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

Fatty acid synthase (FASN) is a critical enzyme in the de novo lipogenesis (DNL) pathway, which produces the majority of the lipids that constitute sebum.[1] FASN inhibition interrupts the final step of fatty acid synthesis, specifically the creation of palmitate.[2] In addition, FASN inhibition also exerts anti-inflammatory effects by disrupting key inflammatory signaling pathways.[3] This represents a dual mechanism of action for treating acne, addressing both the root cause of excessive sebum and the resulting inflammatory cascade.

Denifanstat is an oral FASN inhibitor addressing acne vulgaris by inhibiting de novo lipogenesis in human sebocytes. A previous Phase II clinical trial (NCT05104125) demonstrated that denifanstat was generally well tolerated, with a significant improvement in acne lesions. A 50mg dose was found to be the ideal dose in a Phase II trial. We report results of a Phase III clinical trial that evaluated the efficacy and safety of denifanstat in moderate to severe acne vulgaris.

Methods

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

Efficacy was evaluated based on three primary outcome measures:

1. Percentage of subjects in each group achieving treatment success based on the IGA at Week 12 (where treatment success was defined as: an IGA score of 0 or 1, and a reduction in IGA score of ≥2 from baseline);
2. Percentage change in total skin lesion count (TLC) from baseline for subjects in each group at Week 12; and
3. Percentage change in inflammatory skin lesion count (ILC) from baseline for subjects in each group at Week 12.

The key secondary efficacy indicator was the percentage change in non-inflammatory skin lesion count from baseline for subjects in each group at Week 12. Secondary efficacy endpoints included absolute change in TLC from baseline for subjects in each group at Week 12 and absolute change in ILC from baseline for subjects in each group at Week 12.

Per protocol, safety was evaluated at prespecified timepoints, and adverse events were recorded at each study visit (Day 1, Week 2, Week 4, Week 8, and Week 12).

Results

A total of 480 participants with facial acne vulgaris were enrolled. Baseline demographics and clinical features were well balanced across groups (Table 1).

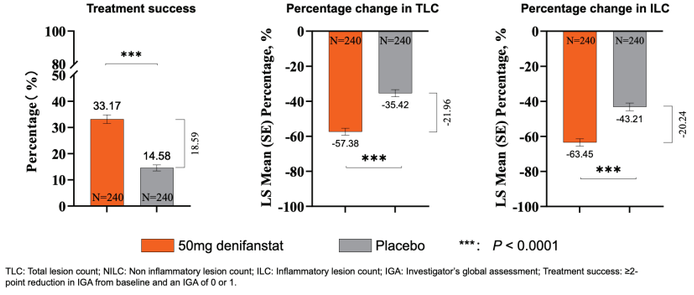
Table 1. Baseline Demographics and Clinical Features

Characteristics	Denifanstat (N=240)	Placebo (N=240)	Total (N=480)
Gender, n(%)			
Male	79 (32.9%)	71 (29.6%)	150 (31.3%)
Female	161 (67.1%)	169 (70.4%)	330 (68.8%)
Age, year, Mean (SD)	22.7 (3.97)	22.5 (3.54)	22.6 (3.75)
Ethnic: Han, n(%)	229 (95.4%)	226 (94.2%)	455 (94.8%)
Height, cm, Mean (SD)	166.25 (7.82)	166.60 (8.24)	166.42 (8.02)
Weight, kg, Mean (SD)	59.92 (11.01)	58.29 (11.19)	59.11 (11.11)
BMI, kg/m^2, Mean(SD)	21.621 (3.24)	20.894 (2.99)	21.258 (3.13)
TLC, Mean(SD)	102.2 (24.61)	102.1 (25.10)	102.1 (24.83)
ILC, Mean(SD)	42.1 (11.68)	43.1 (12.18)	42.6 (11.93)
IGA = 3(Moderate), n(%)	206 (85.8%)	206 (85.8%)	412 (85.8%)
IGA = 4(Severe), n(%)	34 (14.2%)	34 (14.2%)	68 (14.2%)

TLC: Total lesion count; NILC: Non inflammatory lesion count; ILC: Inflammatory lesion count; IGA: Investigator's global assessment.

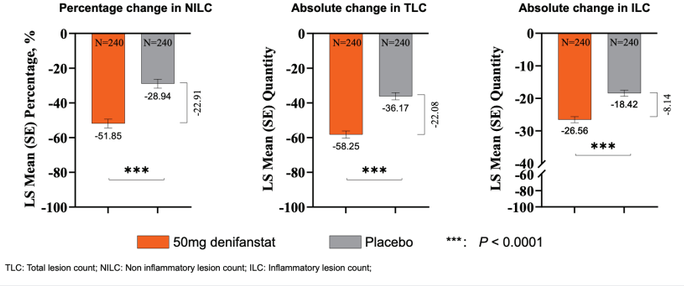
Denifanstat met all primary and secondary efficacy endpoints and significantly improved moderate-to-severe acne compared with placebo (Figures 1 and 2).

