Treatment with delgocitinib cream is associated with reductions in *Staphylococcus aureus* density and pain, and increased microbial diversity in patients with mild to severe Chronic Hand Eczema

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Conclusions

- In patients with mild to severe Chronic Hand Eczema (CHE), *S. aureus* density at baseline was positively correlated with CHE severity and Hand Eczema Symptom Diary (HESD) pain score
- Delgocitinib cream treatment was associated with reduced *S. aureus* density and pain
- From baseline to end of treatment, alpha diversity increased with delgocitinib cream use (8 or 20 mg/g) and correlated with improved CHE severity
- The relative abundance of the most prevalent *Staphylococcus* species on CHE skin (*S. aureus* and *S. caprae*) decreased after treatment with delgocitinib cream 8 or 20 mg/g

Objectives

- The aim of this analysis was to investigate changes in *S. aureus* density, Chronic Hand Eczema (CHE) severity, pain, and microbial (alpha) diversity in patients with CHE

Background

- CHE is a multifactorial skin disease associated with skin barrier dysfunction, immune cell dysregulation and alterations of the skin microbiome[1]
- CHE is defined as hand eczema that persists for more than 3 months or returns twice or more per year[2]
- Pain is one of the most common and burdensome symptoms of CHE, negatively affecting patients' quality of life[1]
- More than 50% of patients with CHE are colonised with *S. aureus*[3]
- Patients with severe CHE have greater *S. aureus* density compared with patients with mild to moderate CHE[3]
- A higher *S. aureus* abundance has been reported in lesional skin compared with non-lesional skin[4]
- Delgocitinib cream 20 mg/g is a non-steroidal, topical, pan-Janus kinase inhibitor approved in multiple countries for the treatment of moderate to severe CHE in adults for whom topical corticosteroids (TCS) are inadequate or inappropriate[5,6]

Methods

Skin swab collection

- A representative lesional (n=216) and/or non-lesional (n=217) skin area of ~2 cm x 5 cm on the dorsal hand, wrist, or fingers was swabbed from each patient (n=220) before the start of treatment (i.e., baseline) and at the end of treatment (EoT) (i.e., Week 16)

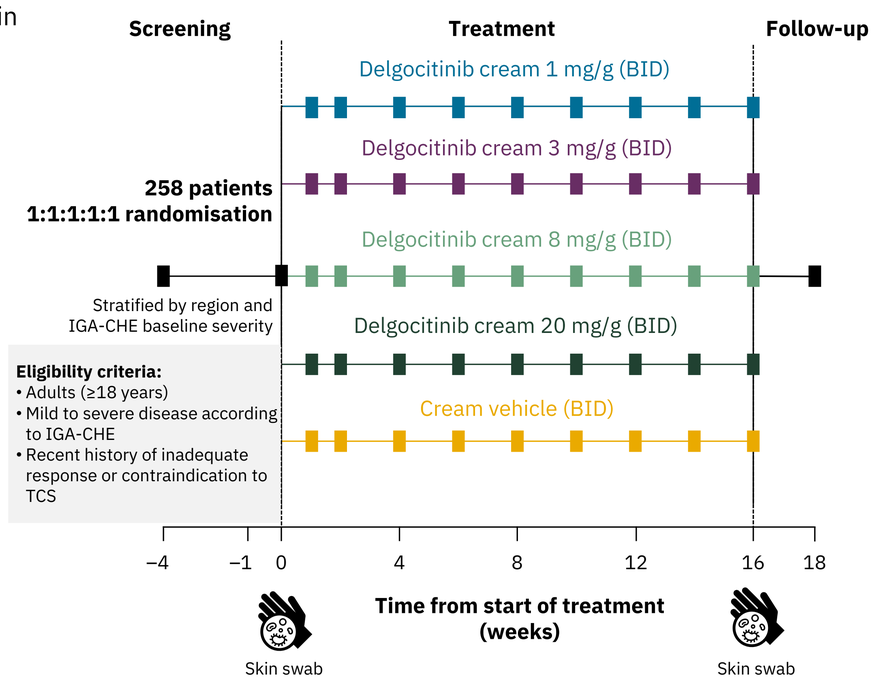
Key outcomes

- ***S. aureus* density:** *S. aureus* genome-copy numbers were quantified by qPCR targeting the femA gene and calculated per cm^2 of skin
- **Investigator's Global Assessment for CHE (IGA-CHE):** Clinician-reported CHE severity evaluated on a 5-point scale (from 0=clear to 4=severe)[2]
- **Hand Eczema Symptom Diary (HESD) pain:** Patient-reported worst severity of pain captured over the past 24 hours on an 11-point numerical rating scale (from 0=no pain to 10=severe pain)[3]
- **Microbial (alpha) diversity:** Assessed using the Shannon diversity index

