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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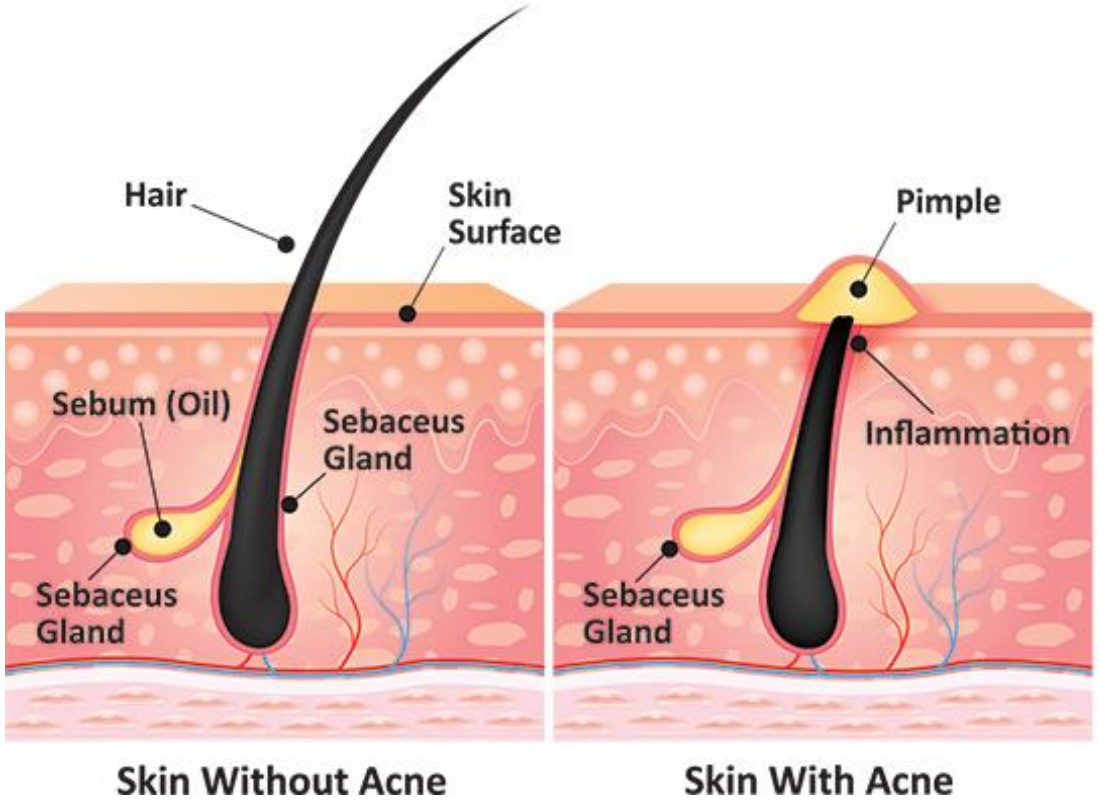
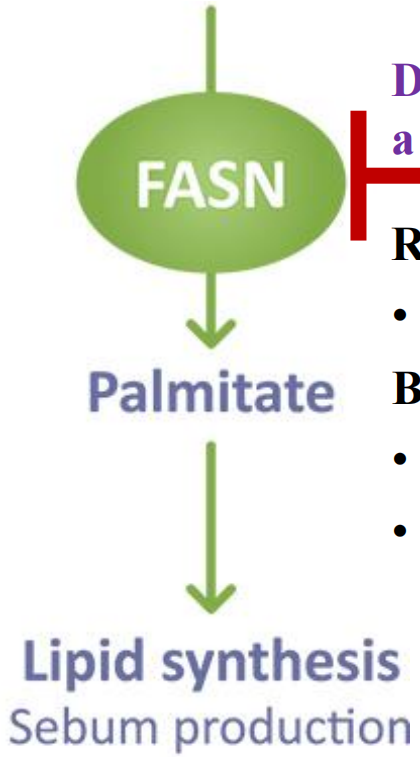
Disclosure

- I served as the principal investigator for three clinical trials of denifanstat in Chinese subjects with acne vulgaris: a Phase 2 study (ASC40-202) and two Phase 3 studies (ASC40-303 & ASC40-304).
- The trials were sponsored by Ascletis BioScience Co., Ltd.

