Fatty acid synthase (FASN) inhibitors decreased sebum lipids in human sebocytes via inhibition of de novo lipogenesis, supporting FASN as a target for acne treatment

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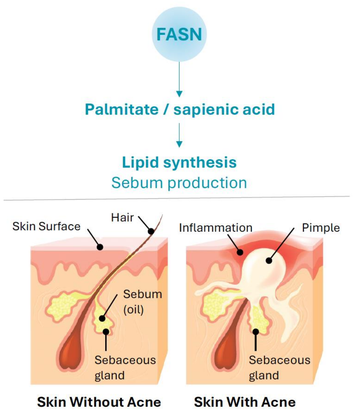
Introduction

- Excess sebum production contributes to acne vulgaris pathogenesis. De novo lipogenesis (DNL) drives sebum production in sebocytes, and FASN is a key enzyme in DNL pathway
- Denifanstat is an oral, once daily FASN inhibitor (FASNi) and reduced cutaneous (skin) sebum lipids in two Phase 1 studies
- FASN inhibition has potential to reduce inflammation through decreasing cytokine secretion and Th17 activation[1]



Background & Aim

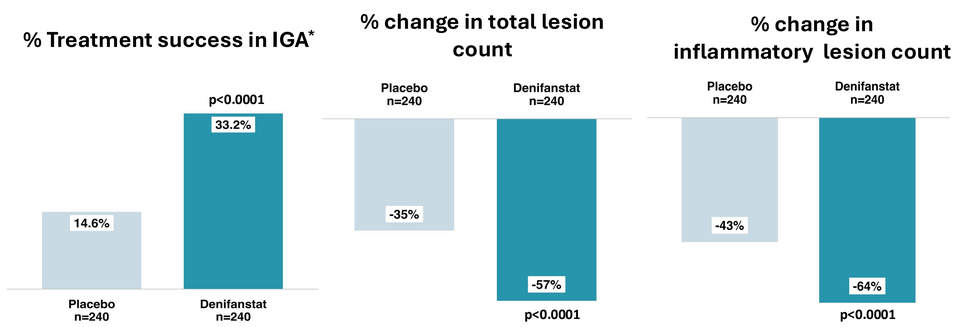
- Denifanstat improved moderate-to-severe acne in a recent Phase 3 clinical trial in China†, achieving treatment success (IGA 0 or 1) and decreasing both inflammatory and non-inflammatory lesion counts
- This study evaluated the effect of FASNi on DNL and sebum lipid composition in human sebocytes in vitro

Methods

- Human primary sebaceous gland cells (Meisen-280-HUM) and liver HepG2 cells were incubated with FASNi (denifanstat and TVB-3567) and ^{14}C-acetate for 18 hours to measure DNL inhibition via conversion of ^{14}C-acetate to ^{14}C-palmitate
- Human sebocyte cells (SZ95) were treated with FASNi (TVB-3567 and TVB-3664) and acetyl-coA carboxylase inhibitor (ACCi, PF-05175157) for 48 hours +/- insulin and the cellular lipids were analyzed by Lipidyzer platform (TNO) for lipidomic profiling

Results

Denifanstat met all primary and secondary endpoints in a Phase 3 clinical trial for moderate to severe acne in China



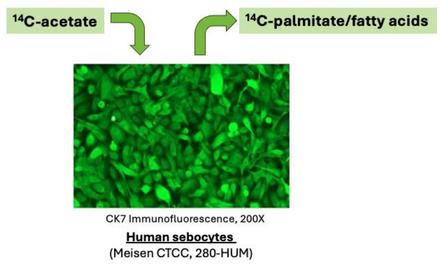
All p-values were derived from Analysis of Covariance (ANCOVA) or Logistic Regression model, with treatment group as an independent variable, and for lesion count endpoints, the baseline value was included as a covariate

Baseline Characteristics	50mg denifanstat (n=240)	Placebo (n=240)
Total lesion count	102.2	102.1
Inflammatory lesion count	42.1	43.1
IGA=3 (moderate), %	85.8	85.8
IGA=4 (severe), %	14.2	14.2

Efficacy endpoints **	50mg denifanstat (n=240)	Placebo (n=240)	50mg denifanstat (placebo adjusted)	p value
% Change in non-inflammatory lesion count (key secondary endpoint)	-51.9	-28.9	-23.0	<0.0001
Absolute change in total lesion count (secondary endpoint)	-58.3	-36.2	-22.1	<0.0001
Absolute change in inflammatory lesion count (secondary endpoint)	-26.6	-18.4	-8.2	<0.0001

Baseline demographics and efficacy endpoints of 50 mg denifanstat oral, once daily for 12 weeks versus Placebo (Intent-to-treat, ITT analysis change from baseline).
* 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.
** The efficacy data are LSMEANs.

