
Article:
Bageta, M.L., Lopez-Balboa, P., Bursnall, M. et al. (2025) Mesenchymal stromal cell infusions of umbilical cord-derived mesenchymal stromal cells in children with recessive dystrophic epidermolysis bullosa (MissionEB): a randomised, double-blind, placebo controlled, crossover, phase 3 trial with an internal phase 1 dose de-escalation phase. EClinicalMedicine, 88. 103417. ISSN: 2589-5370

https://doi.org/10.1016/j.eclinm.2025.103417

Mesenchymal stromal cell infusions of umbilical cord-derived mesenchymal stromal cells in children with recessive dystrophic epidermolysis bullosa (MissionEB): a randomised, double-blind, placebo controlled, crossover, phase 3 trial with an internal phase 1 dose de-escalation phase

Maria L. Bageta,[a,e,f] Pablo Lopez-Balboa,[a,e,f] Matt Bursnall,[b] Rachel Glover,[b] Kate Hutchence,[b] Diana Papaioannou,[b] Katie Biggs,[b] Steven Julious,[b] Isabelle Wilson,[b] Paul Tappenden,[b] Emily Turton,[b] Shamila Ditta,[b] Malobi Ogboli,[c] Marie-Louise Lovgren,[c] Pratima Poudel,[c] Muna Nadeem,[c] John A. McGrath,[d] Cindy Cooper,[b] Gabriela Petrof,[a] and Anna E. Martinez[a,*]

[a]Dermatology Department, Great Ormond Street Hospital NHS Foundation Trust, London, UK
[b]Clinical Trials Research Unit, Sheffield Centre for Health and Related Research (SCHARR), School of Medicine and Population Health, The University of Sheffield, Sheffield, UK
[c]Dermatology Department, Birmingham Women's and Children's Hospital, Birmingham, UK
[d]St John's Institute of Dermatology, King's College London, London, UK

eClinicalMedicine
2025;■: 103417
Published Online XXX
https://doi.org/10.1016/j.eclinm.2025.103417

Summary

Background Recessive dystrophic epidermolysis bullosa (RDEB) is a rare genetic disorder characterised by extensive mucocutaneous blistering. This study aimed to generate evidence to inform commissioning decisions on umbilical cord-derived mesenchymal stromal cells, UC-MSCs, (CORDStrom™) for RDEB.

Methods In this double-blinded, randomised (1:1), placebo-controlled, two-period crossover phase 3 trial, children aged 6 months to 16 years of age with RDEB were enrolled at two UK specialist centres for epidermolysis bullosa (EB). Individuals were excluded if they had received oral or topical corticosteroids for more than 7 consecutive days within 30 days of enrolment into this study, excluding oral viscous budesonide and inhaled fluticasone used as prophylaxis to relieve oesophageal symptoms, an active infection that required treatment with oral or intravenous antibiotics within 7 days of screening, medical history or evidence of active malignancy, the presence of both positive collagen VII ELISA and a positive indirect immunofluorescence (IIF) with binding to the base of salt split skin, administration of MSCs from any source in the previous 9 months and participation in any other interventional trial within 3 months of enrolment into this study. This trial included an internal dose de-escalation (IDD) phase for safety gatekeeping. During IDD, 4 participants were randomised (3:1) to receive two infusions (2–3 × 10^6 cells/kg/infusion or placebo) on days 0 and 14 before the next participant begun treatment. The primary outcome was toxicity defined as a suspected unexpected serious adverse reaction (SUSAR) within 48 h of receiving an infusion. The DMEC reviewed the data and if one (or fewer) patients receiving the active treatment experienced a SUSAR, the dose would be reduced and toxicity evaluated in a further 5 patients randomised (3:2) to UC-MSCs or placebo. If there were no further toxicities, the trial progressed to the main two period crossover study. In the main crossover, patients were randomly assigned (1:1) using a web-based randomisation system SCRAM to receive two intravenous infusions (days 0 and 14), at a dose of 2–3x10^6 cells/kg UC-MSCs or placebo. There were 2 follow-up periods each of 6 months with a 3 month interval between periods, giving a 9 month duration between doses. Clinicians, caregivers, patients, and clinical trial personnel were fully blinded to treatment groups. Trial pharmacists and a team or independent research nurses who only performed administration of the infusion were unblinded to perform security checks of the product but were not involved in any assessments. The primary endpoint was change in disease severity as measured by Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) at three months post infusion assessed in the modified intention to treat (mITT) population (participants providing data at both period baselines and at least one 3-month follow-up). Prespecified subgroups included RDEB severity and age. Safety data were collected for all participants and safety assessment was based on all treatment emergent events in the

*Corresponding author. Great Ormond Street Hospital, London, WC1N 3JH, UK.
E-mail address: Anna.Martinez@gosh.nhs.uk (A.E. Martinez).
[e]Co-first authors.
[f]These authors contributed equally to the work.

safety population (those receiving at least one active or placebo infusion). This trial is registered with ISRCTN, ISRCTN14409785.

Findings Between OCT 06, 2021, and JUL 15, 2024, 44 participants were screened; 37 were randomised (18 UC-MSCs/placebo; 19 Placebo/UC-MSCs), with 34 receiving at least one infusion and 30 in the mITT analysis (14 UC-MSCs/placebo; 16 placebo/UC-MSCs). No toxicities were seen in the IDD phase (primary outcome). At three months no changes in favour of UC-MSCs were seen in the primary outcome EBDASI. The between arm difference in EBDASI at 3 months showed a 3.75 point difference (effect size 0.06) in favour of placebo (95% CI of −1.46, 8.96, p = 0.15) with corresponding figures for UC-MSCs/Placebo and Placebo/UC-MSCs of 5.5 (95% CI of −2.53 to 13.53, p = 0.16) and 2 (95% CI of −5.33 to 9.33, p = 0.58). No serious adverse events were associated with UC-MSCs.

Interpretation UC-MSCs infusions were safe and the primary outcome (EBDASI) did not show MSCs were beneficial. Further evaluation of the long-term efficacy of UC-MSCs is planned. The main strength is that Mission EB is the largest cell therapy study to date providing the most robust evidence on the safety and efficacy of UC-MSCs in children with RDEB. A limitation is that there are no robust validated outcome measures for RDEB.

Funding National Research Collaboration Programme, an NHS England and NIHR partnership (NIHR 127963) and Cure EB.

Keywords: Cell therapy; Clinical trials; Mesenchymal stromal cells; Recessive dystrophic epidermolysis bullosa

Research in context

Evidence before this study

We conducted a literature search of all articles published in the PubMed database through 2025/02/14 using the search terms (mesenchymal stromal cells [Title] OR mesenchymal stem cell [Title] OR stem cells[Title] OR mesenchymal cells [Title] OR cell therapy[Title] OR intravenous allogeneic [Title]) AND (dystrophic epidermolysis bullosa[Title] OR recessive dystrophic epidermolysis bullosa[Title] OR DEB [Title] OR RDEB[Title]). The search yielded 45 results. We included clinical trials and case reports and identified six early-phase clinical trials, and a case report of a patient who was treated with MSCs on compassionate grounds. Across all included studies with intravenous administration of cell therapy, 59 RDEB patients received between one and three intravenous infusions of MSCs from different sources including bone marrow, adipose tissue, umbilical cord and skin. All infusions of allogeneic MSC were administered on an open-label basis, and no control groups were included. It is worth mentioning the first intradermal administration of allogeneic MSCs in two RDEB severe patients which proved to be safe and effective in terms of improvement in wound healing. Overall, MSCs showed a favourable safety and tolerability profile as reported by the clinical outcomes.

Added value of this study

To our knowledge, this is the largest to date cell therapy trial using umbilical cord-derived mesenchymal stromal cells, UC-MSCs, (CORDStrom™) infusions in children with RDEB and the only one with a double-blinded, placebo-controlled crossover design (with an internal dose de-escalation phase for safety gatekeeping). No toxicities were seen in the IDD (primary outcome) and at three months no changes in favour of UC-MSCs were seen in the primary outcome EBDASI. However all patients on average showed a marked reduction in itch sustained at month 6. In our view, this reduction leads to lessened skin damage and chronic wounds, which are a known area of development of squamous cell carcinoma. This might in turn lead to lower incidence of this feared complication, the main cause of death in these patients. Long-term follow up and further research would be needed to support this statement.

Implications of all the available evidence

The landscape of therapeutics in RDEB is rapidly evolving and anti-inflammatory treatments such as cell therapies have proven beneficial to improve the systemic nature of this disease. The use of UC-MSCs has shown safety and trends towards clinically meaningful results in this largest placebo-controlled cohort of children with RDEB as judged by our independent oversight committees who reviewed the data and agreed the degree of efficacy as being clinically meaningful, demonstrating improvement or stabilisation over time in a disease that will otherwise naturally worsen. A follow through study of repeated UC-MSCs infusions is planned to further evaluate therapeutic durability and long-term efficacy.