Statistical analyses

- Differences between groups were evaluated using paired t-test
- The Spearman's rank correlation coefficient (ρ) test was used to assess relationships among *S. aureus* density, IGA-CHE, pain, and alpha diversity

Figure 1 Phase 2b study design (NCT03683719[1])



Results

Patient demographics and baseline characteristics

- There were no major differences in baseline characteristics between the treatment arms (**Table 1**)

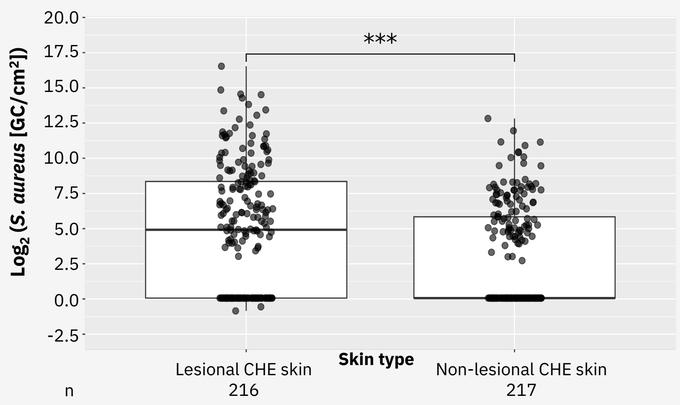
Table 1 Baseline characteristics by treatment arm

	Total[a] (n=220)	Delgocitinib 1 mg/g (n=41)	Delgocitinib 3 mg/g (n=45)	Delgocitinib 8 mg/g (n=45)	Delgocitinib 20 mg/g (n=46)	Cream vehicle (n=43)
Age, years, median (Q1-Q3)	48.5 (34.0-56.0)	46.0 (37.0-55.0)	48.0 (34.0-56.0)	51.0 (38.0-55.0)	47.0 (31.5-56.0)	51.0 (32.5-58.5)
Sex, female, n (%)	137 (62.3)	31 (75.6)	25 (55.6)	26 (57.8)	30 (65.2)	25 (58.1)
CHE duration, years, median (Q1-Q3)	8.0 (3.0-21.25)	7.0 (4.0-16.0)	6.0 (2.0-16.0)	7.0 (3.0-18.0)	10 (2.0-24.0)	9.0 (4.0-24.0)
IGA-CHE score, n (%)						
2 (Mild)	52 (23.6)	12 (29.3)	11 (24.4)	9 (20.0)	10 (21.7)	10 (23.3)
3 (Moderate)	122 (55.5)	22 (53.7)	26 (57.8)	24 (53.3)	26 (56.5)	24 (55.8)
4 (Severe)	46 (20.9)	7 (17.1)	8 (17.8)	12 (26.7)	10 (21.7)	9 (20.9)
HECSI score, median (min-max)	44.5 (5-296)	43.0 (5-182)	44.0 (11-186)	43.0 (6-122)	49.5 (7-296)	45.0 (9-150)

[a]Total number of patients included in analysis.