Mechanism of Denifanstat in Treating Acne Vulgaris





Denifanstat, a FASN inhibitor

Reduces Sebum Production

- Directly inhibits FASN in sebocytes[1]

Blocks Inflammation

- Lowers cytokine release
- Suppresses Th17 cell differentiation[2]

FASN: Fatty Acid Synthase

[1]. Esler, W. P., et al.[J] Sci Transl Med, (2019).DOI: 10.1126/scitranslmed.aau8465;
[2]. O'Farrell, M., et al.[J] Scientific Reports, (2022).DOI: 10.1038/s41598-022-19459-z

Significant Efficacy of Denifanstat in Acne Treatment: Results from Phase 2 clinical trial

Efficacy Endpoints		25 mg Denifanstat (n=45)	50 mg Denifanstat (n=44)	75 mg Denifanstat (n=45)	Placebo (n=45)
At Week 12					
Percentage change from baseline in TLC*	Median	-53.16	-61.25	-53.13	-34.19
	P-value	0.005	0.008	0.008	NA
Percentage change from baseline in ILC*	Median	-54.35	-64.95	-60.00	-31.43
	P-value	0.006	0.003	0.029	NA
Treatment success rate*#	Percentage Rate	10.0	19.4	8.8	5.1
	P-value	0.675	0.079	0.659	NA
Absolute change from baseline in TLC*	Median	-56.0	-60.5	-46.0	-37.0
	P-value	0.024	0.030	0.083	NA
Absolute change from baseline in ILC*	Median	-25.0	-26.0	-22.0	-13.0
	P-value	0.007	0.003	0.032	NA

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

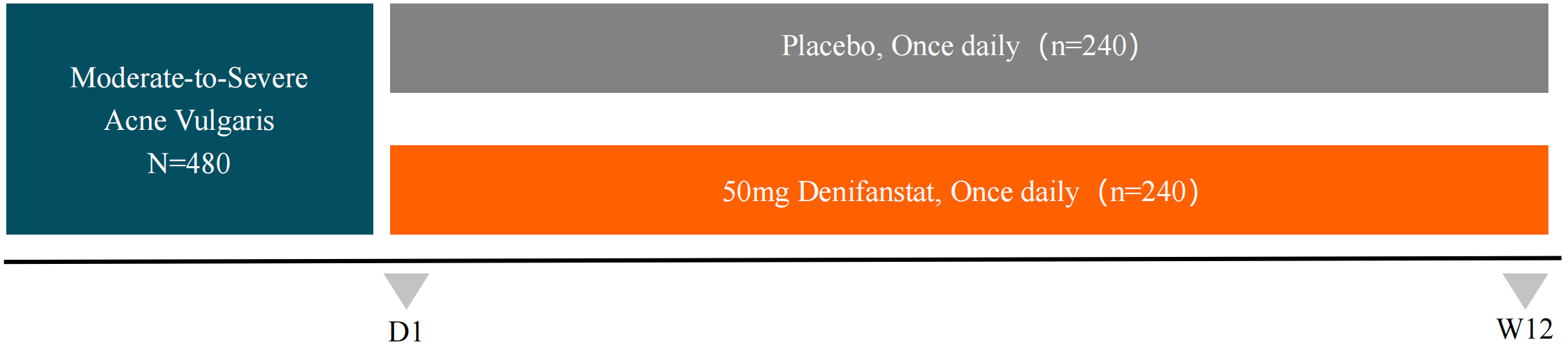
*Missing data were imputed using the Last Observation Carried Forward (LOCF) method. P-values represent the statistical difference between the treatment group and the placebo group. # Treatment success: ≥2-point reduction in IGA from baseline and an IGA of 0 or 1.

Denifanstat demonstrated good safety and tolerability in Phase 2 clinical trial

Safety Results	25 mg Denifanstat (n=45)	50 mg Denifanstat (n=44)	75 mg Denifanstat (n=45)	Placebo (n=45)
TEAEs related to trial drug, n(%)	22(48.89%)	21(47.73%)	28(62.22%)	22(48.89%)
TEAEs of grade 3 or above	0	0	0	0
Serious adverse events	0	0	0	0
TEAEs leading to discontinuation	1(2.22%)	1(2.27%)	3(6.67%)	0
TEAEs leading to study withdrawal	1(2.22%)	0	3(6.67%)	0
TEAEs leading to death	0	0	0	0

TEAE: Treatment-emergent adverse event

Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Denifanstat for Moderate-to-Severe Acne Vulgaris



Primary Objective

To evaluate the efficacy of once-daily Denifanstat tablets compared with placebo in the treatment of moderate-to-severe acne vulgaris after 12 weeks.

Primary Efficacy Endpoints

The percentage of subjects in each group achieving Investigator's Global Assessment (IGA) treatment success at Week 12.