Introduction

Epidermolysis bullosa (EB) is a heterogeneous group of inherited mucocutaneous fragility disorders.[1] Recessive dystrophic EB (RDEB) is a progressive disorder caused by loss-of-function variants in the type VII collagen gene (*COL7A1*) leading to reduced (RDEB-Intermediate) or absent (RDEB-Severe) collagen VII.[2] Patients experience various degrees of blistering following minor mechanical trauma which in severe cases can lead to open wounds, limb contractures, and an increased risk of developing squamous cell carcinoma.[3] Management is supportive with no definite treatment. RDEB has a prevalence of 3 . 3 per million of the population and an incidence of 8.1 per million live births in the UK.[4]

In RDEB, there is an intrinsic dysregulation of immune homeostasis, leading to systemic immune dysregulation and chronic inflammation. The convergence of multiple factors including an inflammatory microenvironment, creates conditions that may promote the development of SCC.[5,6] Recent studies have also identified C-reactive protein as an excellent biomarker for disease severity in RDEB and demonstrated a type 2 inflammatory profile amongst moderate and severe patients correlating with dysregulated circulating immunoglobulins such as IgA, IgE, IgM and IgG.[7] These findings reinforce that systemic inflammation plays a key role in the development of complications in this disease.

Clinical benefits from mesenchymal stromal cells (MSCs) arise from immunomodulatory or anti-inflammatory impact from the cells.[8] MSCs have shown promise in pre-clinical and clinical trials for promoting wound healing and reducing inflammation in EB.[9] Over the past 10 years, open-label studies using initially allogeneic intravenous bone marrow-derived MSCs (BM-MSCs),[10–12] dermal subpopulations of MSCs (ABCB5+ MSCs),[13,14] and umbilical cord-derived MSCs (UC-MSCs)[15] showed good tolerability and improved wound healing, pain and itch.[16] So far, internationally, a total of 34 children with RDEB have been treated with intravenous infusions of MSCs, and UC-MSCs have emerged as a source of MSCs with many advantages over BM-MSCs.[17] Allogeneic BM-MSCs have also been administered intradermally in two RDEB severe patients and proved to be safe and effective in re-epithelization of chronic wounds at the sites of injections with persisting effects in both patients for four months.[18] These studies were uncontrolled and based on small sample sizes.

In the last two decades, significant progress has been achieved in the development of efficient biomedical products to treat RDEB including cell-based therapy approaches and gene therapy methods.

MissionEB is the largest cell therapy trial in children with RDEB to date. It was a phase III, double-blind, placebo-controlled, crossover (A/B) trial with an initial Phase I dose de-escalation study aimed to assess if UC-MSCs versus placebo could benefit children with RDEB and provide the most robust evidence possible to inform a commissioning decision for the use of UC-MSCs in the UK.

Methods

Study design

MissionEB was a phase III, double-blind, placebo-controlled, crossover (A/B) trial to assess the safety and efficacy of intravenous infusions of UC-MSCs (CORDStrom™) for the treatment of children with RDEB. The trial was undertaken across the two nationally commissioned centres for paediatric EB in the UK: Great Ormond Street Hospital (GOSH) and Birmingham Children's Hospital (BCH).

There were 2 periods of 6 months, outcome collection at 3 months (primary) and 6 month and a 3 month interval between periods 1 and 2 to give a 9 month duration between doses. A cross over design was considered appropriate given the chronic nature of the condition and that the effect of the infusions was not expected to last beyond 9 months. Although a carry over effect was considered unlikely a period effect was included in the model as mitigation.

The study was approved by the North East York Research Ethics Committee (reference 21/NE/0016). It was coordinated by the University of Sheffield Clinical Trials Research Unit (CTRU), and oversight was provided by an independent data monitoring and ethics committee (DMEC) and an independent trial steering committee (TSC). This article follows the CONSORT guidelines.

The study aimed to provide evidence to guide commissioning decisions regarding MSCs for RDEB. It focused on achieving the highest quality evidence possible from the limited UK population. The assessment of efficacy was based on the totality of evidence i. e., all clinical outcomes (primary and secondary) as specified in the protocol and endorsed by the funder, external peer reviewers appointed by the funder and independent monitoring committees (TSC/DMEC).

This clinical trial was conducted in accordance with the principles of Good Clinical Practice and the UK Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments. Clinical Trial Authorisation (CTA) was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) under reference number CTA 17328/0229/001-0001.

Patients and their families were involved in the trial design. The Young Persons Advisory Group at GOSH was consulted on document development and regularly updated on the progress of the study. The study design and the totality of the evidence criteria in interpretation were endorsed by NIHR/NHS England, the TSC and DMEC.

Participants

Eligible participants were aged between 6 months and before their 16th birthday at time of written consent with a diagnosis of RDEB based on skin immunofluorescence microscopy and genetic testing. The age range was due to the fact that only paediatric patients are seen at the hospitals where the study was conducted and children under 6 months are excluded mostly due to safety risks associated with limited data in this age group. Individuals were excluded if they had received oral or topical corticosteroids for more than 7 consecutive days within 30 days of enrolment into this study, excluding oral viscous budesonide and inhaled fluticasone used as prophylaxis to relieve oesophageal symptoms. Further exclusion criteria included an active infection that required treatment with oral or intravenous antibiotics within 7 days of screening, medical history or evidence of active malignancy, the presence of both positive collagen VII ELISA and a positive indirect immunofluorescence (IIF) with binding to the base of salt split skin, administration of MSCs from any source in the previous 9 months and participation in any other interventional trial within 3 months of enrolment into this study. Written consent was obtained from parent/guardian and assent was sought from study participants aged 6 years and above after a period of reflection following the provision of age-appropriate information.

Randomisation and masking

The study included an initial Phase I dose de-escalation study (IDD) involving 9 participants randomised into two cohorts, see Supplementary Fig. S1. In the first cohort (Block A, n = 4), participants were randomised in a 3:1 ratio to receive UC-MSCs or placebo, while the second cohort (Block B, n = 5) followed a 3:2 allocation. This resulted in an overall allocation ratio of 6:3 (UC-MSCs:placebo). Following a safety review by the DMEC, which identified no concerns, these participants progressed to the main crossover trial. In the main trial, participants were randomised to UC-MSCs or placebo in a 1:1 ratio for the first treatment period, then crossed over to the alternate treatment after a 3 month interval between periods 1 and 2 (to give a 9 month duration between doses).

Randomisation was conducted using CTRU's centralised, validated, and restricted web-based system (SCRAM), with the allocation sequence generated by a blinded statistician who had no access to the study data. Participants, caregivers, clinicians, research staff, and trial statisticians remained blinded to treatment allocation. Only trial pharmacists were unblinded to perform quality product (QP) certification checks of the UC-MSCs/Placebo. To prevent unblinding an independent research nursing team prepared and administered the infusions in a shielded setting. This team had no contact with trial investigators or participants beyond infusion delivery. Site medical staff at GOSH and BCH obtained informed consent and registered participants in the randomisation system while remaining blinded to treatment allocation.

Procedures

During the study visits, patients underwent various assessments, including clinical scoring and laboratory evaluations for safety (Full blood count, bone profile, liver function tests, renal profile, ferritin, CRP, ESR -see section 8.6, page 55 in the Protocol[19]). The assessments performed at each visit are detailed in Supplementary Fig. S2.

CORDStrom™ is an advanced therapy medicinal product (ATMP) consisting of pooled allogeneic UC-MSCs obtained from umbilical cord blood donors, Dulbecco's Phosphate Buffered Saline (DPBS), ZENALB® (HAS) and dimethyl sulfoxide (DMSO) at 5% concentration. ZENALB® is a human albumin solution for infusion obtained from human plasma and widely used in clinical settings. DMSO is used as a cryoprotectant to avoid the formation of ice crystals. The placebo consisted of only DPBS, ZENALB® (HAS) and DMSO.

During IDD, 4 participants were randomised (3:1) to receive two infusions (2–3 × 10^6 cells/kg/infusion or placebo) on days 0 and 14. Following a DMEC safety review, 5 more participants were randomised (3:2) to UC-MSCs or placebo. A subsequent DMEC review found no safety concerns, enabling progression to the main crossover trial. In the main crossover trial, participants received a total of four intravenous infusions, two in each period two weeks apart. The study had 2 periods of 6 months with a 3 month interval between periods 1 and 2 to give a 9 month duration between doses. Infusions were administered as a slow bolus over 10 min, with chlorphenamine and paracetamol given prior to each infusion. The same dose and administration schedule used in the IDD were also applied during the crossover phase.

Outcomes

The primary outcome of the IDD phase was to assess the safety of intravenous UC-MSCs defined by a patient experiencing a suspected unexpected serious adverse reaction (SUSAR) within 48 h of the infusion.

For the crossover trial, the primary outcome was the change in disease severity, measured using the Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) at three months post-infusion. Secondary continuous outcomes included changes in EBDASI at six months, alongside changes at three and six months in: (1) the Instrument for Scoring Clinical

Outcomes of Research for EB (iscorEB); (2) pain, using the Wong-Baker FACES scale for children aged over six and the Visual Analogue Scale (VAS) for all the children's parents; (3) itch, measured by the Itch Man Scale (children aged 4–13) and the Leuven Itch Scale (children aged 14 and older); and (4) quality of life, assessed via the Child Health Utility 9D (CHU-9D). Discrete secondary outcomes included changes in the clinical appearance of skin disease (via photography) and changes in pain and itch medication, assessed at three and six months. Clinical appearance of skin was converted from an ordinal to a binary outcome counting "much better" and "a little better" as improvements and "about the same", "a little worse" and "a lot worse" as no improvement. Safety was evaluated through adverse events (AEs) and serious adverse events (SAEs, defined as any AE that requires or prolongs hospitalisation, is life-threatening, or results in death). Samples for cytokine analysis (research bloods) were also collected from patients at infusion timepoints and will be analysed as part of a future study.

