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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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Introduction & Objectives:

Delgocitinib is a topical pan-Janus kinase (JAK) inhibitor that was well tolerated and demonstrated significant improvement in primary and all secondary efficacy endpoints in the DELTA 1 (NCT04871711) pivotal phase 3 trial for treatment of chronic hand eczema (CHE). The identical DELTA 2 pivotal phase 3 trial (NCT04872101) was designed to confirm the efficacy, safety, and effect on health-related quality of life of twice-daily applications of delgocitinib cream 20 mg/g compared with cream vehicle in adults with moderate to severe CHE. Here we present additional DELTA 2 analyses examining systemic exposure parameters of delgocitinib cream, which allow comparisons with systemic exposure data of oral delgocitinib from a phase 1 trial (NCT05050279).

Materials & Methods:

DELTA 2 was a randomized, double-blind, vehicle-controlled 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 or were transferred to a 36-week extension trial (NCT04949841). Blood samples collected 2–6 hours after application of the investigational medicinal product at Weeks 1, 4, and 16 were used to analyse plasma concentrations of delgocitinib using a liquid chromatography/mass spectrometry-based method with a lower limit of quantitation of 5 pg/ml. The inhibitory concentration of 50% (IC50) of delgocitinib was assessed using an in vitro IL-4 release assay in whole-blood of healthy volunteers (n=4). In the phase 1 trial, single oral doses of delgocitinib (1.5, 3, 6, and 12 mg) were tested in healthy volunteers (n=40). Data are reported as geometric means.

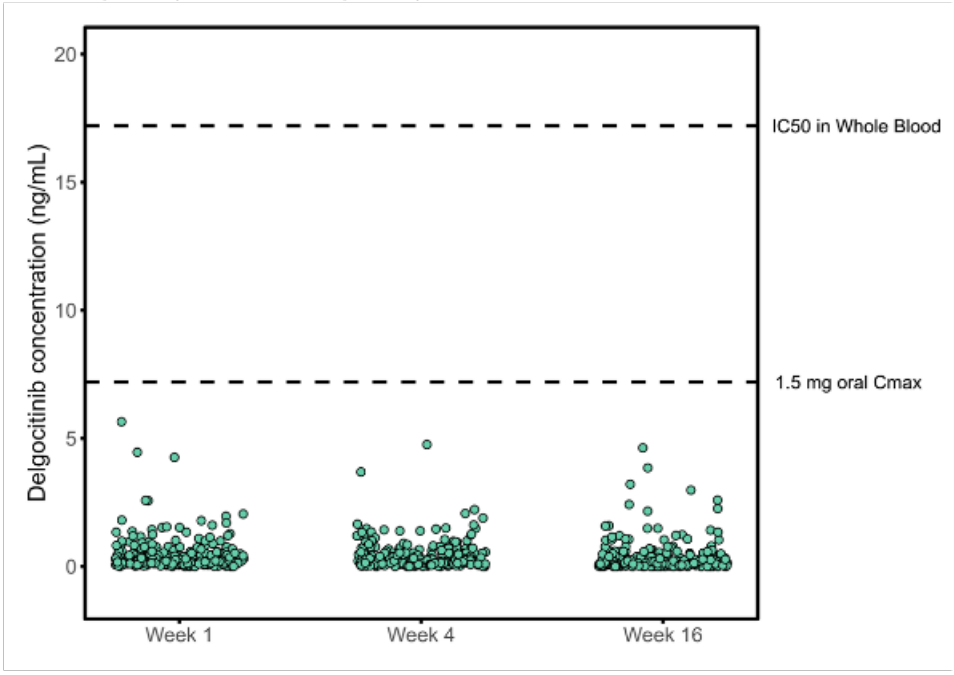
Results:

The DELTA 2 analysis included samples from 313 subjects on active treatment. The plasma concentration of delgocitinib was 0.21, 0.20 and 0.12 ng/ml at Weeks 1, 4 and 16, respectively (Figure 1). IC50 of delgocitinib was 17.2 ng/ml. In the phase 1 study, the lowest tested oral dose of delgocitinib (1.5 mg) was perceived as a sub-therapeutic dose. Peak systemic exposure (Cmax) of the 1.5 mg orally dosed delgocitinib was 7.2 ng/ml, meaning that systemic exposure after topical application in DELTA 2 was ≥30-fold lower (7.2 ng/ml divided by 0.21 ng/ml).

Conclusion:

Twice daily application of delgocitinib cream resulted in minimal systemic exposure, at least 80-fold below the whole-blood IC50 over 16 weeks (17.2 ng/ml divided by 0.21 ng/ml), and at least 30-fold below oral 1.5 mg delgocitinib dose with no overlap in plasma exposure between oral and topical administration. These data further support the favourable safety profile of topical delgocitinib cream and suggest that no systemic pharmacological effect is expected with 20 mg/g dosing in patients with moderate to severe CHE.

Figure 1. Scatter plot[a] of delgocitinib concentration by visit at Week 1 (n=286), Week 4 (n=275) and Week 16 (n=261)



[a]One subject was excluded from this analysis due to an outlier value at Week 4.