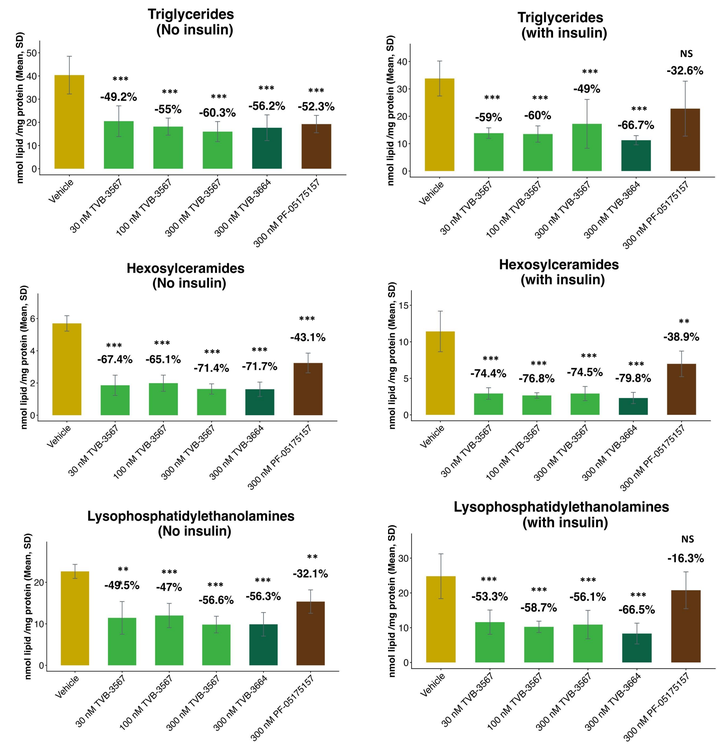
Denifanstat and TVB-3567 inhibited DNL in human sebocytes



IC_{50} in vitro DNL assay

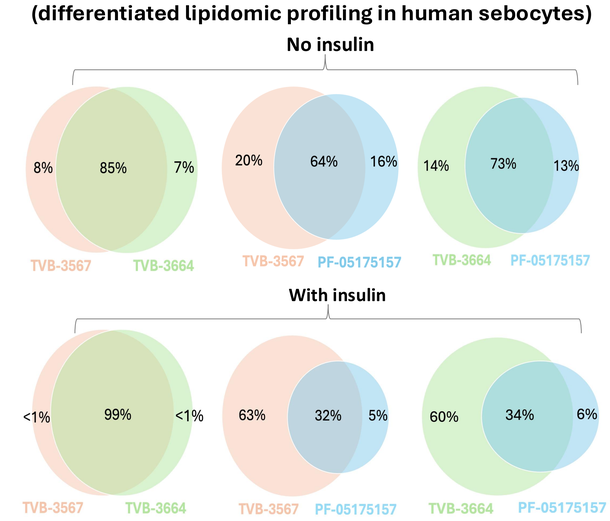
	Denifanstat	TVB-3567
human sebocyte (with FBS)	84 nM	34 nM
human sebocyte (without FBS)	73 nM	24 nM
human hepatocyte (HepG2)	210 nM	54 nM

FASN inhibitors decreased lipids in human sebocytes



Triglycerides, hexosylceramides and lysophosphatidylethanolamines are downstream products of DNL in sebum with different extended synthesis pathways; overproduction of these lipids leads to bumpy/redness skin and promotes inflammation
SZ95 cells; ** p<0.01, *** p<0.001, one-way ANOVA with post-hoc Bonferroni test

FASN inhibitors showed distinct profile from ACC inhibitor (differentiated lipidomic profiling in human sebocytes)



SZ95 cells; all concentrations were in 300 nM; PF-05175157: ACC inhibitor

Conclusions

- FASN inhibitor denifanstat's clinical benefit for the treatment of moderate to severe acne was demonstrated in a 12-week Phase 3 clinical trial
- In preclinical studies, FASN inhibitors reduced sebum-related lipids in human sebocytes, underscoring that FASN inhibition offers a potential mechanism of action to treat acne

†Phase 3 study (ASC40-303) conducted by Sagimet's license partner for China, Ascletis

References

1. O'Farrell M, et al. *Sci Rep*. 2022;12(1):15661.