

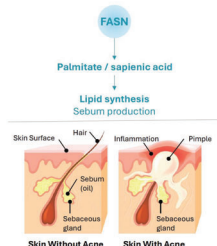
Denifanstat, a fatty acid synthase inhibitor, achieved significant clinical improvement in moderate-to-severe acne vulgaris: a review of mechanistic and clinical data

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Synopsis

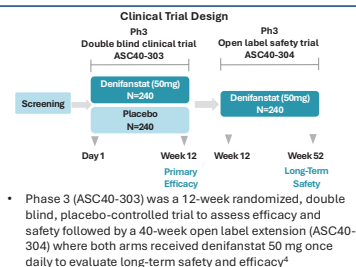
- Acne pathogenesis involves four interconnected factors: elevated sebum, hyperkeratinization, *C. acnes* proliferation, and inflammation
- Fatty acid synthase (FASN) is a key regulator in *de novo* lipogenesis (DNL), cytokine secretion, and Th17 cell activation¹, which can cause elevated sebum and inflammation in acne
- Denifanstat, an oral, once daily FASN inhibitor directly reduced sebum production²⁻³ and achieved clinical efficacy in acne patients⁴



Objectives

- We present a review of recent mechanistic and clinical findings demonstrates:
 - The effect of FASN inhibitors on sebum lipid production in human sebocytes *in vitro*
 - The effect of denifanstat on IGA improvement and lesion count reduction in patients with moderate-to-severe acne in a recent Phase 3 clinical trial in China⁴

Methods

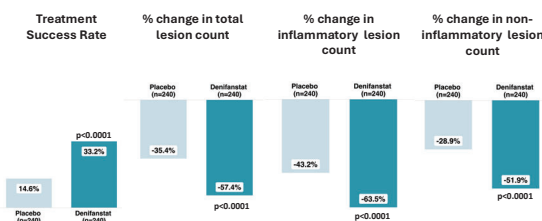


- Phase 3 (ASC40-303) was a 12-week randomized, double blind, placebo-controlled trial to assess efficacy and safety followed by a 40-week open label extension (ASC40-304) where both arms received denifanstat 50 mg once daily to evaluate long-term safety and efficacy⁴
- Preclinical studies**
- Human primary sebaceous gland cells (Meisen-280-HUM) and liver HepG2 cells were incubated with FASN inhibitors (denifanstat and TVB-3567) and ¹⁴C-acetate for 18 hours to measure DNL inhibition by conversion of ¹⁴C-acetate to ¹⁴C-palmitate
- Human sebocyte cells (SZ95) were treated with FASN inhibitors (TVB-3567 and TVB-3664) for 48 hours and cellular lipids were analyzed for lipidomic profiling

Denifanstat met all primary and secondary endpoints in Phase 3 (ASC40-303) clinical trial for moderate-to-severe acne in China (12 weeks)⁴

Baseline Characteristics	Placebo (n=240)	50mg Denifanstat (n=240)
Age, years, mean (SD)	22.5 (3.5)	22.7 (3.9)
Male, n (%)	71 (29.6)	79 (32.9)
Female, n (%)	169 (70.4)	161 (67.1)
IGA-3 (moderate), %	206 (85.8)	206 (85.8)
IGA-4 (severe), %	34 (14.2)	34 (14.2)
Total lesion count, mean (SD)	102.1 (25.1)	102.2 (24.6)
Inflammatory lesion count, mean (SD)	43.1 (12.2)	42.1 (11.7)
Non-inflammatory lesion count, mean (SD)	59.0 (20.0)	60.0 (19.8)

Baseline characteristics and efficacy endpoints of 50 mg denifanstat oral, once daily for 12 weeks versus Placebo, n is number of participants who were randomized in intent-to-treat population



Treatment success is defined as an Investigator's Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) with at least a 2-point decrease from baseline. Treatment success rate, % change in total lesion count and % change in inflammatory skin lesion count from baseline were primary endpoints. % change in non-inflammatory lesion count from baseline was a key secondary endpoint. The efficacy data are LSMEANs.

P-values were derived from logistic regression model to estimate the between-group difference in the rates of IGA treatment success at Week 12. The model includes treatment success (yes/no) as the dependent variable and treatment group and baseline IGA grade (3 or 4) as independent variables. An analysis of covariance (ANCOVA) was performed with percent change from baseline in total lesion counts, inflammatory lesion counts and non-inflammatory lesion counts at Week 12 as the dependent variable, treatment group as the independent variable, and baseline total lesion count as a covariate.

