Phase II clinical study of Injectable Allogeneic Human Dermal Fibroblasts in DEB

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C7 is synthesized by keratinocytes and by fibroblasts.

C7 is the main component of anchoring fibrils at the DEJ, Mutations responsible for RDEB.

Murine data have demonstrated the potential of fibroblast cell therapy in RDEB.
Summary of murine data: RDEB and fibroblasts

**Gene-corrected RDEB fibroblasts**
over-expressing C7 can generate correctly localised C7 at the DEJ


**Normal fibroblasts**
(at sufficient cell density) or gene-corrected RDEB fibroblasts can increase C7 at the DEJ


**Intravenously injected normal or gene-corrected RDEB fibroblasts**
can enhance wound healing in mouse skin


**Hypomorph C7 mouse model of RDEB**
shows single injection of fibroblasts can lead to increased C7 expression at DEJ for at least 100 days

Can fibroblast cell therapy help people living with RDEB?
Intradermal injections of allogeneic fibroblasts can increase C7 at the DEJ (and within basal keratinocytes) in some individuals with RDEB and may thus have therapeutic potential.

- Allogeneic fibroblast injections can lead to a sustained increase in C7 expression at the DEJ for 3+ months.
- Allogeneic fibroblasts are safe, non-inflammatory, but are not detectable after 2 weeks.
- Allogeneic fibroblasts exert a possible paracrine effect on the subjects’ keratinocytes (via HB-EGF) to increase synthesis and secretion of mutant C7.

Wong et al. assessed fibroblast injections into intact skin

The main concern for patients is chronic, non-healing wounds

What about the effects of allogeneic fibroblast injections on wound healing in RDEB?
VAVELTA®— Product description

- Cell source: U.S. neonatal foreskin. Est. up to $10^6$ vials/tissue sample
- 1.8ml DIN glass type 1 vial with 1.2ml fill of $2 \times 10^6$ human dermal fibroblasts/ml. 1ml useable volume
- Medium: Hypothermosal
- Shipping container: Nanocool 852 box (validated at 48h 2-8C)
- Storage temp 2-8 C
- Current Shelf life: 11 days (6 at clinical site). Ongoing work to extend this
- Delivered by 30G needle or larger
Regulatory position

• Regulated in the EU as a Tissue Engineered ATMP for scars, scar contractures and Epidermolysis Bullosa (EB).
  – UK Phase I clinical carried out on healthy volunteers
  – Phase IIa studies completed for acne, lasolabial folds and Dystrophic Epidermolysis Bullosa
  – CTA active for second Phase IIa to treat acne scars

• In the US regulated as a biological
  – IND active for Phase I/II to treat burn contractures
5 patients with six symmetrical lesions received a single intradermal injection of allogeneic fibroblasts vs. transport solution. No benefit detected with allogeneic fibroblasts, over transport solution alone. Both groups improved healing but similar improvement described in both groups.

15 patients with dystrophic EB received a single series of intradermal injections of GMP cultured allogeneic fibroblasts (Vavelta, Intercytex Ltd, UK).

A double-blinded randomised placebo-controlled trial of allogeneic fibroblasts in RDEB wounds demonstrated the safety of the technique (full study unpublished).

An open-label study of allogeneic fibroblasts to RDEB wounds demonstrated clinical improvement in some individuals.
Aim of current study

To assess the effect of intradermal injections of allogeneic fibroblasts on wound healing in RDEB
Sample size calculation

- 2-sided Logrank test used for the analysis
- 5% statistical significance level
- 80% power
- We assumed that we would show at least a 50% reduction in median wound closure time
- Based on estimates from previous studies, a statistical analysis indicated that 120 wounds would be needed to show this difference.
- However, if an average of 6 wounds per subject could be used then we would need just 20 evaluable subjects in order to show a statistically relevant difference in the time to wound closure.
Quality of life assessments and baseline blood tests

Screening visit

Weekly wound photos

Week 12

Day 7

Day 28

Week 24

D0 - Injection day

Day 14

Day 56

Pain score and photographs at every study visit

No skin biopsies
354 patients assessed for eligibility

331 patients excluded for a variety of reasons

23 patients screened

10 patients excluded
- 6 not meeting inclusion criteria
- 3 declined to participate
- 1 rapid healing

13 patients in run-in phase with a total of 91 erosions

2 patients excluded
- 1 selected erosions healed
- 1 had antibodies against C7 detected

11 patients in run-in phase with a total of 91 erosions

11 patients treated with a total of 78 erosions

49 erosions excluded
- 16 healed
- 29 reduced in size >10%
- 3 increased in size over wound limit
- 1 patient refused to expose wound

11 patients treated 29 erosions randomised

16 erosions allocated to ICX-RHY-013

2 did not receive allocated intervention (due to pain)

14 followed up and analysed (ITT)

13 erosions allocated to vehicle

1 did not receive allocated intervention (due to pain)

12 followed up and analysed (ITT)
RDEB wounds screened for the trial
**Investigational Medicinal Product (ICX-RHY-013)**

- The active medicinal product consisted of a suspension of allogeneic human dermal fibroblasts in transport medium vs transport medium alone (vehicle).
- Manufactured at Intercytex Ltd, Manchester, UK.
- ICX-RHY-013 is an Orphan Medicinal Product for EB (European Medicines Agency).