Fig. 1. Denifanstat met all primary efficacy endpoints (ITT analysis) and significantly improved moderate-to-severe acne compared with placebo



TLC: Total lesion count; NILC: Non inflammatory lesion count; ILC: Inflammatory lesion count; IGA: Investigator's global assessment; Treatment success: ≥2-point reduction in IGA from baseline and an IGA of 0 or 1.

Fig. 2. Denifanstat met all secondary efficacy endpoints (ITT analysis) and significantly improved moderate-to-severe acne compared with placebo



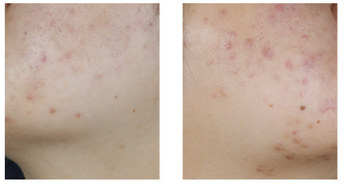
TLC: Total lesion count; NILC: Non inflammatory lesion count; ILC: Inflammatory lesion count;

Denifanstat was generally well-tolerated during the 12-week treatment period. The overall incidence of treatment-emergent adverse events (TEAEs) was similar in the denifanstat (58.6%) and placebo groups (56.3%). Most were Grade 1 (32.6% denifanstat; 32.1% placebo) or Grade 2 (24.3% denifanstat; 22.9% placebo) in severity.

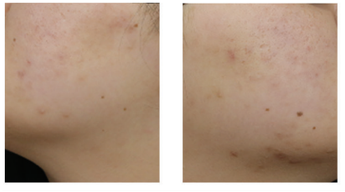
Table 2: Drug-related TEAEs

	Denifanstat (N=239) n(%)	Placebo (N=240) n(%)	Total (N=479) n(%)
Drug-related TEAEs	70 (29.3)	57 (23.8)	127 (26.5)
Xerophthalmia	14 (5.9)	9 (3.8)	23 (4.8)
Dry eye	12 (5.0)	10 (4.2)	22 (4.6)
Reduced tear film breakup time	3 (1.3)	6 (2.5)	9 (1.9)
Elevated blood bilirubin	5 (2.1)	3 (1.3)	8 (1.7)
Urine protein detection	2 (0.8)	3 (1.3)	5 (1.0)
Increased serum creatinine	3 (1.3)	2 (0.8)	5 (1.0)
Dry skin	15 (6.3)	7 (2.9)	22 (4.6)
Skin exfoliation	8 (3.3)	2 (0.8)	10 (2.1)
Hyperuricemia	5 (2.1)	5 (2.1)	10 (2.1)
Urinary tract infection	2 (0.8)	4 (1.7)	6 (1.3)
Conjunctivitis	3 (1.3)	0	3 (0.6)
Irregular menstruation	3 (1.3)	0	3 (0.6)

- Drug-related TEAEs primarily affected the eyes, skin and laboratory parameters.
- Incidence was similar between denifanstat (29.3%) and placebo (23.8%).



Baseline
IGA score: 3
Total lesion count: 74
Inflammatory lesion count: 43
Non inflammatory lesion count: 31



Week 12
IGA score: 1
Total lesion count: 9
Inflammatory lesion count: 7
Non inflammatory lesion count: 2

Conclusions

Denifanstat, an oral FASN inhibitor, significantly improved moderate-to-severe acne in this Phase III study and was generally well tolerated. By reducing de novo lipid synthesis and dampening inflammatory pathways, denifanstat targets two key drivers of acne pathogenesis: sebum overproduction and inflammation.

All primary and secondary endpoints were met. At Week 12, treatment success rates with denifanstat were more than double those of placebo, with marked reductions in both inflammatory and non-inflammatory lesions. Results were consistent with prior Phase II findings, confirming reproducible efficacy.

Denifanstat was generally well tolerated, with a safety profile comparable to placebo. Most treatment-emergent adverse events were mild to moderate in intensity, and drug-related events were infrequent. This supports the potential for chronic use without the limitations associated with antibiotic resistance or systemic retinoid toxicity.

Collectively, these results validate FASN inhibition as a novel therapeutic strategy in acne management. Denifanstat offers a non-hormonal, non-antibiotic, oral option that targets fundamental disease mechanisms, potentially redefining systemic treatment paradigms for acne vulgaris. Once approved, denifanstat may offer dermatologists with a generally well tolerated, mechanism-driven alternative for patients with moderate-to-severe acne who require systemic therapy.

References

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Acknowledgment

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