A qualitative sub-study accompanied the clinical data. Semi-structured interviews with thematic analysis, guided by an interpretative theoretical approach to understand participants' experiences and perspectives in their own words, explored patient and parent experiences during the trial. Participants (children aged six years and older) and their parents were interviewed three months after infusion in each period, providing insights into their perspectives and experiences. We aimed to interview 10 patient and parent pairs (5 from each site) at the 3 month and 12 month visit during the trial. We did not include the patients who participated in the dose-de-escalation phase due to the timing of the ethical approval. Following approval, we invited all participants, all consented to be interviewed and were contacted by the qualitative researcher. We aimed to interview a mix of males and females and a range of ages as far as possible. We were unable to interview some participants due to contact and practical arrangements.

Finally, there was a health economic analysis whose results will be submitted to the funder and are outside the scope of this manuscript.

Statistical analysis

RDEB is a rare disease and the target sample size of 36 was based on the feasibility of recruitment and not formal power calculations (see Fig. 1 and published protocol). As such, the statistical analysis focuses on estimation rather than hypothesis testing and the assessment of efficacy is based on the totality of evidence. Standardised widths for the precision of the trial (for a continuous outcome) as assessed by the half-

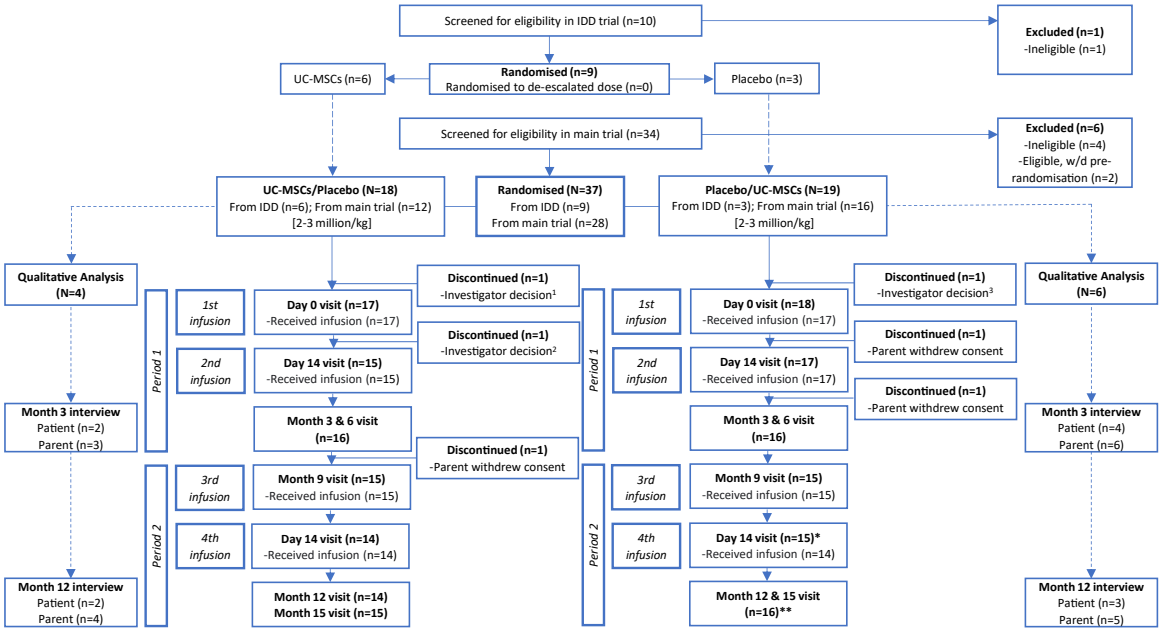

Fig. 1: CONSORT flow diagram. Non-receipt of an infusion does not imply non-attendance at subsequent visits, for example: *15 participants attended this visit, but only 14 received the 4th infusion due to an issue with the integrity of the infusion bag for one participant. **At the subsequent month 12 visit, 16 participants attended - one participant had previously decided to withdraw from treatment but continue with follow-up visits, and the one who did not receive the 4th infusion still attended the follow-up visits. Reasons for investigator decision to discontinue: [1]Multiple delays to first infusion due to infections and following recovery there was lack of engagement with the study team. [2]Infection leading to significant renal injury. [3]Development of squamous cell carcinoma.

width of a 95% confidence interval are given in the protocol. With 30 patients completing the study we would achieve a standardised precision (precision divided by the standard deviation) of 0.53.

The sample sizes for safety gatekeeping during the internal dose de-escalation phase are based on a 4 + 5 design (with feasibility considerations) which is a variant of a 3 + 3 design with controls to allow seamless transition into the main crossover trial.

For the qualitative study the aim was to have 10 participant and parent pairs across both treatment periods.

The primary analysis was modified Intention to Treat (mITT) with singular imputation of up to one period-baseline if missing. Per-protocol (PP) analysis included all participants who received four complete infusions and provided outcomes at baseline and 3-month post infusion within ± 14 days visit window for both periods. Full analysis (baseline available) and complete case populations were also used. All four populations were used for EBDASI and iscorEB outcomes. Analysis for the other quantitative outcomes was restricted to the mITT and PP populations.

In addition to the overall EBDASI and iscorEB, we analysed activity, damage and skin subdomains (EBDASI) and clinician, patient and skin subdomains (iscorEB). All outcomes were analysed for all children combined, as well as separately for four prespecified baseline characteristics subgroups based on age (below 10, 10 or over) and RDEB group (intermediate, severe). Models were not fitted where there were fewer than 7 evaluable participants in the subgroup for an outcome.

The safety analysis uses treatment-emergent AEs (those occurring on or after the day of the first infusion) for all participants receiving at least one active or placebo infusion. Safety modelling was censored at whichever was the latest of four dates: 6 months after the participant's first infusion of the period; last AE reported during washout (if any); withdrawal; or last AE reported in the case of loss to follow up. Analysis was descriptive only with odds ratios and associated 95% confidence intervals reported due to the absence of marked repeated events.

The primary outcome and continuous secondary outcomes were analysed using a linear mixed-effects model, with treatment and period as fixed effects and a random effect for participants. This was used to estimate the between-group mean difference in change from baseline and associated 95% confidence intervals to give a range of plausible effects. As the scores are all measured over different ranges this is contextualised in tables using change as a percentage of observed range and using standardised effect sizes scaling the estimated change by baseline standard deviation. For the discrete outcomes, there were insufficient events to fit the logistic regression models. As such, the discrete outcomes are reported descriptively only using odds ratios unadjusted for period and individual, along with their associated 95% confidence intervals. There is no allowance for multiplicity.

The continuous outcomes have been summarised using forest plots of standardised effect sizes, i.e., the between-arms differences divided by baseline standard deviation and multiplied by minus one for CHU-9D, for which negative differences favour placebo.

For the qualitative sub-study, the framework method which was used to identify initial themes; to label and sort the data by theme and then synthesising the findings. Two coders independently analysed the interviews (KB and SD). The impact of the UC-MSCs on the participants' and families' lives was explored.

Role of the funding source

The funder reviewed the research design and study protocol. The funder of the study had no role in data collection, data analysis, data interpretation, or writing of the report. The funder approved the selection of members for the oversight committees. All authors had full access to the data in the study. AM had final responsibility for the decision to submit for publication.

Results

Between OCT 06, 2021, and JAN 05, 2023, 46 patients entered screening, 44 participants were screened for eligibility (2 were not assessed) and 37 were randomised (18 to UC-MSCs/Placebo and 19 to Placebo/UC-MSCs). There were 30 participants in the modified Intention to Treat (mITT) population (Fig. 1). 34 participants received at least one dose and 28 received all 4 doses (Supplementary Tables S1 and S2). A total of 124 infusions were successfully completed. 31 patients attended the 15-month visit and 6 withdrew post randomisation (Supplementary Table S3). There were 24 participants in the per-protocol (PP) population and 29 in the Complete Case (CC) population (Supplementary Table S4). The pattern of trial withdrawal and per-protocol exclusion was similar in each sequence (see Supplementary Tables S5 and S6).

Baseline characteristics were generally well balanced (Table 1 and Supplementary Tables S7–S11). In the mITT population, RDEB severity subtype groups were equally represented, the younger age subgroup was more prevalent. Children under 10 were evenly split between RDEB subtypes (9/21 intermediate and 12/21 severe) while children over 10 were mainly intermediate RDEB (7/9 intermediate and 2/9 severe).

