	Complete deficiency	xx	xx
	Partial deficiency	xx	xx
	No deficiency	xx	xx
C7 mean immunofluorescence intensity			
Baseline, mean (range)		xx.x (xx.x, xx.x)	
W2, mean (range)		xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Change from W2 to baseline			
	Mean (range)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
	Difference	xx.x	
M3, mean (range)		xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Change from M3 to baseline			
	Mean (range)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
	Difference	xx.x	
M12, mean (range)		xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Change from M12 to baseline			
	Mean (range)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
	Difference	xx.x	
Morphology of anchoring fibrils at the dermal-epidermal junction (DEJ) by transmission electron microscopy (TEM)			
Number of anchoring fibrils			
Baseline, mean (range)		xx.x (xx.x, xx.x)	
W2, mean (range)		xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Change from W2 to baseline			
	Mean (range)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
	Difference	xx.x	
M3, mean (range)		xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Change from M3 to baseline			
	Mean (range)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
	Difference	xx.x	
M12, mean (range)		xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Change from M12 to baseline			
	Mean (range)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
	Difference	xx.x	

Vector copy number by quantitative polymerase chain reaction (qPCR)			
Baseline, mean (range)		xx.x (xx.x, xx.x)	
W2, mean (range)		xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Change from W2 to baseline			
	Mean (range)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
	Difference	xx.x	
M3, mean (range)		xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Change from M3 to baseline			
	Mean (range)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
	Difference	xx.x	
M12, mean (range)		xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Change from M12 to baseline			
	Mean (range)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
	Difference	xx.x	

Acronyms: IF= immunofluorescence.

Table 12: Detection of anti-C7 antibodies by enzyme-linked immunosorbent assay (ELISA) (against NC1 and NC2 domains of C7) from serum analysis per patient

		Baseline	Week 2	Month 1	Month 3	Month 6	Month 12
Patient ID							
001	C7 ELISA[1]						
	C7 titre	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
002	C7 ELISA[1]						
	C7 titre	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
003	C7 ELISA[1]						
	C7 titre	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
004	C7 ELISA[1]						
	C7 titre	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
005	C7 ELISA[1]						
	C7 titre	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
006	C7 ELISA[1]						
	C7 titre	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
007	C7 ELISA[1]						
	C7 titre	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
008	C7 ELISA[1]						
	C7 titre	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
009	C7 ELISA[1]						
	C7 titre	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
010	C7 ELISA[1]						
	C7 titre	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

Acronyms: ELISA= enzyme-linked immunosorbent assay.
[1] C7 ELISA: positive, negative.

Table 13: Detection of anti-C7 antibodies by indirect immunofluorescence (IIF) from serum analysis per patient

		Baseline	Week 2	Month 1	Month 3	Month 6	Month 12
Patient ID							
001	C7 IIF[1]						
002	C7 IIF[1]						
003	C7 IIF[1]						
004	C7 IIF[1]						
005	C7 IIF[1]						
006	C7 IIF[1]						
007	C7 IIF[1]						
008	C7 IIF[1]						
009	C7 IIF[1]						
010	C7 IIF[1]						

Acronyms: IIF=indirect immunofluorescence.
[1] C7 IIF: positive, negative.

Table 14: Detection of T-cell responses to the full length C7 by enzyme-linked immunosorbent spot (ELISPOT) assay from serum analysis per patient

		Baseline	Month 1	Month 6	Month 12
Patient ID					
001	C7 ELISPOT[1]				
	No. of spots	xx.x	xx.x	xx.x	xx.x
002	C7 ELISPOT[1]				
	No. of spots	xx.x	xx.x	xx.x	xx.x
003	C7 ELISPOT[1]				
	No. of spots	xx.x	xx.x	xx.x	xx.x
004	C7 ELISPOT[1]				
	No. of spots	xx.x	xx.x	xx.x	xx.x
005	C7 ELISPOT[1]				
	No. of spots	xx.x	xx.x	xx.x	xx.x
006	C7 ELISPOT[1]				
	No. of spots	xx.x	xx.x	xx.x	xx.x
007	C7 ELISPOT[1]				
	No. of spots	xx.x	xx.x	xx.x	xx.x
008	C7 ELISPOT[1]				
	No. of spots	xx.x	xx.x	xx.x	xx.x
009	C7 ELISPOT[1]				
	No. of spots	xx.x	xx.x	xx.x	xx.x
010	C7 ELISPOT[1]				
	No. of spots	xx.x	xx.x	xx.x	xx.x

Acronyms: ELISPOT=enzyme-linked immunosorbent spot.
[1] C7 ELISPOT: positive, negative.

Table 15: Summary of baseline to post-treatment changes – serum analysis outcomes

			Baseline to post-treatment difference
Detection of anti-C7 antibodies by enzyme-linked immunosorbent assay (ELISA) (against NC1 and NC2 domains of C7) and indirect immunofluorescence (IIF)			
C7 ELISA	**Positive N**	**Negative N**	
Baseline	xx	xx	-
Week 2	xx	xx	-
Month 1	xx	xx	-
Month 3	xx	xx	-
Month 6	xx	xx	-
Month 12	xx	xx	-
C7 ELISA titre			
Baseline, mean (range)	xx.x (xx.x, xx.x)		-
Week 2, mean (range)	xx.x (xx.x, xx.x)		xx.x (xx.x, xx.x)
Month 1, mean (range)	xx.x (xx.x, xx.x)		xx.x (xx.x, xx.x)
Month 3, mean (range)	xx.x (xx.x, xx.x)		xx.x (xx.x, xx.x)
Month 6, mean (range)	xx.x (xx.x, xx.x)		xx.x (xx.x, xx.x)
Month 12, mean (range)	xx.x (xx.x, xx.x)		xx.x (xx.x, xx.x)
C7 IIF	**Positive N**	**Negative N**	
Baseline	xx	xx	-
Week 2	xx	xx	-
Month 1	xx	xx	-
Month 3	xx	xx	-
Month 6	xx	xx	-
Month 12	xx	xx	-
Detection of T-cell responses to the full length C7 by enzyme-linked immunosorbent spot (ELISPOT) assay			
C7 ELISPOT	**Positive N**	**Negative N**	
Baseline	xx	xx	-
Month 1	xx	xx	-
Month 6	xx	xx	-
Month 12	xx	xx	-
Number of spots			
Baseline, mean (range)	xx.x (xx.x, xx.x)		-
Month 1, mean (range)	xx.x (xx.x, xx.x)		xx.x (xx.x, xx.x)
Month 6, mean (range)	xx.x (xx.x, xx.x)		xx.x (xx.x, xx.x)
Month 12, mean (range)	xx.x (xx.x, xx.x)		xx.x (xx.x, xx.x)

Acronyms: ELISA= enzyme-linked immunosorbent assay; IIF=indirect immunofluorescence; and ELISPOT=enzyme-linked immunosorbent spot.