Percent change in total lesion count from baseline to Week 12 in each group

Percent change in inflammatory lesion count from baseline to Week 12 in each group

Secondary Objective

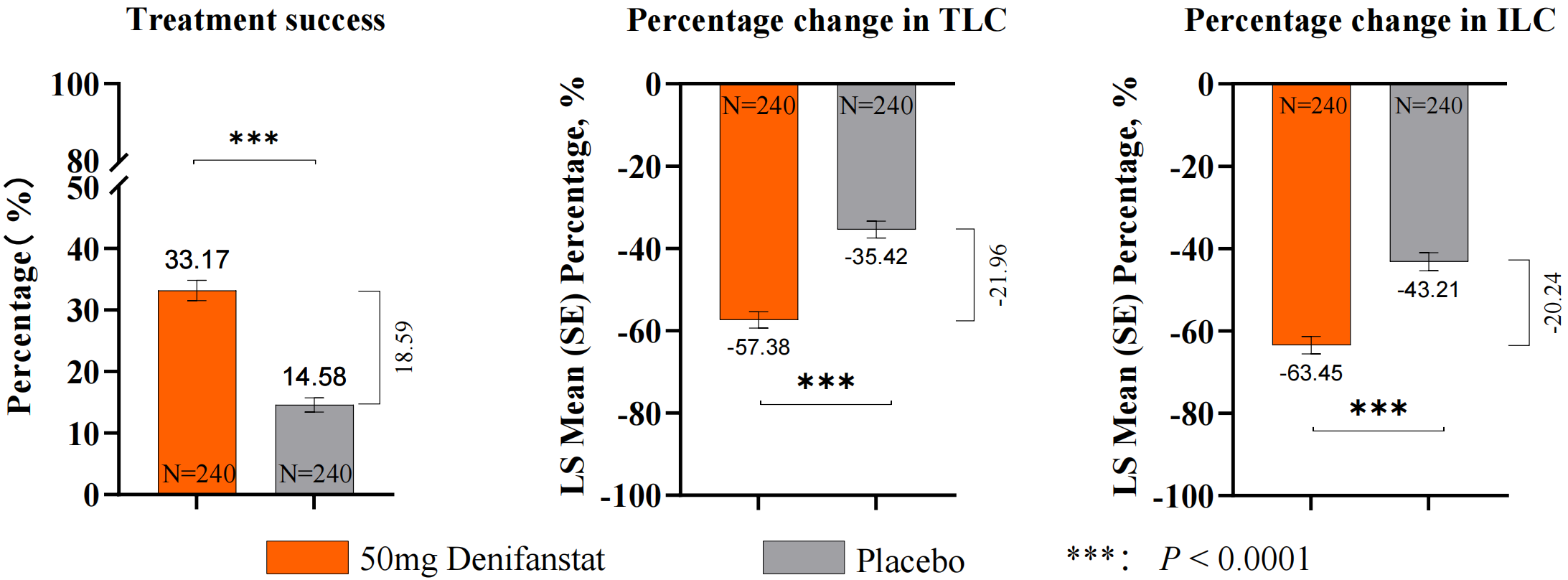
To evaluate the safety of once-daily Denifanstat tablets compared with placebo over 12 weeks in patients with moderate-to-severe acne vulgaris.

Baseline demographics and clinical features were well balanced across groups.

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 (7.818)	166.60 (8.235)	166.42 (8.022)
Weight, kg, Mean (SD)	59.92 (11.006)	58.29 (11.185)	59.11 (11.114)
BMI, kg/m^2, Mean(SD)	21.621 (3.2396)	20.894 (2.9855)	21.258 (3.1331)
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%)

