

Denifanstat for Moderate-to-Severe Acne Vulgaris: Results from an Open-label, Multicenter, Phase III Extension Study

Qinyi Chen, Ruzhi Zhang, Zhuo Fan, Hongfang Han, Jin Chen, Chunjun Yang, Zhenying Zhang, Yanyan Feng, Lihong Chen, Bingjiang Lin, Jingfa Lu, Aie Xu, Wenjie Yan, Liming Wu, Meiyang Jiang, Jinyan Wang, Bin Yang, Chunshui Yu, Qing Guo, Yanling Li, Yue Zheng, Han Ma, Xianwei Cao, Jianyun Lu, Shengbo Yang, Yanxia Yuan, Ying Gao, Songmei Geng, Lunfei Liu, Yangfeng Ding, Hao Cheng, Rixin Chen, Jianglin Zhang, Guoqiang Zhang, Rong Xiao, Hui Chen, Hong Ren, Chao Ci, Zhiming Li, Jinzi Jason Wu, Leihong Xiang.

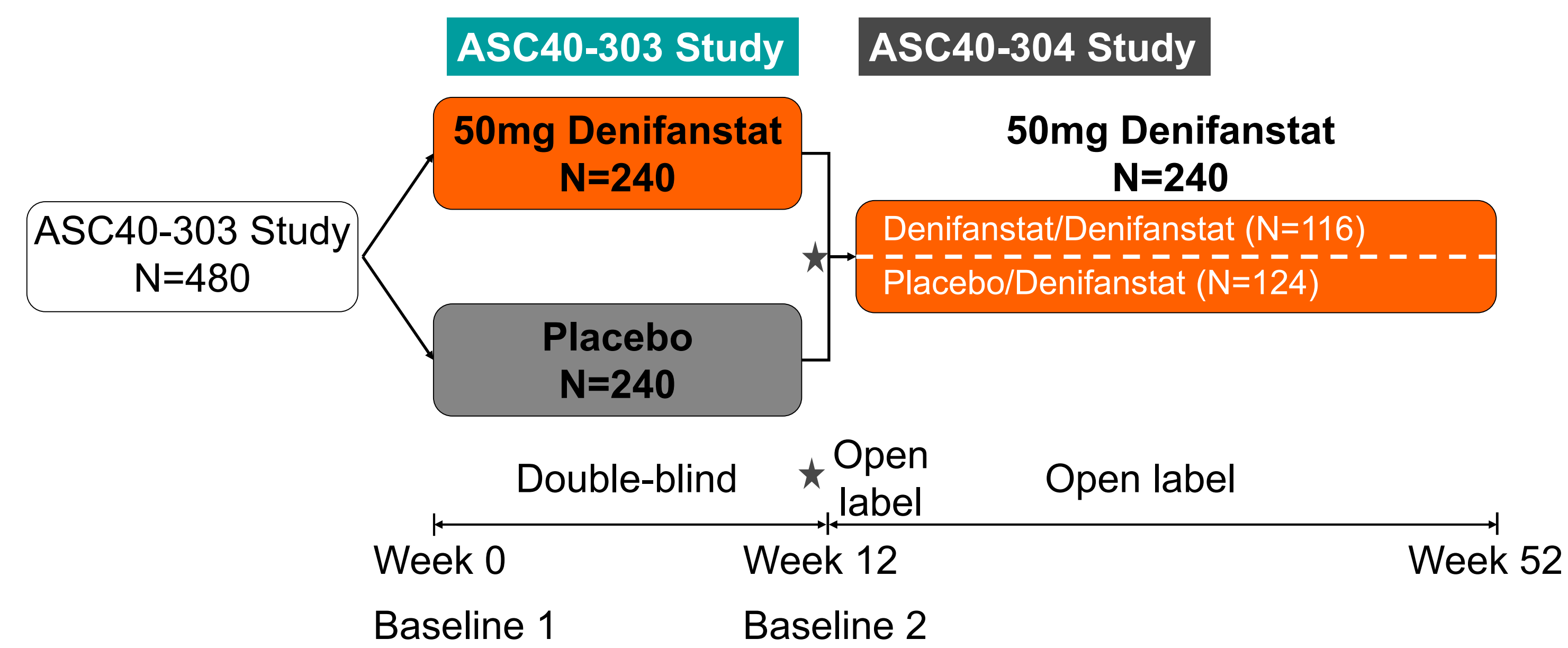
Author affiliations are listed in the abstract.

Introduction

Denifanstat, a fatty acid synthase (FASN) inhibitor, demonstrated efficacy and a favorable safety profile in the randomized, double-blind, placebo-controlled phase 3 ASC40-303 trial (NCT06192264). Once-daily administration of 50 mg for 12 weeks resulted in significantly higher treatment success rates than placebo, defined as Investigator’s Global Assessment (IGA) score of 0 or 1 with ≥ 2-point reduction from baseline, along with improvements in total, inflammatory, and noninflammatory lesion counts. Based on these findings, the ASC40-304 open-label, extension study (NCT06248008) was conducted to evaluate the long-term safety.