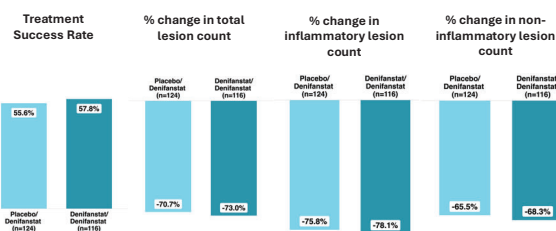
Denifanstat (Deni) was generally well-tolerated in phase 3 trial. Two categories of treatment related adverse events had an incidence of ≥5%: Dry eye 10.9% in deni vs 8% in placebo; Dry skin 6.3% in deni vs 2.9% in placebo. All deni-related AEs were mild or moderate.

Results

Denifanstat was generally well-tolerated in Open-Label Extension (ASC40-304) and all efficacy endpoints improved further during the extended treatment (52 weeks)⁴

Baseline Characteristics	Placebo/Denifanstat (n=124)	Denifanstat/Denifanstat (n=116)
Age, years, mean (SD)	22.3 (3.3)	22.5 (4.1)
Male, n (%)	47 (37.9)	31 (26.7)
Female, n (%)	77 (62.1)	85 (73.3)
IGA-3 (moderate), %	106 (85.5)	101 (87.1)
IGA-4 (severe), %	18 (14.5)	15 (12.9)
Total lesion count, mean (SD)	103.2 (24.4)	102.8 (25.3)
Inflammatory lesion count, mean (SD)	43.5 (11.8)	42 (12.2)
Non-inflammatory lesion count, mean (SD)	59.7 (20.9)	60.8 (19.3)

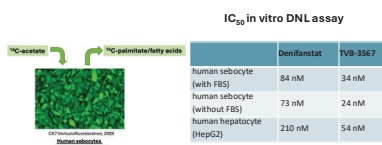
Baseline characteristics and efficacy endpoints of 50 mg denifanstat oral, once daily for 52 weeks in both arms of open label extension (OLE). Baseline is from day 1 of ASC40-303 (12 weeks). n is number of participants who continued into OLE from ASC40-303.



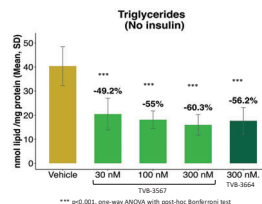
Treatment success rate, % change in total lesion count and % change in inflammatory skin lesion count from baseline (day 1) of ASC40-303 were primary endpoints. % change in non-inflammatory lesion count from baseline of ASC40-303 was a key secondary endpoint. Changes in lesion counts are mean % changes.

Deni was generally well-tolerated in the open-label extension trial with 239 patients receiving deni up to 52 weeks. Only two categories of treatment related AEs had an incidence of ≥5%: dry skin 7.1% and dry eye 5.9% in deni-treated subjects. Incidence in the 40-week OLE alone was 2.5% for dry skin and 2.1% for dry eye. All deni-related AEs were mild or moderate.

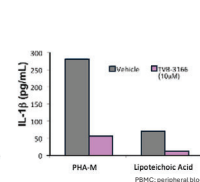
Denifanstat and TVB-3567 inhibited DNL in human sebocytes



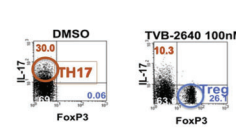
FASN inhibitors decreased lipids in human sebocytes



FASN inhibition reduced IL-1β production in ex-vivo stimulated human PBMC¹



FASN inhibition blocked Th17 and increases Tregs in human T cells¹



Conclusions

- FASN inhibition reduced sebum lipids in human sebocytes *in vitro* and in participants of clinical trials *in vivo*
- Denifanstat, an oral FASN inhibitor, significantly improved IGA scores and reduced lesion counts in patients with moderate-to-severe acne compared to placebo over 12 weeks with significant improvements as early as 4 weeks and further continued clinical improvements through 52 weeks
- Together, the clinical findings and preclinical mechanistic evidence support FASN inhibition as a novel oral therapeutic approach for acne that targets key aspects of acne pathogenesis by reducing *de novo* lipogenesis, sebum production, and inflammation

References

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- Duke G, et al., *AASLD* 2016, November 11-15, 2016.
- Syed-Abdul MM et al., *Hepatology*. 2020;72(1):103.
- Phase 3 clinical trial ASC40-303 (NCT06192264; <https://clinicaltrials.gov/study/NCT06192264>) and phase 3 open label extension ASC40-304 (NCT06248008; <https://clinicaltrials.gov/study/NCT06248008>) were conducted by Sagimet's license partner for China, Ascleitis.