Overall, no changes in favour of UC-MSCs were seen in the primary outcome EBDASI (effect size = 0.06, 95% CI of −0.02 to 0.14, p = 0.15); the key

Variable	Scoring	Total (N = 30)	Sequence	
			Placebo/UC-MSCs (n = 16)	UC-MSCs/Placebo (n = 14)
Site	Birmingham	13 (43.3%)	9 (56.2%)	4 (28.6%)
	GOSH	17 (56.7%)	7 (43.8%)	10 (71.4%)
Sex	Male	15 (50.0%)	8 (50.0%)	7 (50.0%)
	Female	15 (50.0%)	8 (50.0%)	7 (50.0%)
Ethnicity	Asian/Asian British	6 (20.0%)	2 (12.5%)	4 (28.6%)
	Black/African/Caribbean/Black British	1 (3.3%)	0 (0.0%)	1 (7.1%)
	Mixed/multiple ethnic groups	2 (6.7%)	1 (6.2%)	1 (7.1%)
	Other ethnic group	2 (6.7%)	2 (12.5%)	0 (0.0%)
	White	19 (63.3%)	11 (68.8%)	8 (57.1%)
Type of RDEB	Intermediate	16 (53.3%)	9 (56.2%)	7 (50.0%)
	Severe	14 (46.7%)	7 (43.8%)	7 (50.0%)
Age (years)	<10	21 (70.0%)	10 (62.5%)	11 (78.6%)
	≥10	9 (30.0%)	6 (37.5%)	3 (21.4%)
Weight (kg)	n	30	16	14
	Median (IQR)	21.7 (15.2, 28.2)	22.9 (16.9, 32.2)	20.7 (15.0, 26.5)
	Min, Max	6.3, 89.3	6.4, 89.3	6.3, 41.3
BMI (kg/m^2)	n	30	16	14
	Mean (SD)	15.5 (3.2)	16.5 (3.8)	14.4 (1.6)
	Median (IQR)	14.8 (13.8, 16.3)	15.5 (14.0, 17.6)	14.4 (13.2, 14.9)
	Min, Max	11.7, 27.6	12.4, 27.6	11.7, 17.6
EBDASI–overall score[a]	n	30	16	14
	Mean (SD)	130.3 (62.0)	131.1 (64.4)	129.4 (61.5)
	Median (IQR)	146.0 (82.8, 176.8)	153.5 (76.8, 188.5)	137.0 (91.0, 172.5)
	Min, Max	13, 208	28, 206	13, 208
EBDASI–damage score[a]	n	30	16	14
	Mean (SD)	85.3 (41.7)	85.2 (43.3)	85.4 (41.5)
	Median (IQR)	101.5 (53.5, 116.2)	101.5 (55.5, 117.2)	101.5 (58.8, 111.2)
	Min, Max	9, 138	10, 138	9, 138
EBDASI–activity score[a]	n	30	16	14
	Mean (SD)	45.0 (24.2)	45.9 (26.0)	44.0 (22.9)
	Median (IQR)	45.0 (26.8, 59.8)	45.5 (24.2, 63.8)	45.0 (29.5, 58.0)
	Min, Max	4, 86	8, 86	4, 86
EBDASI–skin score[a]	n	30	16	14
	Mean (SD)	57.6 (24.2)	60.3 (21.3)	54.6 (27.6)
	Median (IQR)	62.0 (39.0, 75.8)	64.5 (47.0, 73.0)	53.5 (39.0, 75.8)
	Min, Max	7, 101	24, 92	7, 101
iscorEB–overall score[a]	n	30	16	14
	Mean (SD)	55.0 (22.9)	51.9 (20.4)	58.6 (25.7)
	Median (IQR)	57.9 (36.8, 67.6)	54.2 (35.2, 62.5)	64.2 (37.2, 71.8)
	Min, Max	20, 111	23.8, 88.6	20, 111
iscorEB–clinician score[a]	n	30	16	14
	Mean (SD)	16.8 (12.6)	15.6 (11.2)	18.3 (14.3)
	Median (IQR)	12.6 (10.3, 21.2)	11.2 (5.6, 22.6)	13.4 (11.3, 18.2)
	Min, Max	2, 59.5	3, 37.4	2, 59.5
iscorEB–patient score[a]	n	30	16	14
	Mean (SD)	38.2 (16.1)	36.4 (14.1)	40.3 (18.4)
	Median (IQR)	35.0 (24.5, 49.5)	35.0 (23.5, 45.0)	38.0 (26.0, 55.0)
	Min, Max	16, 74	20, 64	16, 74
iscorEB–skin score[a]	n	30	16	14
	Mean (SD)	6.5 (7.6)	5.8 (5.7)	7.4 (9.4)
	Median (IQR)	3.9 (2.4, 7.8)	3.7 (1.7, 8.5)	4.3 (3.2, 6.9)
	Min, Max	0, 37.5	1, 19.4	0, 37.5

(Table 1 continues on next page)

Variable	Scoring	Total (N = 30)	Sequence	
			Placebo/UC-MSCs (n = 16)	UC-MSCs/Placebo (n = 14)
(Continued from previous page)				
Wong-Baker FACES–average pain[a]	n	20	11	9
	Mean (SD)	4.0 (1.9)	3.8 (1.7)	4.2 (2.3)
	Median (IQR)	4.0 (2.0, 4.5)	4.0 (2.0, 5.0)	4.0 (2.0, 4.0)
	Min, Max	2, 8	2, 6	2, 8
Wong-Baker FACES–worst pain[a]	n	20	11	9
	Mean (SD)	7.0 (2.1)	7.3 (2.1)	6.7 (2.2)
	Median (IQR)	7.0 (6.0, 8.0)	8.0 (6.0, 8.0)	6.0 (6.0, 8.0)
	Min, Max	4, 10	4, 10	4, 10
Visual Analogue Scale–average pain[a]	n	30	16	14
	Mean (SD)	4.0 (1.7)	3.9 (1.3)	4.2 (2.0)
	Median (IQR)	4.0 (3.0, 4.8)	4.0 (3.4, 4.2)	4.0 (2.6, 4.8)
	Min, Max	1, 8	1, 6	2, 8
Visual Analogue Scale–worst pain[a]	n	30	16	14
	Mean (SD)	6.7 (2.2)	6.4 (2.4)	7.1 (1.9)
	Median (IQR)	7.0 (6.0, 8.0)	7.2 (5.7, 8.0)	6.5 (6.0, 8.9)
	Min, Max	1, 10	1, 10	4.5, 10
Itch Man Scale[a]	n	17	8	9
	Mean (SD)	2.0 (0.8)	2.0 (0.8)	2.0 (0.9)
	Median (IQR)	2.0 (1.0, 3.0)	2.0 (1.8, 2.2)	2.0 (1.0, 3.0)
	Min, Max	1, 3	1, 3	1, 3
CHU9D score[b]	n	30	16	14
	Mean (SD)	0.773 (0.121)	0.777 (0.127)	0.768 (0.117)
	Median (IQR)	0.784 (0.700, 0.875)	0.785 (0.721, 0.880)	0.766 (0.696, 0.863)
	Min, Max	0.511, 0.969	0.511, 0.946	0.567, 0.969

[a]Lower scores indicate less severe symptoms. [b]Lower scores indicate lower health utility.

Table 1: **Baseline characteristics by sequence.**

secondary outcome of iscorEB (effect size = 0.04, 95% CI if –0.24, 0.31, p = 0.79) or any other secondary outcome. Of the secondary outcomes a clinically meaningful effect in favour of UC-MSCs was seen in the Itch Man score (effect size = –0.44, 95% CI -1.26, 0.38, p = 0.27), (see Supplementary Table S12).

Due to the use of an age-dependent itch scale, insufficient data were available for the Leuven Itch Scale; therefore, all itch-related results are derived from the Itch Man Scale. Primary interpretation of the results used the mITT population; similar results were obtained in the PP population (see Supplementary Figs. S4–S6 and S8).

We pre-specified sensitivity analysis using severity and age subgroups and EBDASI and iscorEB domains scores. Efficacy results for the pre-specified sensitivity analysis are presented in the forest plots, assessing the totality of evidence (Fig. 2), with iscorEB/EBDASI overall scores excluded to avoid duplication. Results are reported as standardised effect sizes with 95% confidence intervals (CI) and are fully detailed in Supplementary Tables S12–S31 and further forest plots (Supplementary Figs. S3, S4, and S7).

Patients with RDEB-Intermediate showed treatment effects across most of the outcomes (Fig. 2A). No results favouring UC-MSCs were observed in the EBDASI, except for the EBDASI-activity subscore, which showed evidence of improvement. IscorEB-overall, -clinician and -skin subscores and itch also showed evidence of effect. By six months, these improvements had largely diminished in this cohort; however, results continued to favour UC-MSCs, with a further reduction in itch.

In the RDEB-Severe cohort, no improvements were observed at three months in either EBDASI or iscorEB, although a reduction in itch was observed. By six months, this reduction was maintained accompanied by an improvement in all iscorEB scales as observed in Fig. 2B.

In the under-10 cohort, no difference in EBDASI or iscorEB-overall were observed at three months (Fig. 2C). However, improvements in iscorEB-clinician and -skin subscores were noted. An effect in Itch decrease was observed and was maintained to six months alongside an improvement in the iscorEB-overall and its subscores (Fig. 2D).