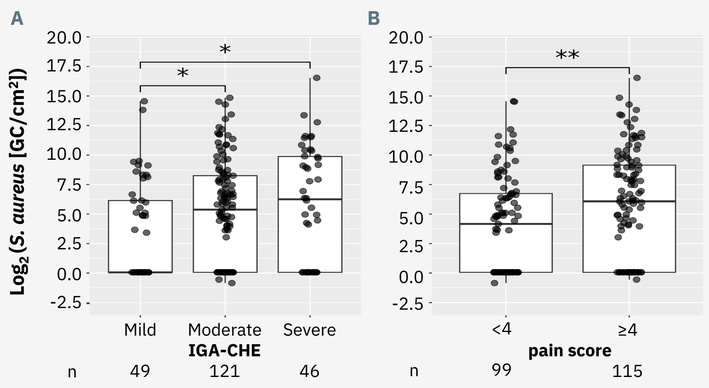
Impact on *S. aureus* density

Figure 2 *S. aureus* density in lesional and non-lesional CHE skin at baseline



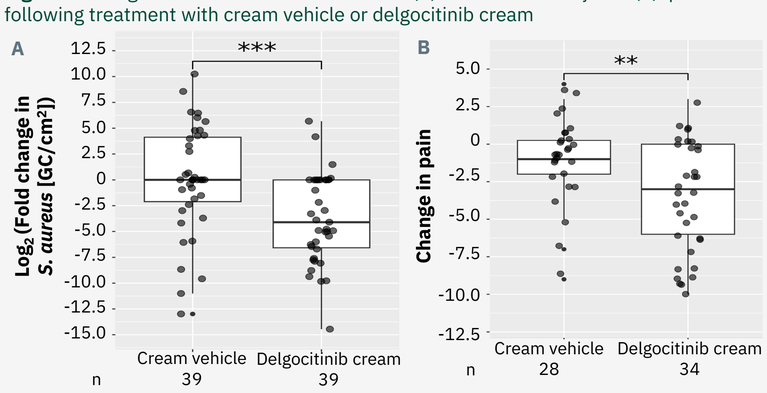
***p<0.001. Differences between groups were evaluated using paired t-test. Log2-transformed genome-copy numbers/cm2 are displayed on the y-axis.

Figure 3 *S. aureus* density in patients at baseline stratified by (**A**) IGA-CHE score and (**B**) pain score



*p<0.05, **p<0.01. Differences between groups were evaluated using t-test. Log2-transformed genome-copy numbers/cm2 are displayed on the y-axis.

Figure 4 Changes from baseline to Week 16 in (**A**) *S. aureus* density and (**B**) pain score following treatment with cream vehicle or delgocitinib cream



**p<0.01, ***p<0.001. Differences between groups were evaluated using t-test. Fold changes in log2-transformed genome-copy numbers/cm2 are displayed on the y-axis.

- At baseline, in the pooled delgocitinib cream and cream vehicle groups, median (IQR) *S. aureus* density was higher in lesional CHE skin (4.92 [0.06-8.35] GC/cm^2) than in non-lesional CHE skin (0.06 [0.06-5.84] GC/cm^2) (p<0.001) (**Figure 2**)
- At baseline, among pooled lesional CHE skin samples, median (IQR) *S. aureus* density was higher in patients with moderate CHE (5.38 [0.06-8.25]) or severe (6.25 [0.06-9.88]) CHE than in those with mild CHE (0.06 [0.06-6.15]) (p<0.05) and in patients with a pain score ≥4 (6.08 [0.06-9.14]) than in those with a score <4 (4.16 [0.06-6.74]) (p<0.01) (**Figure 3**)
- Patients treated with delgocitinib cream 20 mg/g showed greater reductions from baseline to Week 16 in *S. aureus* density (p<0.001) and pain score (p<0.01) than patients treated with cream vehicle (**Figure 4**)
  - Compared with cream vehicle, delgocitinib treatments resulted in 13.2- and 3.6-fold greater reductions from baseline to Week 16 in *S. aureus* density and pain score, respectively

