Minimal Systemic Exposure of Delgocitinib Cream in Adults With Moderate to Severe Chronic Hand Eczema in the Phase 3 DELTA 2 Trial

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Learning Objectives: To examine systemic exposure parameters of delgocitinib cream in the Phase 3 DELTA 2 trial and to compare systemic exposure data between delgocitinib cream and oral delgocitinib from a Phase 1 trial.
Takeaway Message: Based on these data, no systemic pharmacological effect is expected with delgocitinib cream 20 mg/g dosing in patients with moderate to severe CHE.

Background

- CHE is the most frequent chronic inflammatory disease affecting hands and wrists.[1-4]
- It is a heterogeneous disease associated with pain, pruritus, and significant occupational, functional, social, and psychological burden.[1-4]
- Delgocitinib cream (20 mg/g; applied twice-daily), a first-in-class topical pan-JAK inhibitor preventing JAKs' enzymatic activity and targeting key mediators of the pathogenesis of CHE, was well tolerated and demonstrated significant improvement in all primary and secondary efficacy endpoints in the DELTA 1[5] and DELTA 2 pivotal Phase 3 trials for the treatment of moderate to severe CHE in adults.

Methods

- DELTA 2 is a randomized, double-blind, vehicle-controlled, Phase 3 trial :
  - Adults (aged ≥18 years) with moderate to severe CHE were randomized 2:1 to twice-daily delgocitinib cream 20 mg/g (n=314) or cream vehicle (n=159) for 16 weeks followed by a 2-week safety follow-up period.
  - Blood samples collected 2-6 hours after application at Weeks 1, 4, and 16 were used to analyze plasma concentrations of delgocitinib using a LC/MS-based method with a LLQ of 5 pg/ml.
- Phase 1 oral trial: randomized, double-blind, parallel-group, vehicle-controlled
  - Healthy adult volunteers were randomized to a single oral dose of delgocitinib (1.5, 3, 6, and 12 mg; N=40), with samples being collected 30 minutes prior to administration and post-administration at 13 timepoints up to 24 hours.
- IC_{50} of delgocitinib was assessed using an in vitro IL-4 release assay in the whole blood of healthy adults (n=4).

Results

- Minimal systemic exposure was observed in all 3 sampling time points in the DELTA 2 trial (**Table 1**).
  - The DELTA 2 trial analysis included samples from 313 subjects on active treatment.
  - A reduction in delgocitinib plasma concentration was observed from Week 1 (0.21 ng/ml) to Week 16 (0.12 ng/ml).

Table 1. *Peak systemic exposure in the DELTA 2 trial.*[a]

Plasma concentration of delgocitinib	
Week 1 (n=286)	Delgocitinib cream 20 mg/g
Geometric mean (ng/ml)	0.21
CV (%)	219.0
Median (Q_1;Q_3)	0.22 (0.11;0.47)
Min;Max (ng/ml)	0.00;5.7
Week 4 (n=275)	
Geometric mean (ng/ml)	0.20
CV (%)	228.4
Median (Q_1;Q_3)	0.23 (0.11;0.53)
Min;Max (ng/ml)	0.00;4.8
Week 16 (n=261)	
Geometric mean (ng/ml)	0.12
CV (%)	461.3
Median (Q_1;Q_3)	0.14 (0.05;0.37)
Min;Max (ng/ml)	0.00;4.6

[a]One patient was excluded from this analysis due to an outlier value at Week 4.
CV, coefficient of variation (calculated based on log-normal distribution assumption); min, minimum; max, maximum; n, number of patients with data available; Q_1, first quartile; Q_3, third quartile.

- The geometric mean IC_{50} of delgocitinib in an IL-4 release assay (in vitro spiking of whole blood from healthy adults) was 17.2 ng/ml (**Table 2**).
- The topical exposure level observed in the DELTA 2 trial was ≥80-fold below the whole blood IC_{50} value of delgocitinib (17.2 ng/ml divided by 0.21 ng/ml).