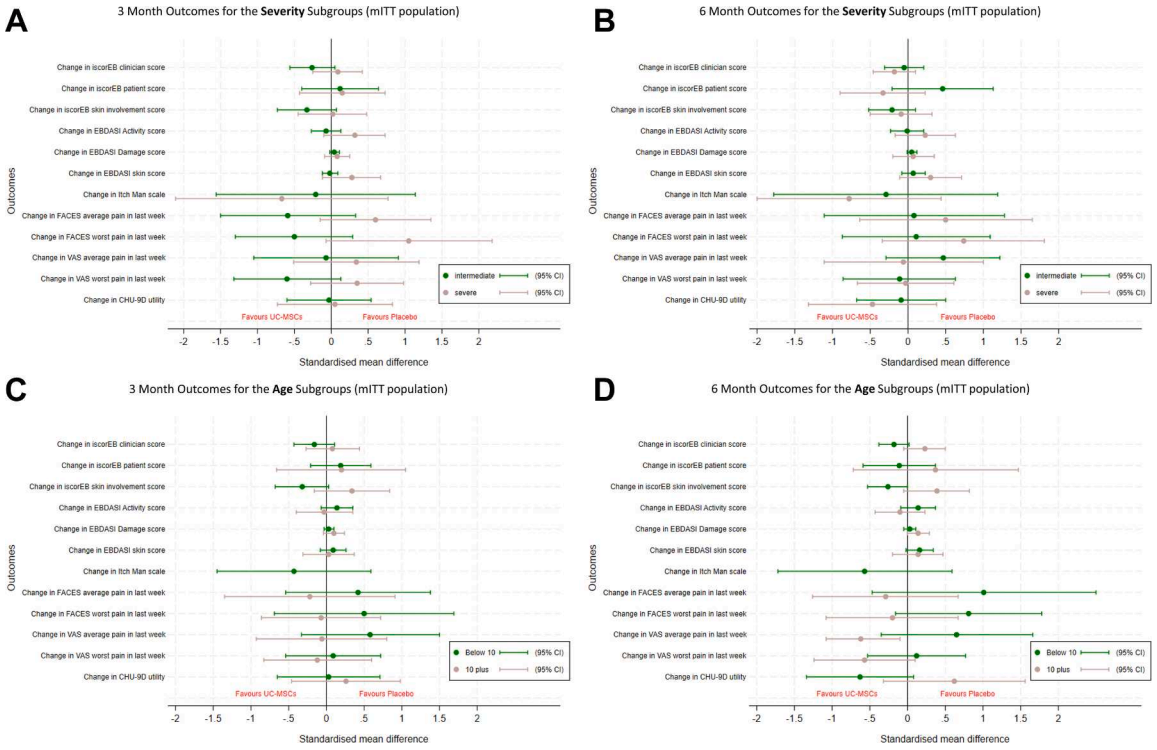

Fig. 2: Forest plots of all outcomes for the four subgroups. A: 3 month outcomes for the severity subgroups (mITT population). B: 6 month outcomes for the severity subgroups (mITT population). C: 3 month outcomes for the age subgroups (mITT population). D: 6 month outcomes for the age subgroups (mITT population). Standardised mean difference = between arm difference in change from baseline divided by standard deviation for subgroup at baseline; Intermediate = Intermediate RDEB, Severe = Severe RDEB. iscorEB = Instrument for Scoring Clinical Outcomes of Research for EB; EBDASI = Epidermolysis Bullosa Disease Activity and Scarring Index; VAS = Visual Analogue Scale; CHU-9D = Child Health Utility Instrument. Point estimates and confidence intervals calculated using mixed effect models with treatment and period as fixed effects, and individuals as random effects. Values displayed include the outlier. Corresponding data found in supplemental materials: panel A (Supplementary Tables S18 and S22); panel B (Supplementary Tables S20 and S24); panel C (Supplementary Tables S26 and S30); panel D (Supplementary Tables S28 and S32). iscorEB and EBDASI overall scores have been excluded to avoid duplication.

In the over-10 cohort, no change in EBDASI and IscorEB-overall were noted (Fig. 2C). A minimal change in EBDASI-activity was observed at three months and this group also saw a reduction in pain scores for both average and worst pain. Regarding itch, insufficient data were available for children over the age of 10 to fit models.

Summary statistics, detailed results and summary charts for EBDASI and iscorEB and provided in Supplementary Tables S32–S45 and Supplementary Figs. S9–S26. Summary statistics and charts for itch Man are provided in Supplementary Tables S46–S49 and Supplementary Figs. S27 and S28.

Although, as mentioned, no differences were observed in wound photography (see Supplementary Table S50 and Supplementary Fig. S29) or analgesia or itch medication (see Supplementary Table S51), results were slightly better for RDEB-Intermediate and under 10 at 3 months.

None of the estimated effects for the primary, secondary or subgroup/exploratory outcomes were statistically significant, with exception of the improvement in the iscorEB-skin subscore in RDEB-intermediate and under-10 subgroups when excluding the outlier (Supplementary Tables S16 and S24).

There were 238 AEs of which 211 were treatment-emergent in the safety population (Table 2 and Supplementary Table S52). Of the 211 AEs reported (111 in the UC-MSCs group and 100 in the placebo group), fourteen (7%) were possibly related to UC-MSCs and eight (4%) to placebo, all were minor. The AE most frequently related to the treatment were headaches (9/13) which resolved within 24 h. One child developed vasovagal symptoms during the infusion which resolved spontaneously. A total of 28 SAEs were reported, 14 in the UC-MSCs group and 14 in the placebo group. None of these were related to the treatment. Two randomised participants died, for reasons unconnected with the treatment or trial (see footnotes in Table 2). No adverse events of special interest (AESI) were observed in the treatment-emergent safety population.

Safety population (All with ≥1 infusion)	Total post infusion (n = 34)		Placebo (n = 32)		UC-MSCs (n = 32)	
	≥1 event, n (%)	All events, n	≥1 event, n (%)	All events, n	≥1 event, n (%)	All events, n
AEs						
Any AE (95% CI)	**32 (94%)**	**211**	**28 (88%) (72%, 95%)**	**100**	**29 (91%) (76%, 97%)**	**111**
Clinician defined categories						
Anaemia	10 (29%)	24	8 (25%)	11	6 (19%)	13
Benign skin lesion	1 (3%)	1	0 (0%)	0	1 (3%)	1
Bone density decreased	1 (3%)	2	1 (3%)	1	1 (3%)	1
Cardiovascular related disorders	6 (18%)	6	2 (6%)	2	4 (12%)	4
Chronic kidney disease	1 (3%)	1	0 (0%)	0	1 (3%)	1
Dental procedure	2 (6%)	2	1 (3%)	1	1 (3%)	1
Eye/Ear related disorders	6 (18%)	8	2 (6%)	3	5 (16%)	5
Gastrointestinal related disorders	16 (47%)	31	12 (38%)	16	10 (31%)	15
Headache	6 (18%)	9	0 (0%)	0	6 (19%)	9[a]
Hydrocele	1 (3%)	1	0 (0%)	0	1 (3%)	1
IV cannula related issues	3 (9%)	3	2 (6%)	2	1 (3%)	1
Infection	28 (82%)	85	23 (72%)	48	20 (62%)	37
Non-specific and self-resolving	11 (32%)	14	7 (22%)	8	4 (12%)	6
Oesophageal dilatation	11 (32%)	15	4 (12%)	4	9 (28%)	11[b]
Respiratory	1 (3%)	1	0 (0%)	0	1 (3%)	1
Surgical intervention	7 (21%)	8	3 (9%)	4	4 (12%)	4
NCI grade						
Life threatening	1 (3%)	1	0 (0%)	0	1 (3%)	1
Mild	26 (76%)	47	18 (56%)	25	13 (41%)	22
Moderate	30 (88%)	138	23 (72%)	62	25 (78%)	76
Severe	12 (35%)	25	8 (25%)	13	8 (25%)	12
Relatedness to IMP						
Reasonable possibility of being related	13 (38%)	22	6 (19%)	8	9 (28%)	14
No reasonable possibility of being related	31 (91%)	189	28 (88%)	92	27 (84%)	97
Relatedness to trial procedure						
Reasonable possibility of being related	11 (32%)	16	7 (22%)	9	5 (16%)	7
No reasonable possibility of being related	31 (91%)	194	27 (84%)	91	27 (84%)	103
Not assessable	1 (3%)	1	0 (0%)	0	1 (3%)	1
Related to another known cause						
Yes	18 (53%)	73	14 (44%)	32	16 (50%)	41
Nothing specified	32 (94%)	138	27 (84%)	68	25 (78%)	70
SAEs						
Any SAE (95% CI)	**12 (35%)**	**28**	**8 (25%) (13%, 42%)**	**14**	**7 (22%) (11%, 39%)**	**14**
Clinician defined categories						
Anaemia	2 (6%)	2	2 (6%)	2	0 (0%)	0
Chronic kidney disease	1 (3%)	1	0 (0%)	0	1 (3%)	1[c]
Dental procedure	1 (3%)	1	0 (0%)	0	1 (3%)	1
Gastrointestinal related disorders	5 (15%)	6	3 (9%)	3	3 (9%)	3
Infection	6 (18%)	11	5 (16%)	6	3 (9%)	5
Oesophageal dilatation	2 (6%)	2	0 (0%)	0	2 (6%)	2[d]
Surgical intervention	5 (15%)	5	3 (9%)	3	2 (6%)	2
NCI grade						
Life threatening	1 (3%)	1	0 (0%)	0	1 (3%)	1
Moderate	2 (6%)	3	1 (3%)	1	1 (3%)	2
Severe	12 (35%)	24	8 (25%)	13	7 (22%)	11
Related to IMP						
Reasonable possibility of being related (95% CI)	0 (0%)	0	0 (0%) (0%, 9.4%)	0	0 (0%) (0%, 9.4%)	0
Related to trial procedure						
Reasonable possibility of being related (95% CI)	0 (0%)	0	0 (0%) (0%, 9.4%)	0	0 (0%) (0%, 9.4%)	0
SAE of special interest						
SCC[e] (95% CI)	0 (0%)	0	0 (0%) (0%, 9.4%)	0	0 (0%) (0%, 9.4%)	0