**Wound measurement software (Elixr™ Imago Care ltd, UK)**

- Calibration and mapping
- Surface area measurement
Results

• 26 wounds in 11 RDEB subjects were injected.
• 14 wounds received fibroblasts and 12 vehicle.
• All follow-up visits were completed.
• No significant adverse events.
• Pain scores reduced for both fibroblasts and vehicle (but not statistically significant).
• No major changes in Quality of Life scores.
A single injection of allogeneic fibroblasts accelerates initial wound healing in RDEB wounds

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<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 28</th>
<th>Day 56</th>
<th>Week 12</th>
<th>Week 26</th>
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<tbody>
<tr>
<td><strong>Erosion area (in cm²) over 26 weeks</strong></td>
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<tr>
<td>Mean (SD) (ICX-RHY-013)</td>
<td>19.5 (10.3)</td>
<td>10.7 (8.2)</td>
<td>11.5 (9.3)</td>
<td>9.8 (8.7)</td>
<td>17.0 (21.6)</td>
<td>8.4 (9.4)</td>
<td>6.7 (5.4)</td>
</tr>
<tr>
<td>Mean (SD) (vehicle)</td>
<td>18.7 (9.7)</td>
<td>14.0 (10.9)</td>
<td>13.8 (12.3)</td>
<td>13.1 (15.2)</td>
<td>13.7 (14.3)</td>
<td>8.0 (9.1)</td>
<td>4.8 (7.1)</td>
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<tr>
<td><strong>Treatment difference (ICX-RHY-013 – Vehicle)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Difference (95%CI)</td>
<td>-4.39</td>
<td>-3.85</td>
<td>-5.20</td>
<td>2.49</td>
<td>-009</td>
<td>1.15</td>
<td>(-8.91 to 0.12)</td>
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<tr>
<td>p value</td>
<td>0.056</td>
<td>0.20</td>
<td>0.26</td>
<td>0.70</td>
<td>0.98</td>
<td>0.68</td>
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<tr>
<td><strong>Percentage change in erosion area (in cm²) over 26 weeks</strong></td>
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<tr>
<td>Mean (SD) (ICX-RHY-013)</td>
<td>-49.8 (29.4)</td>
<td>-42.8 (32.2)</td>
<td>-54.4 (36.0)</td>
<td>-18.4 (65.0)</td>
<td>-55.9 (39.6)</td>
<td>-61.2 (29.3)</td>
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<tr>
<td>Mean (SD) (vehicle)</td>
<td>-31.9 (28.6)</td>
<td>-33.5 (41.5)</td>
<td>-37.8 (57.1)</td>
<td>-33.1 (58.7)</td>
<td>-62.8 (33.3)</td>
<td>-75.8 (30.6)</td>
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<tr>
<td><strong>Treatment difference (ICX-RHY-013 – Vehicle)</strong></td>
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<tr>
<td>Difference (95%CI)</td>
<td>-23.50</td>
<td>-19.15</td>
<td>-28.83</td>
<td>8.61</td>
<td>3.28</td>
<td>10.33</td>
<td>(-43.48 to -3.51)</td>
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<td>p value</td>
<td>0.025</td>
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<td>0.11</td>
<td>0.70</td>
<td>0.81</td>
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Allogeneic fibroblasts increase the rate of wound healing within the first 28 days.

![Graph showing the comparison of erosion size (cm²) over days for ICX-RHY-013 and Vehicle groups.](image-url)
• Beyond Day 28 changes in mean wound area did not differ significantly between the 2 groups.

• Blinded independent assessment of photographs showed **78.6%** (at Day 28) and **92.8%** (at Month 6) of the wounds treated with ICX-RHY-013 improved compared to Day 0.
Patient P5

Wound 1 at Day 0

Wound 1 at Day 28

FIBROBLASTS

Wound 2 at Day 0

Wound 2 at Day 28

VEHICLE
Conclusions

Single injection of allogeneic fibroblasts accelerates wound healing during the first 28 days.