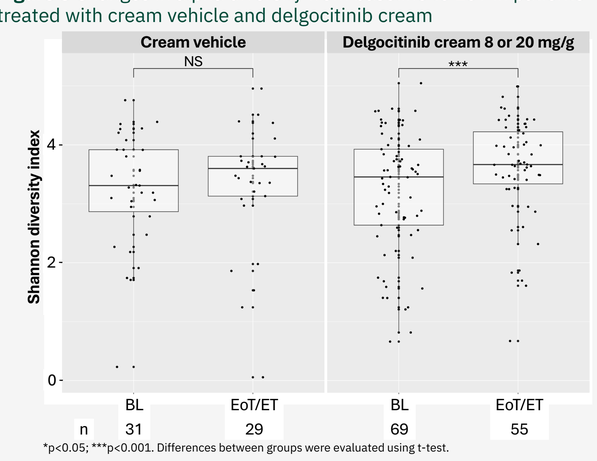
Impact on alpha diversity

- In patients treated with cream vehicle, no significant difference in mean (SD) alpha diversity was observed from baseline (3.23 [0.98]) to EoT (3.31 [1.06]) (p>0.05) (**Figure 5**)
- In patients treated with delgocitinib cream 8 or 20 mg/g, mean (SD) alpha diversity increased from baseline (3.21 [1.03]) to EoT (3.59 [0.87]) (p<0.001) (**Figure 5**)
- Across pooled treatment groups and timepoints, alpha diversity negatively correlated with CHE severity (ρ= −0.3)
- Patients with severe CHE had lower alpha diversity than those with clear/almost clear CHE (p<0.001) (**Figure 6**)

Mean (SD) alpha diversity by IGA-CHE score was:

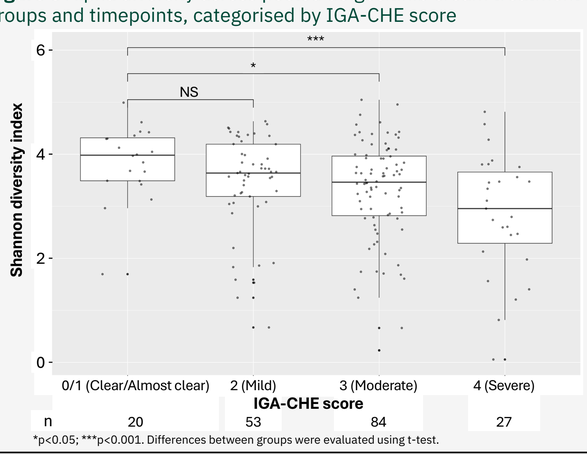
- **0/1 (Clear/almost clear):** 3.85 (0.72)
- **2 (Mild):** 3.46 (0.92)
- **3 (Moderate):** 3.31 (0.97)
- **4 (Severe):** 2.86 (1.16)

Figure 5 Changes in alpha diversity from baseline to EoT in patients treated with cream vehicle and delgocitinib cream



*p<0.05; ***p<0.001. Differences between groups were evaluated using t-test.

Figure 6 Alpha diversity across pooled delgocitinib cream treatment groups and timepoints, categorised by IGA-CHE score



*p<0.05; ***p<0.001. Differences between groups were evaluated using t-test.

Impact on *Staphylococcus* relative abundance

- The most prevalent bacterial pathogens detected on CHE skin were *S. aureus*, *S. caprae*, and *Streptococcus oralis* (**Figure 7A**)
  - *Streptococcus oralis* is typically part of the oral microbiota rather than the skin
- Its presence on the skin may result from indirect transfer through hand-to-mouth contact
- The relative abundance of *S. aureus* and *S. caprae* decreased after treatment with delgocitinib cream 8 or 20 mg/g (p<0.05) (**Figure 7A**)
- Most prevalent *Staphylococcus* species on CHE skin were *S. aureus* and S. *caprae* (**Figure 7B**)
- The relative abundance of *S. aureus* and *S. caprae* decreased after treatment with delgocitinib cream 8 or 20 mg/g (p<0.05) (**Figure 7B**)

Figure 7 Mean relative abundances of (**A**) top 20 bacterial species and (**B**) top 100 *Staphylococcus* species in CHE patients at baseline and after 16 weeks of treatment with cream vehicle or delgocitinib cream

Abbreviations BL, baseline; CHE, Chronic Hand Eczema; EoT, end of treatment; ET, early termination; GC/cm^2, genome-copy numbers per cm^2; HECSI, Hand Eczema Severity Index; Hand Eczema Symptom Diary; IGA-CHE, Investigator's Global Assessment for CHE; IQR, interquartile range; log_2, log_2-transformed value; n, number of patients with observation; NS, not significant; qPCR, quantitative polymerase chain reaction; SD, standard deviation; TCS, topical corticosteroids.

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