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# First-in-Class FASN Inhibitor Denifanstat Achieved All Endpoints in the Treatment of Acne Vulgaris: Results from a Phase III Randomised Placebo Controlled Trial

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**Introduction**

Denifanstat is a fatty acid synthase (FASN) inhibitor that addresses acne vulgaris by inhibiting *de novo* fatty acid synthesis in human sebocytes. A previous Phase II clinical trial (NCT05104125) showed that denifanstat was safe and well tolerated, leading to a significant improvement in acne lesions. Optimal efficacy was observed at a dose of 50mg. Here we report results from a Phase III clinical trial conducted to further evaluate the efficacy and safety of denifanstat in the treatment of acne vulgaris in a larger cohort of patients.

**Materials and Methods**

This randomised, double-blind, placebo-controlled, multicentre Phase III clinical trial (NCT06192264) was conducted in China. Patients with moderate to severe acne (Investigator's Global Assessment 3 and 4) were randomly assigned at a 1:1 ratio to receive either 50 mg of oral denifanstat tablets or a matching placebo once daily for 12 weeks.

**Results**

480 patients with moderate-to-severe facial acne vulgaris were enrolled in the trial. The mean age of participants was 22.6 years, with 68.8% female and 94.8% of Han ethnicity. At baseline, the mean inflammatory and non-inflammatory lesion counts were 42.6 and 59.5, respectively. Approximately 85.8% of subjects had an Investigator's Global Assessment (IGA) score of 3 (moderate).

By week 12, the treatment success rate (defined as a ≥2-point reduction in IGA from baseline and an IGA of 0 or 1) was significantly higher in the 50 mg denifanstat group (33.17%) than in the placebo group (14.58%). The difference between the two groups was 18.59% (95% CI: 15.58%, 21.61%, $P < 0.0001$). The denifanstat group showed a significant 57.38% reduction in total lesion count from baseline, which was markedly superior to the 35.42% reduction observed in the placebo group (an inter-group difference of -21.96%, with a 95% CI of -27.51% to -16.40% and a *P*-value of < 0.0001). Specifically, inflammatory lesions decreased by 63.45% in the denifanstat group compared to 43.21% in the placebo group (difference: -20.24%, 95% CI: -26.21%, -14.27%, $P < 0.0001$). Non-inflammatory lesions decreased by 51.85% compared to 28.94% in the placebo group (difference: -22.91%, 95% CI: -30.02%, -15.80%, $P < 0.0001$). Detailed efficacy outcomes are summarized in Table 1.
During the 12-week treatment period, denifanstat at a dose of 50 mg demonstrated a favourable safety and tolerability profile. The overall incidence of treatment-emergent adverse events (TEAEs) was similar in the denifanstat and placebo groups. The incidence of trial drug-related TEAEs was below 10% in both groups. Dry skin (6.3% vs 2.9%) and dry eye (5.9% vs 3.8%) were the only TEAEs to occur in more than 5% of patients in the treatment group. All drug-related adverse events were mild or moderate (Grade 1-2), with no Grade 3 or higher adverse events or serious adverse events (SAEs) reported, and no deaths.

**Table 1 Efficacy Outcomes for Denifanstat vs. Placebo at Week 12 (Intention-To-Treat Analysis)**

| Efficacy endpoints | 50mg Denifanstat (N=240) | Placebo (N=240) | Difference LS Mean(95%CI) | *P*-value |
|---|---|---|---|---|
| Treatment success，n(%) | 75 (33.17%) | 33 (14.58%) | 18.59 (15.58, 21.61) | <0.0001 |
| PCFB in TL, LS Mean (SE), % | -57.38(1.99) | -35.42 (2.03) | -21.96 (-27.51, -16.40) | <0.0001 |
| PCFB in IL, LS Mean (SE), % | -63.45 (2.14) | -43.21 (2.18) | -20.24 (-26.41, -14.27) | <0.0001 |
| PCFB in NIL, LS Mean (SE), % | -51.85 (2.55) | -28.94 (2.58) | -22.91 (-30.02, -15.80) | <0.0001 |
| ACFB in TL, LS Mean (SE) | -58.25 (2.06) | -36.17 (2.08) | -22.08 (-27.79, -16.37) | <0.0001 |
| ACFB in IL, LS Mean (SE) | -26.56 (0.94) | -18.42 (0.95) | -8.14 (-10.74, -5.54) | <0.0001 |

Treatment success was defined as a ≥2-point reduction in IGA score from baseline and an absolute score of 0 or 1. PCFB: Percent Change from Baseline; ACFB: Absolute Change from Baseline; TL: Total Lesions; IL: Inflammatory Lesions; NIL: Non-inflammatory Lesions; LS: Least Squares; SE: Standard Error. P-values were calculated using ANCOVA.

## Conclusion

Once daily 50 mg denifanstat achieved highly statistically significant and clinically meaningful improvements across all efficacy endpoints. The exceptional efficacy of denifanstat coupled with its favorable safety and

tolerability profile represents a potential major break-through for the treatment of acne vulgaris.