Materials and Methods

The ASC40-304 study design is depicted in **Figure 1**. The primary safety endpoints evaluate the incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and treatment discontinuations driven by AEs



Baseline 1 was defined as the assessment obtained before initiation of treatment in the 12-week randomized, double-blind ASC40-303 study. Baseline 2 was defined as the assessment obtained before initiation of treatment in the 40-week extension study (ASC40-304), after completion of the 12-week randomized, double-blind study. In the open-label ASC40-304 study, participants with an IGA Grade 0 at Baseline 2 may not be dispensed study drug. During the 40-week treatment period, treatment may be discontinued at the investigator’s discretion if an IGA Grade 0 or 1 is achieved and may be reinitiated if deemed necessary by the investigator.

Figure 1. Study design

Results

Of 240 enrolled patients, 239 comprised the safety population: 116 in the continuous denifanstat arm (1 untreated) and 124 in the placebo-to-denifanstat switch arm. Baseline features were well-balanced in ASC40-303, but diverged at ASC40-304 entry post-12-week double-blind treatment. Disease severity was lower in the Denifanstat/Denifanstat group vs. Placebo/Denifanstat (Grade 3/4 IGA: 24.2% vs. 44.3%; TLC: 42.6 vs. 65.2; **Table 1**).

Table 1. Baseline Demographics & Clinical Features

Characteristics	Denifanstat/Denifanstat (N=116)	Placebo/Denifanstat (N=124)
Gender, n(%)		
Male	31 (26.7%)	47 (37.9%)
Female	85 (73.3%)	77 (62.1%)
Age, year, Mean (SD)	22.5 (4.13)	22.3 (3.33)
BMI, kg/m ² , Mean (SD)	21.075 (3.1846)	21.132 (3.3315)

Assessment Based on Baseline 1

IGA Score		
0	0	0
1	0	0
2	0	0
3	101 (87.1%)	106 (85.5%)
4	15 (12.9%)	18 (14.5%)
TLC	102.8 (25.27)	103.2 (24.39)
ILC	42.0 (12.21)	43.5(11.80)
NILC	60.8(19.25)	59.7 (20.93)

Assessment Based on Baseline 2

IGA Score		
0	2 (1.7%)	0
1	41 (35.3%)	21 (16.9%)
2	45 (38.8%)	48 (38.7%)
3	27 (23.3%)	49 (39.5%)
4	1 (0.9%)	6 (4.8%)
TLC	42.6 (27.20)	65.2(37.69)
ILC	14.4(11.92)	22.9(16.72)
NILC	28.3 (19.23)	42.2(27.49)

Notes: TLC: total lesion count; ILC: inflammatory lesion count ; NILC: non-inflammatory lesion count. IGA score: Investigator’s Global Assessment score.

Denifanstat demonstrated favorable safety and tolerability regardless of whether the ASC40-303 baseline (capturing cumulative exposure) or the ASC40-304 baseline (reflecting extension period safety) was utilized (**Table 2**). Compared with the 12-week ASC40-303 period, 52-week exposure yielded higher rates of selected mild (Grade 1-2) treatment-related AEs, primarily dry eye, dry skin, and skin desquamation, alongside low-frequency mild TEAEs (≥1% and <5%).

Table 2. Summary of Safety Outcomes

	Denifanstat /Denifanstat (N=115)	Placebo /Denifanstat (N=124)	Total (N=239)
Assessment Based on Baseline 1 (cumulative safety from randomization)			
All TEAE	88 (76.5)	108 (87.1)	196 (82.0)
Serious adverse events	0	2 (1.6)	2 (0.8)P
Permanent discontinuation of Study Drug Due to AEs	0	0	0
Treatment-Related TEAEs of CTCAE Grade ≥3	0	0	0
Treatment-Related TEAEs Occurring in ≥5% of Patients	22 (19.1)	14 (11.3)	36 (15.1)
Dry skin	10 (8.7)	7 (5.6)	17 (7.1)
Dry eye disease	9 (7.8)	5 (4.0)	14 (5.9)
skin desquamation	6 (5.2)	3 (2.4)	9 (3.8)

Assessment Based on Baseline 2 (safety during open-label extension)

All TEAE	70 (60.9)	86 (69.4)	156 (65.3)
Serious adverse events	0	2 (1.6)	2 (0.8)
Permanent discontinuation of Study Drug Due to AEs	0	0	0
Treatment-Related TEAEs of CTCAE Grade ≥3	0	0	0
Treatment-Related TEAEs Occurring in ≥5% of Patients	0	0	0

Note: Data are n (%).

Following randomization, the two treatment groups showed broadly comparable efficacy. Using Baseline 1 (**Figure 2, Panel 1**), mean reductions in TLC, ILC, and NILC were 73.00%, 78.08%, and 68.29% in the Denifanstat/Denifanstat group versus 70.70%, 75.75%, and 65.52% in the Placebo/Denifanstat group. Treatment success rates were 57.8% and 55.6%, respectively, while IGA reductions of ≥2 points were observed in 62.1% and 59.7%. Efficacy generally plateaued by Weeks 24-36. **Figure 2, Panel 2** presents cumulative efficacy from Baseline 1 for the denifanstat/denifanstat group and open-label efficacy from Baseline 2 for the placebo/denifanstat group.