Table 2. *Delgocitinib whole blood potency in healthy adults.*

Delgocitinib	
Potency in whole blood assay (n=4) Geometric mean (lower and upper 95% CI)	
IC_{20} ng/ml (95% CI)	7.2 (3.9 – 13.4)
IC_{50} ng/ml (95% CI)	17.2 (11.8 – 25.2)
IC_{80} ng/ml (95% CI)	40.8 (15.6 – 106.5)

CI, confidence interval; IC20/50/80, concentration of drug required for 20%/50%/80% inhibition; n, number of patients with data available.

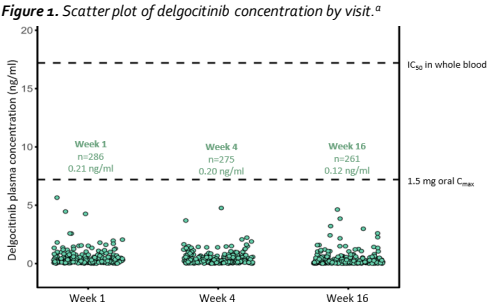
- In the Phase 1 study, the lowest tested oral dose of delgocitinib (1.5 mg) is regarded as a subtherapeutic dose.
  - The lowest oral delgocitinib dose tested (1.5 mg; n=8) is regarded as subtherapeutic and showed a peak systemic exposure (geometric mean C_{max}) of 7.2 ng/ml (**Table 3**).
- Systemic exposure of topical application in the DELTA 2 trial was ≥30-fold lower than the lowest oral dose of delgocitinib tested (7.2 ng/ml divided by 0.21 ng/ml; **Figure 1**).

Table 3. *Peak systemic exposure in the Phase 1 trial.*

Dose (mg)	N	$AUC_{0-\infty}$ (h*ng/ml)	C_{max} (ng/ml)	t_{max} (h) median	$t_{1/2}$ (h)
1.5	8	39.6	7.2	1.0	2.0
3	8	66.6	18.4	0.84	2.3
6	8	211.0	51.0	0.83	2.9
12	8	408.0	99.3	1.0	2.8

$AUC_{0-\infty}$, extrapolated area under the plasma concentration-time curve; C_{max}, peak drug plasma concentration; IC_{50}, concentration of drug required for 50% inhibition; n, number of patients with data available; $t_{1/2}$, time required for drug plasma concentration to decrease by 50%; t_{max}, time to peak drug plasma concentration.

Figure 1. *Scatter plot of delgocitinib concentration by visit.*[a]



Horizontal dashed lines represent geometric mean values.
[a]One patient was excluded from this analysis due to an outlier value at Week 4.
C_{max}, peak drug plasma concentration; IC_{50}, concentration of drug required for 50% inhibition.

Conclusions

- Twice-daily application of delgocitinib cream 20 mg/g resulted in minimal systemic exposure in moderate to severe CHE patients over 16 weeks.
  - Highest topical systemic exposure level (geometric mean: 0.21 ng/ml at Week 1) was ≥80-fold below the whole blood IC_{50} value of delgocitinib (17.2 ng/ml).
  - Highest topical systemic exposure level (geometric mean: 0.21 ng/ml at Week 1) was ≥30-fold lower than the lowest oral dose of delgocitinib tested (1.5 mg; 7.2 ng/ml) with no overlap in plasma exposure between oral and topical administration.
- These data support that no meaningful systemic pharmacological effect is expected with twice-daily application of delgocitinib cream 20 mg/g in patients with moderate to severe CHE.

References:
1. Capucci S et al. *Dermatitis.* 2020;31(3):178-184. **2.** Thyssen JP et al. *Contact Dermatitis.* 2022;86(5):357-378. **3.** Politiek K et al. *Contact Dermatitis.* 2016;75(2):67-76. **4.** Kouris A et al. *Contact Dermatitis.* 2015;72(6):367-370. **5.** Bissonnette R et al. Late Breaker presentation on 18th March at the 81st Annual Meeting of the American Academy of Dermatology (AAD) in New Orleans, LA, USA.
Abbreviations:
CHE, chronic hand eczema; C_{max} peak drug plasma concentration; IC_{50}, concentration of drug required for 50% inhibition; IL, interleukin; JAK, Janus kinase; LC/MS, liquid chromatography/mass spectrometry; LLQ, lower limit of quantitation.

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