[a]All 9 were NCI grade mild-seven began while receiving the infusion, one immediately afterwards and one 3 h afterwards. [b]13 AEs, all occurred 11 or more days after infusion and NCI grade moderate, and 2 SAEs. [c]The patient was under investigation for abnormal renal function prior to recruitment. At screening, creatinine levels were within the normal range, and the patient received one infusion of UC-MSCs. Following an episode of sepsis, renal function deteriorated rapidly. The patient was withdrawn, before receiving the 2nd infusion, from the study and died shortly thereafter. The authorities (MHRA and REC) were informed, and it was determined that this did not constitute a serious breach. [d]Both occurred 119 or more days after infusion, were NCI grade severe and not related to IMP or trial. [e]None of the patients in the safety population experienced an SCC. One patient was diagnosed with SCC after randomisation. The patient did not receive any infusions and as such they are excluded from the safety population. The patient subsequently died.

Table 2: **Treatment emergent adverse events by treatment.**

More detailed information on safety is provided in Supplementary Tables S53 and S54 and the trellis plots in Supplementary Figs. S30 and S31. The Trellis plots show that a very small proportion of AEs were related to the infusions, none of them were serious and they were equally likely to occur with placebo as with UC-MSCs.

For completeness, the additional tables are included in the Supplementary tables. Supplementary Tables S55–S67, show the results for the pain scales; Leuven Itch and CHU-9D scores respectively.

For the qualitative sub-study (Table 3) ten parents and six participant children were interviewed. Interviews were conducted three months after the infusions in both the first and second periods. Data for three individuals were incomplete: one child-parent pair withdrew from the trial after receiving only the placebo infusion and were interviewed only once (three months after first infusion), while another parent was interviewed only at the second time point (three months after second infusion). These participants reported positive effects after receiving the placebo; however, these could not be compared to periods when they received UC-MSCs.

Thirteen individuals (eight parents and five children) completed interviews during both periods. Of these, ten (seven parents and three children) reported improvements after receiving UC-MSCs, with no improvements noted during the placebo period.

The other three participants included: a parent of a child aged under one who reported a positive effect from the first infusion (UC-MSCs), which persisted after the placebo period (A in Table 3), likely to be due anti-inflammatory therapy benefitting for longer periods in this age group; a RDEB-Severe patient aged over 10 who reported minimal or no changes in symptoms or quality of life during both periods, with their parents interviewed only during one period due to illness (D in Table 3); and a child under 10 years with RDEB-Intermediate symptoms who reported benefits in both periods, although the parent perceived improvement only during the UC-MSCs period (E in Table 3). The lack of improvement in iscorEB patient score in comparison to the qualitative data, we believe to be due to lack of sensitivity of this outcome measure, as it focused in a very specific timeframe (4 weeks) whilst qualitative interviews reviewed the whole treatment period.

Discussion

Although the primary outcome, the EBDASI, did not show a clinically meaningful effect, the study results showed trends towards clinically meaningful improvement based on the judgements of the independent oversight committees, with the totality of the evidence showing the largest effects in RDEB-Intermediate patients. Of the secondary endpoints there was a consistent effect in itch across subgroups, with the largest effect observed in the RDEB-Severe group, an effect we and our independent oversight committees believed to be clinically relevant. We speculate that this reduction in itch over time contributes to improved wound closure, reducing the frequency of chronic wounded skin which is a known area in which squamous cell carcinomas develop.[20] We hypothesize that over time this could be disease-modifying and is likely to reduce the long-term risk of squamous cell carcinoma although further research and long-term follow-up would be required to support this statement. UC-MSCs raised no safety concerns and can be administered within 10 min without sedation, with children resuming normal activities within an hour.

RDEB is a devastating multisystemic disorder characterised by progressive chronic wound formation,[1] typically developing well before the age of 10 and affecting the entire skin and mucous membranes. This leads to fibrosis, scarring, contractures, excruciating pain, treatment-resistant itch, and a significantly increased risk of squamous cell carcinoma formation at these chronic wound sites.[21]

In the last two decades, the knowledge of molecular mechanisms of RDEB and the advances in medical technology have promoted major advances in the treatment of this disease. Currently, two main strategies are considered: (1) the development of methods targeted at the secondary inflammation-related pathology aiming to reduce the disease severity by slowing down its progression and improving the life quality; and (2) the creation of technologies that could replace or correct the defective *COL7A1* gene and, therefore, to affect the root cause of the disease.[22] To date, there are two gene therapy products that were granted U.S. Food and Drug Administration (FDA) approval in 2023 and 2025 respectively: Beremagene geperpavec (Vyjuvek™),[23,24] the topical gene product engineered on the basis of non-replicating *COL7A1*-containing herpes simplex virus type 1 vector aimed to restore the collagen VII synthesis and ZEVASKYN™,[25] an autologous gene-corrected epidermal sheet therapy for the treatment of wounds in adult and paediatric patients with RDEB. Our study demonstrated that UC-MSCs are safe and effective in the treatment of RDEB when considering the totality of the evidence and in line with results from other cell therapy trials. The complexity of mechanisms underlying RDEB will likely require a combined approach to achieve optimal clinical outcomes.

It is globally recognised that there is disease progression over time in patients with RDEB.[1] Therefore, patients' disease being stable over a period of six-month or more, or any sustained improvement without

ID	Patient details	Role	UC-MSCs	Placebo
A	Under 6 years* RDEB intermediate Order of infusions: UC-MSC/Placebo	Parent	• Parent described that wound healing was quicker and had changed in form and this reduced the frequency of dressing changes. • It was difficult to monitor whether the treatment had made a difference to some symptoms.	• Positive changes such as fewer blisters on the feet, fewer open wounds and as a result, less dressing changes. • Seemed to be talking about improvement since the start of the trial, rather than since the most recent infusion.
B	Under 6 years* RDEB intermediate Order of infusions: UC-MSC/Placebo	Parent	• Reported a huge improvement all round: Improvements in energy, eating, wound healing and recovery time from illness was quicker.	• Reported no change this time, compared to 1st infusion where there was a great improvement.
C	Over 10 years RDEB intermediate Order of infusions: UC-MSC/Placebo	Patient	• Reported a significant decrease of wounds and blisters, less pain and that new wounds healed faster. Improved sleep and general activities have become easier to do.	• Said there was no impact of this infusion, and compared to the first infusion where they thought it had helped.
		Parent	• Felt that there was significant positive change since the infusion, skin was less sensitive, wound healing was quicker and less itchiness and pain.	• Reported eye pain and itchiness was worse after the 2nd infusion. • Compared this time to last time by saying that the 1st infusion was much better.
D	Over 10 years RDEB severe Order of infusions: UC-MSC/Placebo	Patient	• Reported having one positive experience where their skin had improved on holiday but that this returned to normal when he came back to the UK. • Nothing else had changed in relation to his EB symptoms.	• Reported a small positive change in pain and itchiness, wounds on their legs had decreased but when they returned, this was more difficult to deal with. • No impact on dressings, bathing or sleep.
		Parent	Was not interviewed at this time due to illness.	• Noticed improvement in wound healing; these improvements lasted two months and their legs were 'clear' for three weeks. • These changes had improved their social life as they were able to walk more and being abroad was easier due to fewer complications.
E	Under 10 years RDEB intermediate Order of infusions: Placebo/UC-MSC	Patient	• Reported positive changes such as fewer blisters, quicker wound healing, less pain during bathing and EB activities took less time due to the decrease in pain. • Positive impact on quality of life e.g., able to socialise more with peers.	• Positive impact on their regular activities and playing with friends, and some reference to less pain. • No impact on wound healing or itching. •
		Parent	• Described less pain and that wounds had healed quicker. This made bath times easier and impacted positively on their mental wellbeing. • They felt that the participant was more positive now because of the improvement and more willing to be engaged in activities.	• Reported no change in any symptoms or quality of life.
F	Over 10 years RDEB intermediate Order of infusions: Placebo/UC-MSC	Patient	• A bit less pain and itchiness since the infusion. Did not last long. Improved school and sleep.	• Reported no change in any symptoms or quality of life.
		Parent	• Reported improvements in itchiness, pain and activities at school and sleep.	• Reported no change in any symptoms or quality of life.
G	Over 10 years RDEB intermediate Order of infusions: Placebo/UC-MSC	Patient	Withdrawn	• Improvement in skin, fewer cuts and they have healed quicker, less itchiness and were able to write longer at school because of the positive changes.
		Parent	Withdrawn	• Highlighted positive improvement in wound healing and formation of blisters.
H	Under 6 years* RDEB severe Order of infusions: Placebo/UC-MSC	Parent	• Reported improved sleep, energy, and mood. • No impact on skin and wounds.	• No change, stated everything is still the same.
I	Under 6 years* RDEB severe Order of infusions: Placebo/UC-MSC	Parent	• Unclear but thinks there may have been some improvement in the healing of wounds. Noticed less scratching but thought this could just be them growing up. • Childminder thought the skin had improved.	• Reported no change in any symptoms or quality of life, some more itching reported.
J	Under 10 years RDEB severe Order of infusions: Placebo/UC-MSC	Patient	• Reported that pain reduced a little, itchiness improved slightly and they had played with their sibling more since treatment. • No impact on sleep, their eyes or dressings.	• Initially said pain and itch had improved a little but later in the interview said it had not improved, no impact on activities.
		Parent	• Wounds are healing quicker. • Reported less waking but not certain if this is due to infusion or getting used to it.	• Reported no change in any symptoms or quality of life, except more itching.