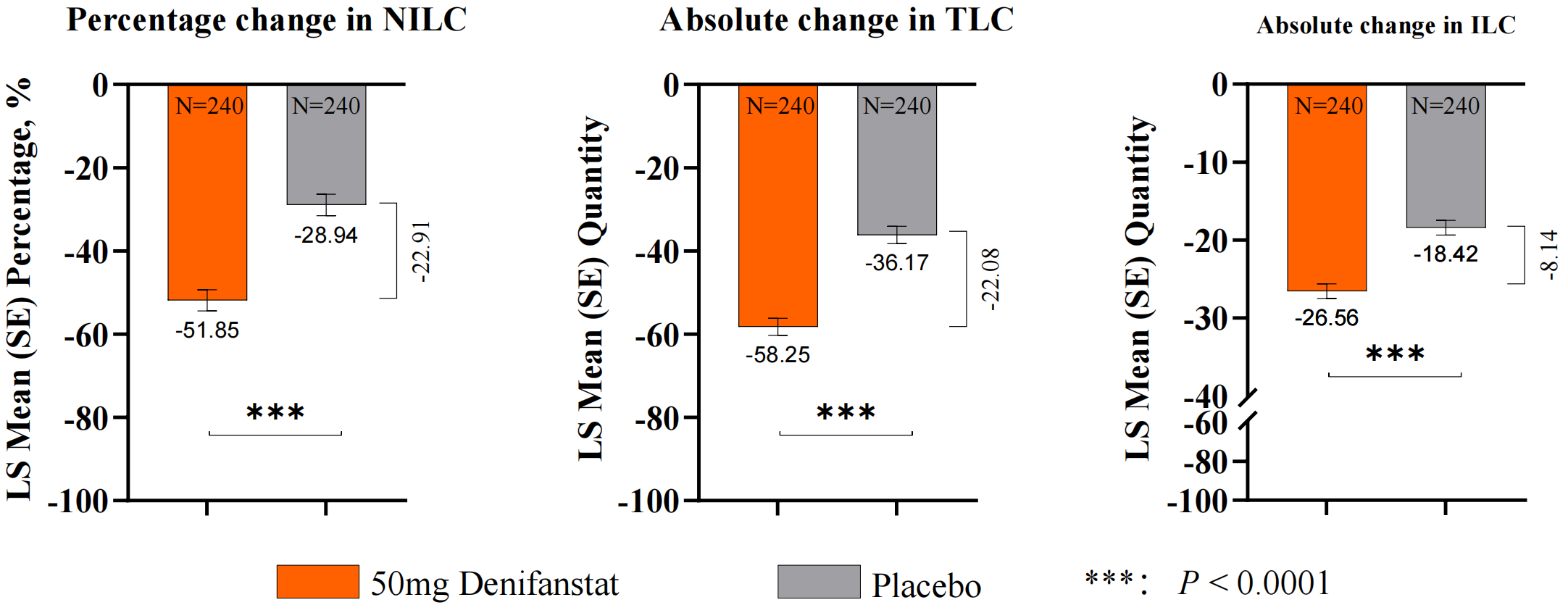
TLC: Total lesion count; NILC: Non inflammatory lesion count; ILC: Inflammatory lesion count; IGA: Investigator's global assessment.

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



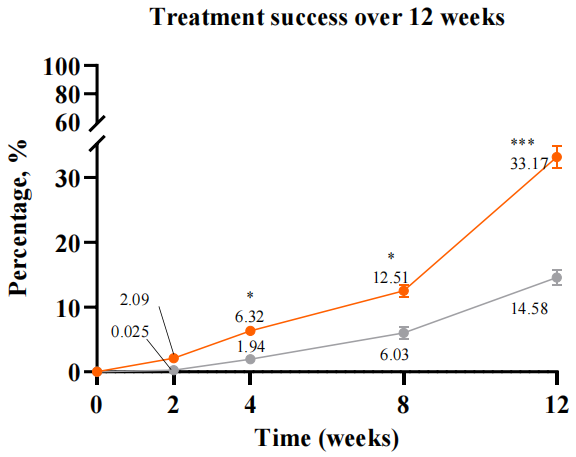
TLC: Total lesion count; NILC: Non inflammatory lesion count; ILC: Inflammatory lesion count; IGA: Investigator's global assessment; Treatment success: ≥2-point reduction in IGA from baseline and an IGA of 0 or 1.

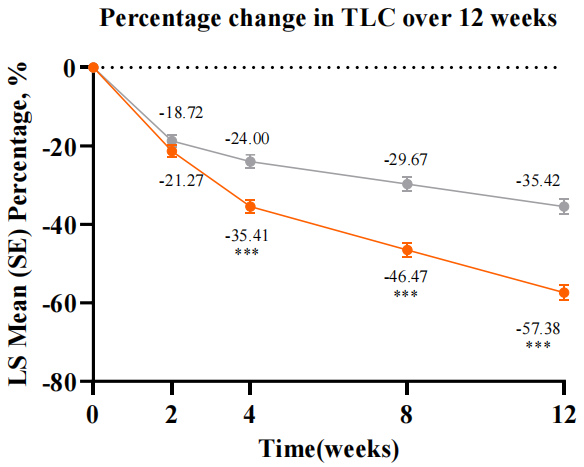
Denifanstat met all secondary efficacy endpoints (ITT analysis) and significantly improved moderate-to-severe acne compared with placebo