Allogeneic fibroblasts represent a new disease-modifying advanced medicinal product that has clinical utility in RDEB.

Further studies are needed to optimise cell dosage, frequency of re-treatment and best mode of cell delivery.
Clinical Trial findings

- Intradermal injection was painful for EB patients
- Injecting vehicle intradermally had some effect on wound healing response
- Injecting Vavelta had an increased effect over vehicle which even on the small numbers of patients treated showed a significant difference at early time points. Ulcers that had not decreased in size in the month before treatment, reduced by an average of 49.8% in 7 days following treatment
- Beyond Day 28 of this single injection series changes in wound area between treatment and vehicle groups was the same. The effect of repeated injections was not examined in this study
- Blinded independent assessment of photographs showed 78.6% (at day 28) and 92.8% (at Month 6) of wounds treated with vavelta improved compared to Day 0
3. The provisions of this Directive shall not affect the powers of the Member States' authorities either as regards the setting of prices for medicinal products or their inclusion in the scope of national health insurance schemes, on the basis of health, economic and social conditions.

4. This Directive shall not affect the application of national legislation prohibiting or restricting the sale, supply or use of medicinal products as contraceptives or abortifacients. The Member States shall communicate the national legislation concerned to the Commission.

Article 8

1. In order to obtain an authorization to place a medicinal product on the market regardless of the procedure established by Regulation (EEC) No 2309/93, an application shall be made to the competent authority of the Member State concerned.

2. A marketing authorization may only be granted to an applicant established in the Community.

3. The application shall be accompanied by the following particulars and documents, submitted in accordance with Annex I:

(a) Name or corporate name and permanent address of the applicant and, where applicable, of the manufacturer.

(b) Name of the medicinal product.

(c) Qualitative and quantitative particulars of all the
1 INTRODUCTION

1.1 The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for ensuring that medicines and medical devices work, are safe and of appropriate quality. The MHRA's primary aim is to safeguard public health through a system of regulation. Pharmaceutical manufacturers and distributors operating in the UK marketplace are subject to a system of licensing and inspection, which ensures that licensed medicinal products conform to internationally-agreed standards, and that those medicines are manufactured, stored and distributed in compliance with the required regulatory standards.

1.2 Unless exempt, relevant medicinal products must have marketing authorisations or product licences before being placed on the market. In the UK an unlicensed relevant medicinal product may only be supplied in accordance with the provisions of Schedule 1 of The Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994 [SI 1994/3144], (the MA Regs.) Schedule 1 (see Appendix 1) exempts from the need for a marketing authorisation a relevant medicinal product which is supplied to fill a "special need" and in response to a bona fide unsolicited order, formulated in accordance with the specification of a doctor, dentist or supplementary prescriber and for use by his individual patients on his direct responsibility. In the interest of public health the exemption is narrowly drawn, because these products, unlike licensed products, may not have been assessed by the Licensing Authority against the criteria of safety, quality and efficacy.
10 EXPORT TO OTHER MEMBER STATES

10.1 Export from the UK to other EU/EEA Member States, of unlicensed relevant medicinal products may take place if:
   - they are manufactured in the UK by holders of Manufacturer’s “Specials” Licence (MS);
   - they are imported from within the EU/EEA by holders of Wholesale Dealer’s Licence (WL) or from outside the EU/EEA by holders of Manufacturer’s “Specials” Licence for Import.

10.2 Holders of the above licences may export unlicensed relevant medicinal products to other EU/EEA Member States, subject to the following conditions:
   - national legislation in the receiving Member State, in accordance with Article 5 of Directive 2001/83/EC, as amended, permits importation and supply of unlicensed relevant medicinal products;
   - the UK exporter (i.e. the holder of an MS or WL) has assured himself that importation and supply of an unlicensed relevant medicinal product is lawful in the Member State concerned before proceeding with the transaction;
   - in the case of unlicensed relevant medicinal products, imported into the UK for subsequent export to another Member State, the holder of a MS or WL is required to comply with the import notification requirements of Manufacturing and Wholesale Dealing Regulations (See Section 5).
Next Steps

• Clinical trial publication submitted
• Cell Therapy Catapult developing a “painless” injector system for ICX
• Manchester University’s MIMIT working with ICX to examine micro-needle delivery systems
• Technology Strategy Board provided grant obtained to examine shelf life extension. Early work suggests shelf of around a month may be possible
• Product to be supplied to clinics via “specials”. Full reimbursement already provided by NHS (National Commissioning) for first three patient treatments on a named patient basis. These patients have requested additional treatments (Includes patient 14)
• Aim is to examine repeated treatment effects prior to next clinical study
• Breakthrough therapy designation from FDA? (One of first 7 therapies designated is for EB treatment)
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