*Patients under 6 years were too young to be interviewed.

Table 3: **Summary of qualitative interviews.**

intervention would be unexpected. Existing outcome measures are known and accepted to be inadequate and often fail to capture the condition's multidimensional nature. A recent review highlighted the critical need for better robust, disease-representative outcome measures, noting that over 200 different instruments have been used across EB trials, contributing to inconsistency and limited comparability.[21] In response, an international collaboration looking at core outcome sets for EB (COSEB) was established in 2023 to develop more comprehensive and standardised outcome measures for this heterogeneous disease.[26] Although the

primary outcome was an improvement in EBDASI, with various secondary outcomes, efficacy was to be assessed based on the totality of evidence, in particular any improvement in any of the outcome measures which clinically would not be expected in this disease.

The data suggests UC-MSCs reduced disease activity, skin involvement and itch across all ages and RDEB subtypes. Children with RDEB under the age of 10 were the largest subgroup in our cohort with 21 out of 30 individuals of the mITT population, and the majority were RDEB-Severe. This cohort showed mild improvement in disease activity assessment and skin involvement, with greater reductions in itch compared to placebo which was sustained after 6 months. This sustained reduction in itch over the 6-month period is interpreted by us and our independent oversight committees as clinically relevant, as it was accompanied by consistent improvements in other key clinical scores, including the iscorEB-overall, and -clinician, -patient and -skin involvement subscores.

In contrast, patients aged over 10 years exhibited improvements in pain scores, as reported by both patients and their parents, for both average and worst pain levels at three months post-treatment. These improvements became even more pronounced at six months, with a further reduction in reported pain. A notable limitation for these subgroups was the use of age-dependent scales: the Wong-Baker FACES scale for children aged 6 years or older and the Leuven Itch Scale for those aged 14 years or older. This methodological approach likely influenced the outcomes, potentially contributing to the absence of observed changes in pain among the under-10 cohort and in itch among the over-10 cohort.

Children with RDEB-Intermediate experienced the greatest overall benefits at 3 months, showing improvements in disease activity scores, skin involvement, pain, and itch. In comparison, patients with RDEB-Severe across all age groups showed no improvements in skin assessments at this time. However, UC-MSCs markedly reduced itch in this subgroup, which was maintained after 6 months (see Fig. 2B), suggesting that itch relief was the most pronounced therapeutic effect. With sustained itch reduction we observed improvements in iscorEB (including skin, clinician and patient subscores) and VAS pain score at 6 months in RDEB-Severe.

Qualitative data fully supported these findings: 10 out of 13 participants, blinded to their treatment allocation, reported benefits after cells and not from the placebo. This was supported by the data from CHU-9 at six months.

The DMEC and TSC, composed of international experts in EB and UC-MSCs, reviewed the data and concluded the study demonstrated improvements in skin involvement, pain and itch (see Supplementary Figs. S36 and S37 in the Supplementary materials for the TSC and DMEC letters of support). Qualitative data reinforced these findings, with trends favouring the active treatment group receiving UC-MSCs over placebo. However, we acknowledge that the assessment of whether the totality of evidence demonstrates a clinically meaningful effect may be subjective and is open to interpretation.

As previously mentioned, outcome measurement instruments for EB are globally recognised to be sub-optimal. Whilst awaiting better outcome measures, we used two validated scoring outcome tools for this study: EBDASI and iscorEB, both having limitations. To our knowledge, there is no agreed change in either of these scoring tools that defines a clinically significant change. According to Jain et al.,[27] a reduction in EBDASI activity scores greater than 9 indicated clinically meaningful improvement, and for iscorEB clinician score, Bruckner et al.,[28] suggested the minimal important difference to show clinical significance was 5 . 5 points across all types of EB. However, due to the different stages of the disease and natural progression[1] as well as differences observed between intermediate and severe RDEB patients, we observed a very wide range in the EBDASI activity score from 4 to 86 points and iscorEB clinician score from 2 to 59.5 points. Therefore, it is very unlikely that young and intermediate patients will show a reduction in either scoring tools of that magnitude.

We believe that using a percentage of change in scores from baseline, with each individual acting as their own control is more meaningful. The lack or very mild response observed in EBDASI compared to iscorEB is believed by the authors to be due to EBDASI's difficulty in detecting short-term changes in children. This is because iscorEB measures the percentage of the body area affected, whilst EBDASI is guided by pre-defined wound size in cm. The authors feel this is less precise because it does not consider the proportion of the surface area affected i.e., a 6 cm wound in an infant is proportionally much larger than a 6 cm in a 10-year-old.

Our study revealed a substantial placebo effect, likely diminishing the observed impact of UC-MSCs. This effect can be attributed to the intensive monitoring patients received during the trial. Wound infections were promptly detected and treated, while patients' nutritional status was optimised, and blood deficiencies were corrected through more frequent laboratory assessments. These comprehensive care measures may have contributed to improvements independent of the experimental treatment.

The study has several major strengths, including being the largest randomised, double-blinded, placebo-controlled, crossover paediatric RDEB trial conducted worldwide. It features blinded independent assessment of photography and includes a blinded qualitative sub-study. However, the study also has some limitations. The sample size was small, necessitating close collaboration with stakeholders—such as funders,

policymakers, and patients—independent of the study team. These stakeholders contributed to the co-design process to ensure a robust study design and implementation. Additionally, due to the rarity of the condition, the clinical outcomes were not as thoroughly validated as they might have been in a trial involving a larger population.

From our clinical observation, patients under the age of 10 (including those with RDEB-Severe) and the intermediate cohort showed greater benefit due to their lower baseline disease severity and reduced baseline levels of inflammation. However, in the RDEB-Severe cohort we observed the largest reduction in itch which was sustained at 6 months with improvements then in their skin scores. Administering this treatment therefore to all patients under the age of 16 years with RDEB, regardless of disease severity, is likely to be beneficial. Given the limited treatment options currently available for RDEB, we believe that intravenous UC-MSCs represent a safe systemic therapy that appears to reduce disease severity.

In conclusion, administering UC-MSCs early and at regular intervals has the potential to reduce inflammation, effectively modulate disease activity, and lead to sustained improvements in both disease progression and quality of life. An open-label extension study is planned and will help us further evaluate the long-term safety and outcomes of repeated UC-MSCs infusions in children with RDEB.

Contributors

Conceptualisation was performed by MLB, PLB, DP, KB, SJ, PT, SD, MO, MLL, JAM, CC, GP, and AEM. Data Curation was handled by MLB, PLB, MBu, KB, SJ, IW, ET, SD, MO, MLL, PP, MN, GP, and AEM. Formal Analysis was conducted by PLB, MBu, KB, SJ, IW, SD, GP, and AEM. Funding Acquisition was secured by DP, KB, SJ, PT, MO, MLL, JAM, CC, GP, and AEM. Investigation was carried out by MLB, PLB, MBu, RG, KH, KB, SJ, IW, SD, MO, MLL, PP, MN, GP, and AEM. Methodology was contributed by MLB, PLB, MBu, DP, KB, SJ, PT, MO, MLL, JAM, CC, GP, and AEM. Project Administration was managed by MLB, PLB, RG, KH, DP, ET, MO, MLL, PP, MN, CC, GP, and AEM. Resources were provided by MLB, PLB, ET, SD, MO, MLL, PP, MN, GP, and AEM. Software was developed by PLB, MBu, SJ, IW and ET. Supervision was provided by MLB, PLB, MBu, RG, KH, DP, SJ, MO, M-LL, JAM, CC, GP, and AEM. Validation was performed by MLB, PLB, GP and AEM from the clinical team, and MBu, SJ, IW, ET, CC from the academic team. MBu and IW have access to and verify the underlying data. Visualisation was completed by MLB, PLB, RG, KH, GP, and AEM. Writing—Original Draft was prepared by MLB, PLB, MBu, DP, KH, SJ, GP, and AEM. Writing—Review & Editing was done by MLB, PLB, MBu, RG, DP, KH, RG, KB, SJ, IW, PT, ET, MO, M-LL, PP, MN, JAM, CC, GP, and AEM.

Data sharing statement

The data that support the findings of this study will be available from the corresponding author 2 years from publication upon request. Access to the data will require approval from Great Ormond Street Hospital NHS Foundation Trust.