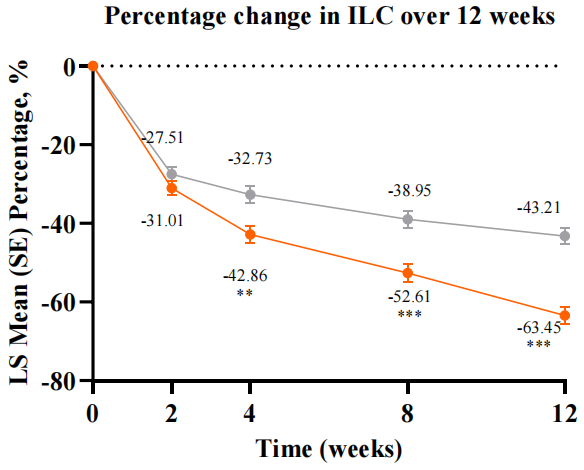


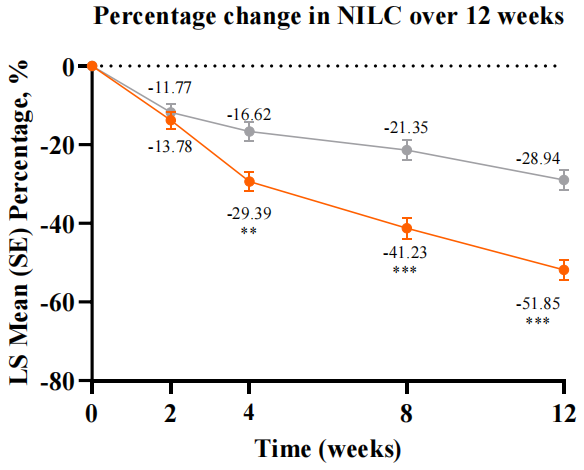
TLC: Total lesion count; NILC: Non inflammatory lesion count; ILC: Inflammatory lesion count;

A significant treatment effect of Denifanstat over placebo was observed as early as Week 4









Starting from Week 4 of treatment, the Denifanstat group showed statistically significant improvements ($P < 0.05$) over placebo in multiple efficacy endpoints, including treatment success, TLC, ILC, and NILC.

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

50mg Denifanstat Placebo *: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.0001$

TEAE rates were similar between the Denifanstat and placebo groups

	Denifanstat (N=239) n(%)	Placebo (N=240) n(%)	Total (N=479) n(%)
All TEAEs	140 (58.6)	135 (56.3)	275 (57.4)
Grade 1	78 (32.6)	77 (32.1)	155 (32.4)
Grade 2	58 (24.3)	55 (22.9)	113 (23.6)
≥ Grade 3	4 (1.7)	3 (1.3)	7 (1.5)
Serious TEAEs	0	0	0
TEAEs leading to death	0	0	0
TEAEs leading to temporary interruption	1 (0.4)	3 (1.3)	4 (0.8)
TEAEs leading to dose adjustment	0	0	0
TEAEs leading to permanent discontinuation	0	2 (0.8)	2 (0.4)
TEAEs leading to study withdrawal	0	3 (1.3)	3 (0.6)
Study drug–related TEAEs	70 (29.3)	57 (23.8)	127 (26.5)
≥ Grade 3	0	0	0
Serious TEAE	0	0	0
TEAEs leading to death	0	0	0
TEAEs leading to temporary interruption	1 (0.4)	0	1 (0.2)
TEAEs leading to dose adjustment	0	0	0
TEAEs leading to permanent discontinuation	0	2 (0.8)	2 (0.4)
TEAEs leading to study withdrawal	0	3 (1.3)	3 (0.6)

Note: One participant voluntarily withdrew before medication. TEAEs: The incidence of treatment-emergent adverse events.

No category of study drug–related TEAEs exceeded an incidence of 10%. Dry skin and xerophthalmia were the only events occurring in over 5% of patients

	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%).

Summary:
Denifanstat 50 mg once daily for 12 weeks demonstrated safety and efficacy in the treatment of moderate-to-severe acne.

- **Once-daily oral Denifanstat, a FASN inhibitor, achieved statistically significant and clinically meaningful improvements over placebo across all primary, key secondary, and secondary endpoints.**
  - 33.17% of participants achieved IGA treatment success
  - Percent reductions from baseline at Week 12:
    - Total lesion count: −57.38%
    - Inflammatory lesion count: −63.45%
    - Non-inflammatory lesion count: −51.85%
- **Denifanstat 50 mg once daily for 12 weeks demonstrated good safety and tolerability.**
  - The TEAEs in the Denifanstat group was comparable to placebo: 58.6% (140/239) vs. 56.3% (135/240). The majority of TEAEs were mild (Grade 1) or moderate (Grade 2).
  - No Denifanstat related Grade ≥3 TEAEs, SAEs, deaths, permanent treatment discontinuations, or withdrawals were observed.

Thanks