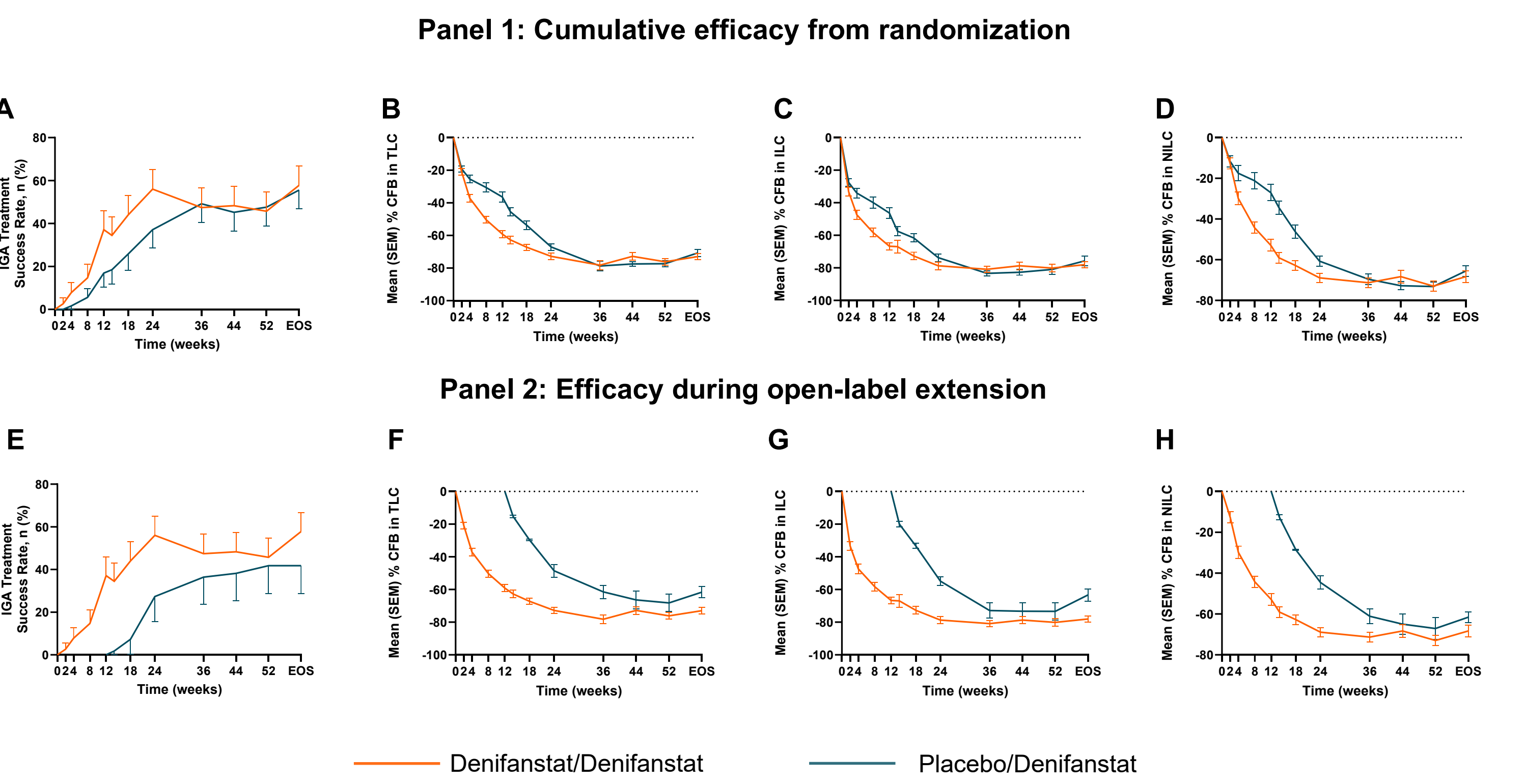


Figure 2. Efficacy outcomes at end of study

Notes: EOS: End of study includes the final visit after 40-week open-label extension or early termination. CFB: change from baseline. Treatment Success was defined as Investigator’s Global Assessment (IGA) score of 0 or 1 with a ≥ 2-point reduction from baseline (in patients with baseline IGA ≥3).

Conclusions

- Favorable Long-Term Safety Profile (up to 52 weeks)
 - Denifanstat 50 mg QD was safe and well-tolerated in moderate-to-severe acne.
 - No drug-related SAEs or permanent treatment discontinuation due to AEs were observed.
- Continued improvement and sustained efficacy
 - Continued long-term treatment yielded cumulative improvements in IGA response rates and lesion counts, with sustained efficacy after 24-36 wks.
- Extended Exposure Safety Trends (52-Wk vs. 12-Wk):
 - Longer exposure showed a slight increase in selected mild (Grade 1-2) TRAEs.
 - Emergence of new TEAEs was restricted to low-frequency, mild events.

Disclosure: Aseletis licensed denifanstat (ASC40) from Sagimet Biosciences Inc. for exclusive rights in Greater China.