Declaration of interests

AEM has received payment or honoraria for lectures, presentations or educational events from Amryt Pharma and Krystal Biotech and investigator in current clinical trial with TWi Biotechnology. GP has received payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events, from Amryt Pharma, Sanofi, Krystal Biotech, Pfizer, and Incyte. PLB and MLB are involved in previous and current clinical trials with Rheacell GmbH & Co. KG. MLB is a co-investigator in current clinical trials with TWi biotechnology. All other authors declare no competing interests.

Acknowledgements

The authors acknowledge the Sheffield Clinical Trials Research Unit (CTRU) for their coordination and management of the trial, including Simon Waterhouse, Zoe Guy, and Esther Herbert. We would like to express our special gratitude to Mike Bradburn for their invaluable statistical guidance, expertise and support in shaping the trial design and analysis. We extend our thanks to the members of the Trial Steering Committee (TSC)—Prof. Jemima Mellerio, Prof. Gareth Griffiths, Dr. Fiona Browne, Prof. Chris Bojke, and Ms. Nuria Tarrats—and the Data Monitoring and Ethics Committee (DMEC)—Prof. Peter Bader, Prof. Elena Pope, Dr. Christine Prodinger, and Mr. Richard Jackson—for their valuable oversight, contributions, and management of safety and monitoring throughout the study. We thank Deirdre Leyden and the GOSH Young Person's Advisory Group for their valuable input into the trial.

This research was funded by the National Research Collaboration Programme (NIHR127963), an NHS England and National Institute for Health and Care Research Partnership, with additional funds provided by Cure EB, and we are grateful for their support. We also acknowledge the NIHR-funded clinical research facilities and staff at GOSH and BCH for their assistance in running the trial.

We thank INmuneBio for producing the umbilical cord-derived mesenchymal stromal cells product used in this study. Special thanks go to their lead investigators, Prof. Mark Lowdell and Dr. Ben Weil, for their expertise and dedication. We also acknowledge the generosity of the umbilical cord donors, whose contributions through the Anthony Nolan charity were vital to the development of this research.

Finally, we express our sincere gratitude to the patients and their families. Their participation and trust were instrumental in enabling this study and advancing cell therapy-based treatments in RDEB.

The views expressed are those of the author(s) and not necessarily those of the NHS England, NIHR or the Department of Health and Social Care.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103417.

References

1 Bageta ML, Yerlett N, McGrath JA, Mellerio JE, Petrof G, Martinez AE. The natural history of severe recessive dystrophic epidermolysis bullosa – 4 phases which may help determine different therapeutic approaches. *J Dermatol Venereol*. 2021;2(2):20–21.

2 Has C, Bauer JW, Bodemer C, et al. Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol*. 2020;183(4):614–627.

3 Bardhan A, Bruckner-Tuderman L, Chapple ILC, et al. Epidermolysis bullosa. *Nat Rev Dis Primers*. 2020;6(1):78.

4 Petrof G, Papanikolaou M, Martinez AE, et al. The epidemiology of epidermolysis bullosa in England and Wales: data from the national epidermolysis bullosa database. *Br J Dermatol*. 2022;186(5):843–848.

5 Hirt N, Manchon E, Chen Q, et al. Systems immunology integrates the complex endotypes of recessive dystrophic epidermolysis bullosa. *Nat Commun*. 2025;16(1):664.

6 Santucci C, Alexandru M, Chen X, Mellerio JE, Karagiannis SN, Jacków-Malinowska J. Unravelling drivers of cutaneous squamous cell carcinoma in recessive dystrophic epidermolysis bullosa. *Hum Immunol*. 2024;85(3):110805.

7 Quintana-Castanedo L, Sánchez-Ramón S, Maseda R, et al. Unveiling the value of C-reactive protein as a severity biomarker and the IL4/IL13 pathway as a therapeutic target in recessive dystrophic epidermolysis bullosa: a multiparametric cross-sectional study. *Exp Dermatol*. 2024 Aug;33(8):e15146.

8 Hou PC, Del Agua N, Lwin SM, Hsu CK, McGrath JA. Innovations in the treatment of dystrophic epidermolysis bullosa (DEB): current landscape and prospects. *Ther Clin Risk Manag*. 2023;19:455–473.
9 Raoufinia R, Rahimi Hr, Keyhanvar N, et al. Advances in treatments for epidermolysis bullosa (EB): emphasis on stem cell-based therapy. *Stem Cell Rev Rep*. 2024;20(5):1200–1212.
10 Petrof G, Lwin SM, Martinez-Queipo M, et al. Potential of systemic allogeneic mesenchymal stromal cell therapy for children with recessive dystrophic epidermolysis bullosa. *J Invest Dermatol*. 2015;135(9):2319–2321.
11 El-Darouti M, Fawzy M, Amin I, et al. Treatment of dystrophic epidermolysis bullosa with bone marrow non-hematopoeitic stem cells: a randomized controlled trial. *Dermatol Ther*. 2016;29(2):96–100.
12 Rashidghamat E, Kadiyirire T, Ayis S, et al. Phase I/II open-label trial of intravenous allogeneic mesenchymal stromal cell therapy in adults with recessive dystrophic epidermolysis bullosa. *J Am Acad Dermatol*. 2020;83(2):447–454.
13 Kiritsi D, Dieter K, Niebergall-Roth E, et al. Clinical trial of ABCB5 + mesenchymal stem cells for recessive dystrophic epidermolysis bullosa. *JCI Insight*. 2021;6(22).
14 Dieter K, Niebergall-Roth E, Daniele C, et al. ABCB5+ mesenchymal stromal cells facilitate complete and durable wound closure in recessive dystrophic epidermolysis bullosa. *Cytotherapy*. 2023;25(7):782–788.
15 Lee SE, Lee SJ, Kim SE, et al. Intravenous allogeneic umbilical cord blood-derived mesenchymal stem cell therapy in recessive dystrophic epidermolysis bullosa patients. *JCI Insight*. 2021;6(2).
16 Niebergall-Roth E, Dieter K, Frank MH, Kluth MA. Systemic treatment of recessive dystrophic epidermolysis bullosa with mesenchymal stromal cells: a scoping review of the literature and conclusions for future clinical research. *J Dermatol Treat*. 2024;35(1):2419931.
17 Nagamura-Inoue T, He H. Umbilical cord-derived mesenchymal stem cells: their advantages and potential clinical utility. *World J Stem Cells*. 2014;6(2):195–202. https://doi.org/10.4252/wjsc.v6.i2.195.
18 Conget P, Rodriguez F, Kramer S, et al. Replenishment of type VII collagen and re-epithelialization of chronically ulcerated skin after intradermal administration of allogeneic mesenchymal stromal cells in two patients with recessive dystrophic epidermolysis bullosa. *Cytotherapy*. 2010;12(3):429–431.
19 Bageta ML, López-Balboa P, Dimairo M, et al. Mesenchymal intravenous stromal cell infusions in children with recessive dystrophic epidermolysis bullosa: MissionEB protocol for a randomised, double-blinded, placebo-controlled, two-centre, crossover trial with an internal phase I dose de-escalation phase and open-label extension. *BMJ Open*. 2025;15(5):e089857.
20 South AP, Laimer M, Gueye M, et al. Type VII collagen deficiency in the oncogenesis of cutaneous squamous cell carcinoma in dystrophic epidermolysis bullosa. *J Invest Dermatol*. 2023;143(11):2108–2119. https://doi.org/10.1016/j.jid.2023.05.024.
21 Korte EWH, Welponer T, Kottner J, et al. Heterogeneity of reported outcomes in epidermolysis bullosa clinical research: a scoping review as a first step towards outcome harmonization. *Br J Dermatol (1951)*. 2023;189(1):80–90.
22 Zorina A, Zorin V, Isaev A, et al. Current status of biomedical products for gene and cell therapy of recessive dystrophic epidermolysis bullosa. *Int J Mol Sci*. 2024;25(19):10270.
23 Guide SV, Gonzalez ME, Bağcı IS, et al. Trial of Beremagene geperpavec (B-VEC) for dystrophic epidermolysis bullosa. *N Engl J Med*. 2022;387(24):2211–2219.
24 Gurevich I, Agarwal P, Zhang P, et al. In vivo topical gene therapy for recessive dystrophic epidermolysis bullosa: a phase 1 and 2 trial. *Nat Med*. 2022;28(4):780–788.
25 *U.S. FDA approves ZEVASKYN™ (prademagene zamikeracel), the first and only cell-based gene therapy for patients with recessive dystrophic epidermolysis bullosa (RDEB) [press release]*. 2025, 29/04/2025. Date accessed 09/05/2025.
26 Korte EWH, Pasmooij AMG, Bolling MC, et al. Towards a roadmap for COSEB: the next steps in harmonization of outcomes for epidermolysis bullosa. *Br J Dermatol (1951)*. 2024;191(3):463–465.
27 Jain SV, Harris AG, Su JC, et al. The Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI): grading disease severity and assessing responsiveness to clinical change in epidermolysis bullosa. *J Eur Acad Dermatol Venereol*. 2017;31(4):692–698.
28 Bruckner AL, Fairclough DL, Feinstein JA, et al. Reliability and validity of the instrument for scoring clinical outcomes of research for epidermolysis bullosa (iscorEB). *Br J Dermatol*. 2018;178(5):1128–1134.